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- Size exclusion chromatography (SEC)
- Capillary electrophoresis sodium dodecyl sulfate (CE-SDS) reduced
- Capillary electrophoresis sodium dodecyl sulfate (CE-SDS) non-reduced
- Intact mass and glycan analysis

Monoclonal IgG Reference Standards

<table>
<thead>
<tr>
<th>Reference Standard</th>
<th>Catalog Number</th>
</tr>
</thead>
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<tr>
<td>Monoclonal IgG System Suitability (2mg)</td>
<td>#1445550</td>
</tr>
<tr>
<td>USP mAb 001 RS, Monoclonal IgG1</td>
<td>#1445539</td>
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<tr>
<td>USP mAb 002 RS, Monoclonal IgG1</td>
<td>#1445547</td>
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<tr>
<td>USP mAb 003 RS, Monoclonal IgG1</td>
<td>#1445595</td>
</tr>
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About USP Bivalirudin RS
- Only pharmacopeial standard on Bivalirudin
- These are the only existing public standards for this product

Bivalirudin RS
USP Catalog No: #1076013 | 5 mg/vial

[ASP-9]-Bivalirudin RS
USP Catalog No: #1076024 | 1 mg/vial

[DES-GLU13] Bivalirudin
USP Catalog No: #1076035 | 1 mg/vial

Learn more about all our Reference Standards at usp.org/biologics
To contact someone directly about USP Reference Standards please email RSTech@usp.org
The JP Morgan Healthcare conference in San Francisco is the pharmaceutical world’s equivalent of the world economic development forum in Davos—an event CEOs and innovators schedule the rest of the year’s calendar around. It was with a heavy heart late last year the decision was made due to go to an all-virtual event. As a city, San Francisco was denied a vigorous financial stream, while participants were held back from in-person catchups and in-person partnering and deal making.

But much was maintained. The pandemic has raised drug production and supply to the forefront of both the general public and investors of various stripes—angel, institutional, strategic industrial, private investment in public equity, and public private partnerships.

This capital influx allows biotech companies the luxury of retaining control much longer (i.e., of staying private companies). In turn, this has pushed up sector valuations. So, while mergers and acquisitions remained somewhat quiet after a stellar 2019, licensing and partnerships predicates upon back-end payouts have proliferated.

This is in tune with a cultural shift during the two years of pandemic where all parties have kept in far closer conversation than had been previously typical. This built-up of trust and empathy for each other’s situations and goals, reduced barriers and resistance to license agreements. It’s been more collegial. Decisions are made with less uncertainty. Outsourcing contract development and manufacturing organizations (CDMOs) have space booked a year in advance, “the outside economic environment is encouraging,” Ramesh Subramanian, Chief Commercial Officer, Aragen, says. He affirms it is a buoyant time for R&D outsourcing. He specifies that this buoyancy can be attributed primarily to three reasons, “... increased funds flowing into [the R&D outsourcing] space, a high number of targets in the pipeline, and renewed interest in pharma R&D due to the COVID-19 pandemic.”

However you are placed coming out of the past two years, it is a certainty you are busy. And busy is good for business.

Mike Hennessy, Jr. 
President and CEO 
MJH Life Sciences™
COVER STORY

10 Analysis of mRNA Therapeutics and Vaccines
Analytical approaches must keep pace to ensure the identity, safety, and efficacy of evolving mRNA candidates.

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**From the Editor**

**Celebrate the New**

The process of reshaping inevitably leads to fresh insights.

The start of a new year always brings energy and ideas. In January, we smashed the champagne bottle of good fortune on our sister magazine’s, *Pharmaceutical Technology*, first podcast series (called “Drug Solutions”), it’s first video interview series (called “Drug Digest”), and a new e-newsletter for *BioPharm International* (named “BP Elements”). Turns out much of the energy and fresh ideas in 2022 are coming in the form of outside expert interviews. I don’t know if this exactly qualifies as outsourcing our thinking, but as part of our response to the pandemic, that’s perhaps not a bad way to look at it.

Great lessons over the past two years include better engagement to experts and ways to form supporting networks in a durable manner. I was mildly interested in oral recombinant vaccine manufacture until I heard the company founder presenting clinical trial highlights alongside the technical explanations of how this platform can be made to work in a durable manner. I was mildly interested in oral recombinant vaccine manufacture until I heard the company founder presenting clinical trial highlights alongside the technical explanations of how this platform can be made to work in a durable manner. I was mildly interested in oral recombinant vaccine manufacture until I heard the company founder presenting clinical trial highlights alongside the technical explanations of how this platform can be made to work in a durable manner.

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Having these videos and podcasts out in the real world has already provided quite unexpected feedback and comment. Multiple new contacts have spent time to offer novel topics or have asked us to question why we chose a certain approach to a particular field. This kind of interaction is always to be welcomed, especially if we recall lord Reith (founder of the BCC in 1922) said saeva indignatio was not to be had for the mere asking. It was Reith who famously set the mission of broadcasting as being to inform, educate, and entertain.

As we fill out the schedule of topics, personalities, and priorities for these new formats, the terrain seems alive with possibilities. The process of reshaping inevitably leads to fresh insights, even though we have been planning and preparing over most of last year. Great things take time it seems, but time taken repays efforts at the finish line, at the packaging center, and at the sales meeting. In an industry revved up by the need to move quickly, usable information and thoughtful perspective must be distilled and enlivened—just like champagne! ♦
2022 PDA Annual Meeting

Level Up: Agility in the New Normal

Join PDA In Person for the 2022 Annual Meeting!

Through plenary, concurrent, and interest group sessions, all built around the theme, Level Up: Agility in the New Normal, you will find out what's in store for the future of pharmaceutical manufacturing!

Here are just a few of the confirmed industry-leading experts who will be sharing insights on adapting to the current manufacturing environment through the adoption of innovative approaches and processes:

- Jeffrey C. Baker, PhD, Consultant and Former Deputy Director, Office of Biotechnology Products, CDER, U.S. FDA
- Donna Boyce, Senior Vice President, Head of Global Regulatory Affairs, Pfizer
- Benjamin Borgo, PhD, MBA, Head of Portfolio Management, Genome Engineering and Modulation, MilliporeSigma
- Robert Dean, MBA, Director/Team Leader, Advertising and Promotion, Merck & Co., Inc.
- Kelvin H. Lee, PhD, Director, NIIMBL, and Gore Professor, Chemical and Biomolecular Engineering, University of Delaware
- John J. Lewin, III, PharmD, MBA, BCCP, FASHP, FCCM, FNCS, Chief Medical Officer, On Demand Pharmaceuticals

Concurrent sessions will focus on four important topics: Aseptic Processing and Sterilization, Biopharmaceuticals and Biotechnology, Manufacturing Science, and Quality and Regulatory.

Don't miss the return of this signature conference to in person to take advantage of networking opportunities and the chance to connect with numerous vendors and suppliers in the Exhibit Hall!

No matter what your area of focus, you are sure to come away with tangible, practical solutions to improve your operations and your standing within your company.

Visit pda.org/2022annual for updates on the intriguing lineup of sessions, speakers, and engaging networking activities!
Global Vaccine Access Challenges FDA and Industry

The global nature of the COVID-19 pandemic emphasizes the critical importance of expanded vaccination.

As public health authorities, patients, and manufacturers applaud the fast development and production of billions of doses of innovative vaccines against COVID-19, the campaign continues to extend global access to the life-saving preventives. The “America first” vaccination and treatment policy of the United States through the initial 18 months of the outbreak generated loud criticism from international health organizations and patient advocates. The emergence of the omicron variant, moreover, has demonstrated clearly the global nature of the pandemic and the critical importance of expanded vaccination in Africa and other regions to control COVID-19 in all regions.

Global vaccine access concerns came to a head in the US in the fall of 2021 when FDA authorized booster doses of vaccines from Pfizer-BioNTech, Moderna, and Johnson & Johnson while most of the world still awaited initial protection. Marion Gruber, the head of the Office of Vaccine Research and Review in the Center for Biologics Evaluation and Research (CBER), and her deputy, resigned in protest. Gruber recently joined IAVI, an international organization that advances the development and distribution of innovative vaccines and therapeutics.

Prospects have brightened for broader access to COVID-19 vaccines as production has soared to more than 11 billion doses in 2021, supporting predictions for doubling that amount by mid-2022. The COVAX vaccine sharing initiative recently announced that in 2021 it shipped more than 1 billion doses to 144 countries and territories—a noteworthy achievement, but still far short of the 2-billion-plus vaccine goal set earlier last year. Manufacturing difficulties in the US, European Union, and India prompted curbs on vaccine exports, while several vaccine candidates from other manufacturers failed to gain regulatory approval from FDA and the European Medicines Agency. These setbacks limited efforts by COVAX, the Gavi Alliance, and the Coalition for Epidemic Preparedness Innovations (CEPI) to obtain and distribute needed preventives.

Prospects have brightened for broader access to COVID-19 vaccines.

SUPPORT FOR GLOBAL PRODUCTION

Vaccine supplies for poorer regions have improved with expanded vaccine production in India and other nations and the development of new vaccine formulations with extended shelf-lives and reduced deep-freeze requirements that facilitate distribution. A report from Medecins Sans Frontieres identifies 120 biopharma manufacturers in third-world countries capable of producing mRNA-based vaccines, findings based on evidence that firms able to make sterile injectables can produce mRNA treatments (1). Established drug makers in Africa, Asia, and South America are collaborating with researchers to develop and test additional COVID-19 vaccines, a process that could be facilitated by licensing agreements to make

Jill Wechsler is BioPharm International’s Washington editor, jillwechsler7@gmail.com.
existing mRNA formulations by Moderna and Pfizer-BioNTech that have been slow to appear.

Meanwhile, BioNTech has unveiled plans to build a modern facility in Rwanda to utilize messenger RNA (mRNA) technology to develop new preventives against malaria, tuberculosis, and other diseases (2). And Moderna says it will fund an mRNA vaccine facility in Africa, possibly at sites in Senegal, Rwanda, or South Africa (3).

Gavi now aims to raise $5 billion from the US and other industrial nations and international organizations to boost vaccine access and bring the pandemic under control (4). Global vaccine supplies may expand, moreover, as several biopharma companies that fell behind on testing and producing COVID-19 vaccines are moving toward regulatory approval. Novavax recently filed data to support FDA Emergency Use Authorization (EUA) of a vaccine that utilizes more conventional recombinant technology and recently gained conditional marketing authorization in the European Union, Indonesia, the Philippines, and Australia (5). Similarly, the German biotech CureVac has linked up with GlaxoSmithKline to test a second-generation mRNA vaccine candidate, with plans to launch Phase I studies in 2022.

A notable new entry is the Corbevax COVID vaccine, which has been licensed by a research team at the Baylor College of Medicine in Houston to Biological E in India for production of a low-cost preventive for lower- and middle-income countries (6). Indian regulators have approved emergency use of the shot, but scale-up and production present notable challenges.

Global vaccine supplies may expand, moreover, as several biopharma companies that fell behind on testing and producing COVID-19 vaccines are moving toward regulatory approval.

As FDA and vaccine makers examine the need to update COVID-19 vaccines to better attack omicron and other variants, a consensus has emerged on the importance of international collaboration among regulatory authorities to ensure the effectiveness of revised preventives under different mixed-and-match treatment scenarios. The World Health Organization and regulatory authorities are examining what evidence is needed to determine that a revised vaccine works well against current and potential variants, with an eye to avoiding widely differing booster options. Such collaboration will be even more important if annual COVID booster shots become the norm.

**REFERENCES**


—Jill Wechsler
Analysis of mRNA Therapeutics and Vaccines

Analytical approaches must keep pace to ensure the identity, safety, and efficacy of evolving mRNA candidates.

CYNTHIA A. CHALLENER

The success of the messenger RNA (mRNA) vaccines against the SARS-CoV-2 virus brought attention to a field that has steadily advanced for many years. Investment in this space has ramped up dramatically, and many applications of mRNA technology are rapidly advancing through pre-clinical development as well as clinical trials.

As with all drug or vaccine candidates, proposed mRNA products must meet regulatory requirements for analytical characterization as outlined by the International Conference on Harmonisation (ICH), the World Health Organization (WHO), FDA, the European Medicines Agency (EMA), and other health authorities around the globe.

Unlike most other drug substances, mRNA must be formulated within specialized nanoparticles, most commonly consisting of lipids, both to protect it from degradation and to facilitate its transit across cell membranes. Additional analytics are therefore required to ensure the quality and safety of the nanoparticle formulation as well as the mRNA molecule itself.

A key activity in the early development phase of mRNA therapeutics is extensive characterization of mRNA and nanoparticle quality attributes as these are known to strongly influence biological efficacy. Given the shrinking timelines for drug development, access to faster and higher-throughput analytical methods has become vital. Indeed, it is essential that analytical approaches for use during mRNA product development and quality-control (QC) testing must keep pace to ensure the identity, safety, and efficacy of these new prophylactic and therapeutic modalities.

WIDE RANGE OF ANALYTICAL NEEDS

Although analytical requirements for mRNA candidates are more complex than those for traditional biologics, some testing needs are similar while others are quite different. “There is a common need to adequately characterize both protein therapeutics and mRNA therapeutics to confidently identify and quantify any quality attributes that will impact their efficacy and safety,” says Todd Stawicki, global marketing manager, mass spectrometry, for the biopharmaceutical industry at SCIEX. He points to the need to identify process-related
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impurities—host-cell proteins (HCPs) in the case of protein therapeutics and a variety of genetic impurities like truncated transcripts or incorrect DNA template in the case of mRNA.

The differences are notable, however. Rather than focusing on post-translational modifications as is the case for protein therapeutics, there is a lot of emphasis on characterization of mRNA, the delivery systems, and cellular uptake at the discovery phase of drug development, because unlike engineered proteins and monoclonal antibodies (mAbs) that are ready to start functioning upon delivery, mRNA once delivered to cells provides instructions for producing the proteins that do the work, according to Brian Liau, a solution development scientist at Agilent Technologies, Singapore.

Manufacturing for mRNA products, furthermore, requires unique process steps such as in vitro transcription (IVT) and lipid nanoparticle formulation, which naturally creates different analytical needs, adds Ryan Hanko, manager of quality control for Catalent. IVT is a chemical rather than a cell-based process, expounds Joe Fredette, senior business development manager of biopharmaceuticals at Waters. It also involves the use of an enzyme called an RNA polymerase that transcribes DNA into mRNA.

As an example of different analytical needs, Hanko notes that mRNA products require QC assays to be developed that measure residual enzyme (such as polymerase or endonuclease), which may be present after the IVT step, to ensure that it is not present in the final product. Confirmation of the RNA sequence and determination of the efficiency of capping at the 5’ end and poly(A) tail distribution at the 3’ end are also unique to mRNA, notes Ashleigh Wake, business development director for Intertek Pharmaceutical Services. The potential impurity profile is also quite different to other molecules, and methods to quantify any residual plasmid or double-stranded RNA are also required.

In addition, lipid analysis workflows are necessary for characterization and chemistry, manufacturing, and controls (CMC) testing of mRNA products, including liquid nanoparticle (LNP) composition analysis to ensure the right mix ratio of lipids within the formulation, lipid ID confirmation, and impurities analysis and screening, according to Fredette.

In essence, summarizes Wake, there is a similarity in the overall requirements for product characterization in that the intent is to assess or confirm identity, purity/impurities, stability, activity, etc. “However,” she underscores, “to fully accomplish this, there is a need to include mRNA-specific analytics that allow assessment of these attributes.”

**EVOLVING ANALYTICAL NEEDS FROM EARLY TO LATE-PHASE DEVELOPMENT**

Another important difference between the development of protein- and mRNA-based products is the analytical burden during the early discovery phase. As traditional drug development typically involves mAbs, says Dr. Liau, bioanalytical requirements tend to be relatively modest because even sub-optimal molecules may be used to demonstrate target engagement and a therapeutic effect. In contrast, mRNA products require several biological processes, including cellular uptake, endosomal escape, and protein translation to take place efficiently before any effect may be observed. Hence, analytical characterization of mRNA and delivery vehicle quality attributes are important from the outset.

“For process scale-up and GMP [good manufacturing practice] manufacturing/product release, chemical characterization of mRNA remain important. However, the focus tends to shift towards ensuring consistent size polydispersity and mRNA encapsulation in the formulated product, as well as identifying process-related impurities,” Dr. Liau comments.

With mRNA candidates, Stawicki adds that scale up of the enzymatic process requires significant and difficult scale up for all upstream raw materials—nucleoside triphosphate (NTPs), enzymes, capping reagents, cofactors, and multiple classes of lipids. “The majority of these components are large, complicated biomolecules with their own associated scale up, purification, and analytical challenges,” he explains.

There are also some differences in the attributes that are monitored during production, according to Hanko. A260 concentration checks and osmolarity testing are the primary monitoring assays in early development and process scaleup for in-process observations, while during GMP manufacture RNase testing is important to ensure the final product will not be compromised by incidental contamination from non-product materials.

Core release tests include identity determinations, final concentration, impurity content (e.g., residual protein, dsRNA, rDNA), capping efficiency, and poly-A tail, in addition to typical compendial evaluations for safety and quality attributes.

**MANY CRITICAL QUALITY ATTRIBUTES**

There is an extensive list of critical quality attributes (CQAs) that must be monitored to meet regulatory requirements regarding the assessment of the identity, functionality, and safety of mRNA therapeutic/vaccine products (see Table I). “Confirmation that the specific mRNA sequence has been generated, that the mRNA solution is at target pH, and that any potential process impurities (solvent, protein, DNA-related) have been controlled will be required,” says Matthew Howard, a senior specialist in quality assurance at Catalent.
Assurance will also be needed that the translation-promoting and degradation-preventing characteristics of the 5’ cap and poly-A tail are sufficient, says Howard. The efficiency of capping at the 5’ end can influence both target protein production and overall immunogenicity, while the length/distribution of the poly(A) tail is critical for translation and overall protection of the mRNA, Wake explains.

Adds Maxwell Meller, senior scientist, quality control, with Catalent: “The 5’-capping of the mRNA molecule is critical to its integrity upon delivery to the target site and is a unique requirement for mRNA production compared to other kinds of drugs. Characterization and monitoring of capped material, however, have proven to be time- and resource-intensive.”

For the lipid components, confirmation of the identity of each lipid in the LNP mix and that they are present in the correct ratio is essential as these CQAs can directly impact LNP formation and efficacy, according to Fredette. It is also important, he emphasizes, to ensure that lipid impurities are well controlled for and under critical thresholds, as both lipid and mRNA impurities can adversely impact process outcomes and in some cases lower the potency of the mRNA.

**Table I. Key critical quality attributes (CQAs) that must be monitored for messenger RNA (mRNA) therapeutic/vaccine products.**

<table>
<thead>
<tr>
<th>CQA</th>
</tr>
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<tbody>
<tr>
<td>mRNA purity</td>
</tr>
<tr>
<td>mRNA identity/sequence</td>
</tr>
<tr>
<td>% Poly A Tail RNA and length</td>
</tr>
<tr>
<td>Efficiency of 5’Capping of mRNA</td>
</tr>
<tr>
<td>Product- and process-related impurities</td>
</tr>
<tr>
<td>Residual DNA template</td>
</tr>
<tr>
<td>Nucleic acid content/quantity</td>
</tr>
<tr>
<td>pH at mRNA synthesis stage, encapsulation stage, and final packaging</td>
</tr>
<tr>
<td>Lipid component identities</td>
</tr>
<tr>
<td>Lipid ratios</td>
</tr>
<tr>
<td>Lipid impurities</td>
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</tbody>
</table>

**THE NEED FOR RNASE-FREE ZONES**

The sensitivity of mRNA to degradation by enzymes, particularly RNase, creates additional unique requirements when working with mRNA-based therapeutics and vaccines. For instance, Hanko observes that the use of RNase-eliminating preparations is vital and laboratories should consider physical space segregation in addition to personnel training and awareness regarding the maintenance of RNAse-free zones, equipment, and personal protective equipment (PPE).

These actions are important, Hanko says, because a compromised mRNA sample will show lower-than-expected purity in those assays. Some analyses, as those for residual impurities, are arguably not impacted by compromised mRNA and others may only require heightened RNase sensitivity depending on solution preparations and material manipulations. “Even so,” Hanko states, “the core method performance expectations must be understood for all methods regardless of the level of mitigation required.”

**TIME IS OFTEN THE ENEMY**

One of the biggest issues facing mRNA analysis is experienced across the board in the biopharmaceutical industry. “The great enemy here is time,” Stawicki asserts. “The unfortunate reality is that many of the current functional and biophysical tests are still too slow to generate actionable answers in a timeframe that enables intervention in the process,” he explains.

For instance, Stawicki highlights cell-based functional assays, which are the gold standard today. “This test is the best early indication that you’ve got everything right,” he says. “You dose your formulated mRNA LNP to cells and see if you get sufficient yield of the right protein or antigen. The problem is that it can take days to get a read out. Therefore, often times developers have to proceed at risk in their processes without having the analytical data to back up their process parameters.”

**USE OF NUMEROUS COMPLEMENTARY TECHNIQUES DURING EARLY DEVELOPMENT**

Bioanalysis of mRNA products requires a combination of familiar and more novel analytical techniques and technologies. It also necessitates, Hanko reiterates, the control and elimination of RNase enzymes, which may compromise product integrity.

A wide variety of analytical techniques are employed to evaluate these properties. What is interesting to Stawicki is that they have come from a variety of different backgrounds. High-performance liquid chromatography (HPLC) and mass spectrometry (MS) have migrated from protein-therapeutic characterization. Electrophoretic techniques (most notably capillary electrophoresis) have come from classic molecular biology use. Particle sizing techniques that have come from polymer analysis or materials lab use. “Since mRNA therapeutics are such large, heterogenous complexes, it really comes down to which part or parts of the candidate require characterization,” Stawicki remarks. For the mRNA component, he notes that capillary electrophoresis or even slab-gel electrophoresis methods are preferred. For
characterization of lipids and LNPs, HPLC with charged aerosol detection (CAD) or LC-MS are generally the methods of choice. For complete mRNA-LNP complexes, techniques such as particle sizing or cryo-electron microscopy are preferred.

Some common activities during early development are mRNA codon optimization and selection of optimal 5’ and 3’ untranslated regions (UTRs), says Dr. Liau. As this entails cloning coding sequences out of libraries and combining them in multiple plasmids with different UTRs, Sanger sequencing, capillary or slab-gel electrophoresis, and polymerase chain reaction (PCR) remain mainstay analytical methods during this phase of development.

Characterization and CMC testing for the mRNA component of the drug, according to Fredette, includes a range of nucleic acid (DNA/RNA) analytical workflows to confirm the identity and purity of the mRNA, including 5’ Cap analysis, PolyA tail analysis, oligo mapping (similar to peptide mapping, but for nucleic acids), and MS-based sequencing.

MS, meanwhile, is also used to establish key quality attributes such as capping efficiency and poly(A) tail distribution, notes Wake. She adds that all of these analyses are performed in addition to more traditional QC requirements, such as assay [ultraviolet (UV)/HPLC]) analytics, residual solvents, metals, etc.

To confirm the biological activity of mRNA candidates, well-studied lipid delivery systems using cationic or ionizable lipids may be used to transfect standard cell lines in vitro. “For such early-stage experiments,” Liau observes, “it is often unnecessary to use highly purified mRNA or monodisperse preparations of lipid nanoparticles. Instead, bulk dynamic light-scattering and zeta potential measurements are often used to ensure the nanoparticles have approximately the correct size and surface-charge properties to permit efficient cell transfection. Biological activity may then be determined by fluorescence microscopy, enzymatic assays, or immuno-staining as appropriate.”

LOOKING FOR SIMPLER, MORE ROBUST SOLUTIONS DURING LATE-STAGE DEVELOPMENT

Similar analytical techniques are generally used from early in development through the GMP environment. For instance, LC and LC-MS workflows bring value across all stages of development and for process monitoring in manufacturing, Fredette observes.

Because the goals of process optimization and scaleup are often quite different from those of early-stage development studies, however, Liau comments that different analytical techniques are required in some cases. “During process optimization and scaleup, the mRNA sequence is fixed, and its biological activity known, and the focus is on monitoring and/or improving the process yield and mRNA quality attributes,” he says.

LC-MS is very useful both for monitoring the progress of in vitro transcription reactions and determining the status of critical quality attributes such as 5’ capping, Liau adds. Separation-based techniques such as size-exclusion chromatography-multireangle light scattering (SEC-MALS) and field-flow fractionation (FFF)-MALS may, meanwhile, be useful for monitoring the properties of LNPs and optimizing the complexation process.

One important trend noted by Stawicki that is also seen with protein therapeutics is the preference for increasingly robust and simpler techniques the further down the pipeline programs get, Meller agrees. For instance, he notes that while LC-MS is a promising tool for characterizing and quantitating capped species, a more simplistic approach lends itself more appropriately to routine use. “In the QC environment,” says Meller, “the chromatography analysis must be condensed to an HPLC assay to prioritize speed and efficient data analysis.”

In general, Wake believes that many of the methods or approaches used to fully understand mRNA are novel in the QC area, when compared to those used for other modalities. “To fully support all regulatory requirements, greater use of technologies such as next-generation sequencing, which have not been typical technologies operated in a GMP environment, has been necessary,” she explains.

For other considerations such as capping, however, Wake says that the technologies used are more familiar and tend to be heavily MS-based. Even in these cases, though, she remarks that the overall sample preparation approach is often novel and challenging. “A lot of work is being done in our and other laboratories to develop platform approaches to overcome these challenges considering best science, quality data, and regulatory compliance,” she concludes.

SIGNIFICANT INNOVATION UNDERWAY

There is, in fact, tremendous effort being made to advance analytics for mRNA vaccines and therapeutics. “Scientists have been working with mRNA for decades, but a lot of that effort has focused optimizing analytical methods to enable production-grade techniques. With the explosion of genetic therapies and the now intense interest in mRNA, you are seeing a tremendous amount of investment and innovation by scientists and instrument companies to develop the best analytical solutions to support that work,” Stawicki contends.

SCIEX, for instance, has introduced electron activated dissociation (EAD) as a new MS fragmentation technology in the ZenoTOF 7600. Initially launched with small-molecule and protein therapeutics in mind, the company has since learned, according to Stawicki, that EAD technology is also powerful for analyzing mRNA products. “EAD has amazing utility for both oligonucleotide and LNP characterization, allowing, for example, the
sensitive and complete structural characterization of lipids including double bond positions and isomer configurations in a single experiment."

Stawicki also points to SCIEX’s new BioPhase 8800 multi-capillary CE instrument, which allows up to eight analyses to be performed simultaneously on the same or different samples. “We are exploring how to leverage the high throughput capabilities of the BioPhase for a whole range of different mRNA applications,” he says.

Agilent recently developed an improved method for rapid analysis of mRNA 5’ capping by LC-MS, according to Liau. Enzymatic cleavage is required for this analysis because mRNA is such a large molecule. The established method required two challenging sample preparation steps: affinity capture using biotinylated oligonucleotide probes, and site-directed cleavage of affinity-captured mRNA using RNase-H.

This method failed to work reliably with some mRNA sequences due to inefficient affinity purification, so Agilent developed an improved sample preparation method comprising site-directed cleavage in solution without affinity capture followed by purification of the cleaved oligos and mRNA sample matrix using silica-based columns. Using a thermostable version of RNase-H enzyme allowed the sample preparation time to be reduced as well.

The total process—sample prep, analysis, and data processing—requires just 75 minutes and allows separation of the oligos of interest from the mRNA sample matrix without further sample cleanup. “When used in conjunction with a specially-designed flushing protocol to mitigate sample matrix buildup on the column, this method yielded superior linearity, sensitivity, and reproducibility,” Liau says.

Howard highlights several promising techniques currently being refined for the evaluation of protein expression in cells, such as flow-cytometry for the detection of intracellular dsRNA levels and antigen-specific fluorescent detection of expressed proteins, both of which provide rapid results for cell uptake, RNA amplification, and protein production.

 “Such direct measurements could reduce the turn-around time for in vivo antigen studies. The new techniques certainly look promising and could be practical in the next few years,” he believes.

It is important to remember that mRNA technology itself is advancing rapidly and evolving on a continual basis.

Wake returns her attention to NGS technology, even though it isn’t new in general, its use in the GMP environment is, and for mRNA products the introduction of NGS is vital to achieving the required quality of control. Similarly, she says that electron microscopy is an essential technique, along with approaches for establishing in vitro release performance, for evaluating encapsulated products. Doing so, however, has required the adaptation of a kit that has mainly been associated with US Pharmacopeia type 4 dissolution testing.

The importance of developing platform analytical technologies is also reiterated by Wake. The continual improvement of platform approaches suited for establishing if mRNA is truly encapsulated within the nanoparticle system at the right internal liposome pH to support early-phase products without the need for extensive development is a promising example, she says. As the product moves into later phases, these same methods are optimized and eventually validated for each specific product. “However,” Wake argues, “understanding these critical aspects as early as possible in the development cycle necessitates the need for a general approach.”

STILL EARLY DAYS IN mRNA ANALYTICS

It is important to remember that mRNA technology itself is advancing rapidly and evolving on a continual basis. Developers of analytical methods for mRNA therapeutics and vaccines are therefore challenged not only by the complexity of these biomolecules and their delivery vehicles, but also by the need to develop flexible methods that can accommodate the ongoing changes in mRNA structures and final formulations.

As an example, Wake notes that while to date mRNA products have been developed as injectables, inhalation and nasal delivery present viable alternatives. “These routes of delivery can not only aid in achieving improved bioavailability, but also lead to products that can be delivered in a less evasive manner, even in the absence of a healthcare lead administration system,” she explains.

Scientists, Fredette recommends, should think about the analytical platforms and workflows they need to deploy across their organizations as they grow and how best to harmonize everything, from method development and method/data transfer; to ensuring data integrity, traceability, and compliance; to the level of service and support they want and need.

“I don’t even think we have started to approach the steady state for what analytics look like for mRNA therapeutics,” states Stawicki. “Just the space of what we consider mRNA therapeutics continues to grow rapidly since elasomeran (Spikevax) from Moderna and tozinamrun (Comirnaty) from Pfizer-BioNTech became world-changing vaccines. Many companies are now developing variations on mRNA such as self-amplifying mRNA and circular mRNA. In addition, scientists are developing new types of vehicles and targeting strategies for mRNA therapies. So yes, we are still at the beginning stages of this technology revolution,” he concludes.
Gaining Ground: The Rise of Regenerative Medicines
A rich clinical pipeline of regenerative medicine product candidates bodes well for a robust future.

FELIZA MIRASOL

Regenerative medicines encompass a range of emerging biotherapies, the most well-known of which are cell and gene therapies. Tissue therapies are also a category of regenerative medicines. The development of regenerative medicines has sparked some of the most innovative therapeutic targets and biomolecules. However, the complex nature of these medicines makes successful commercial development quite challenging. With significant leaps in drug development technologies over the past few years, where does the market for regenerative medicines stand today?

ATTRACTING INVESTMENT

Much of the progress that regenerative medicines have made in the past two years would not have been possible without infusion of funds, and the investment patterns seen in 2021 are expected to strongly support the long-term growth and success of this sector. In the Alliance for Regenerative Medicine’s (ARM’s) 2022 state of the industry address (1), Janet Lambert, CEO of ARM, noted that the regenerative medicines sector, specifically cell and gene therapies, had another record-breaking year of investment in 2021. In particular, the rise of gene editing continued at a strong pace, which Lambert attributed to a hefty infusion of venture capital into early-stage companies.

According to Lambert in her state-of-the-industry presentation, 2021 set another investment record for cell, gene, and tissue-derived therapies, with $23.1 billion raised over the course of that year, reflecting a 16% increase from 2020. Lambert emphasized that gene therapy developers raised the most capital in 2021 with $10.6 billion raised, followed closely by cell-based immuno-oncology (cell IO) developers, with $10.1 billion raised. “Although gene therapy out-raised cell IO, cell IO continues to show the strongest growth with 26% increase in financings year-over-year,” Lambert said in the presentation.

Meanwhile, companies active in gene editing raised a total of $8.5 billion in 2021, which accounted for more than one-third of the total amount raised sector-wide, according to Lambert. A breakdown showed that companies active in gene editing made up $4.7 billion of the financing in the gene therapy category, or approximately 45% of the total gene therapy financings in 2021, up from 38% three years ago. “Excitement in this sub-sector is driven by the in-vivo CRISPR [clustered regularly interspaced short palindromic repeats] data from Intellia [Therapeutics] Development
The year 2021 was notable for new regenerative medicine product approvals. With six new products approved, 2021 was the second best year on record, following the approvals of nine new regenerative medicines in 2016, stated Lambert in her state-of-the-industry address. Additionally, 2021 was a notable year for approvals of cell-based immuno-oncology, with three new chimeric antigen receptor T cell (CAR T) therapies approved across the United States, Europe, and China, including the first approval of a B cell maturation antigen (BCMA)-targeted CAR T therapy, Abecma (idecabtagene vicleucel) by Celgene, a Bristol Myers Squibb company (2). Lambert noted that this product was also the first CAR T therapy approved for treating multiple myeloma.

Furthermore, 2021 also saw notable product approvals for regenerative medicine products for treating a serious inherited neurological disorder, a rare and historically fatal birth defect, and severe burns. 2021 was a breakout year for FDA’s regenerative medicine advanced therapy (RMAT) designation (3), in which three out of the four products approved in the US had RMAT designation. “This designation, which ARM played a leading role in creating, was established in 2016 and is intended to expedite patient access to innovative regenerative medicine therapies. To date, 67 regenerative medicine programs have been awarded RMAT designation,” said Lambert her presentation.

ARM is currently tracking 2261 active global clinical trials in regenerative medicine, including both industry-sponsored trials and academic and government-sponsored trials. Lambert presented clinical trial data in her state-of-the-industry address, which represents data from the third quarter of 2021 (end-of-year clinical data not yet reported at the time Lambert’s state-of-the-industry was given). Looking at specific indications, cancer is shown as the number one target for cell and gene therapies, with 1354 ongoing trials in cancer indications. There is also significant clinical development activity in other disease categories, namely neurological disorders, diabetes and diabetes-related disorders, cardiovascular, rare genetic disease, and stroke, according to ARM’s findings.

“The complex nature of these medicines makes ... commercial development quite challenging.”

“Of these [2261 active global clinical trials in regenerative medicine], there are 1129 active industry-sponsored regenerative medicine trials globally,” said Lambert. Cell-based immuno-oncology makes up the largest portion of the regenerative medicine clinical trial landscape, which is primarily due to a large number of Phase I trials in immuno-oncology indications. According to data collected by ARM, cell-based immuno-oncology makes up more than half of all Phase I industry-sponsored regenerative medicine trials, which reflects a relatively recent tilt towards the immuno-oncology field. With 143 Phase III industry-sponsored trials currently underway, 44% are in cell therapy, 33% are in gene therapy, and 22% are in immuno-oncology, according to ARM.

“We’re also tracking 1100 academic and government-sponsored trials worldwide, about the same number as industry trials. As a whole, these trials, not surprisingly, tend to be earlier stage with a significantly different technology mix. In academia, we also see a much larger proportion of cell therapy trials and a much lower proportion of gene therapy trials,” explained Lambert in her address.

FUTURE IS ON TRACK

Based on a rich pipeline, ARM anticipates that 2022 may be a record year of approvals for new gene therapies targeting rare diseases. “It could be a really active year, with as many as 15 anticipated decisions across the US and Europe, including nine on never-before approved products,” Lambert emphasized in her state-of-the-industry address. “As of now, we’re due to have regulatory decisions on five new products across the US and Europe from BioMarin Pharmaceutical, Genzyme Therapeutics, PTC Therapeutics, uniQure and CSL Behring, and Crystal-Bio. We will very likely see a record number of approvals for this product class in 2022.”

Looking at the clinical pipeline for regenerative medicines beyond 2022, Lambert expects that the industry will gradually see an evolution from rare monogenic diseases and liquid tumors to more prevalent diseases and solid tumor cancers. “We have many late-stage programs in a variety of cancers. Importantly, the first gene therapy for a prevalent disease could be just a few years out. The oft quoted 2019 FDA prediction of 10–20 approvals by the year 2025 still looks doable, albeit likely at the lower end of that range. This is something [FDA] has recently reinforced in conversations with us,” Lambert stated in her presentation.

REFERENCES

The growing use of automation and digitalization technologies push cell culture bioprocessing forward.

FELIZA MIRASOL

Enhanced media, selective starting materials, genetically enhanced cell lines, and even animal-free cell culture parameters have all been working toward optimizing product output in the bioreactor. The cell culture process has come a long way with the common utilization of these process-optimizing tools and techniques.

LATEST CELL CULTURE TRENDS

The biopharmaceutical market is seeing fast growth, and two expression systems are competing for market dominance, mammalian cells and microorganisms, says Daniel Kopec, manager of Cell Culture Technologies at Sartorius. Kopec notes that, in recent years and based on the rise of antibody-based therapeutics, new biotherapeutic approvals have favored mammalian host cells. Emerging biotherapeutic molecules, however, have been facilitating the use of microbial host cells, he observes.

“Microbial platforms are capable of delivering, in a scalable and affordable manner, a range of functional recombinant therapeutics such as vaccines, hormones, interferons, and growth factors as well as non-pharma products, such as industrial enzymes,” Kopec states.

Meanwhile, for mammalian cell applications, there has been a trend in past years toward serum-free, xeno-free, and chemically defined cell-culture media and intensified processes. “Serum-free, xeno-free, and chemically defined media represent a huge advantage in comparison to traditional serum requiring media, in terms of costs of goods (qualified serum is very expensive), time to market (consistent media yields predictable, reproducible results), and biosafety (not using serum rules out the risk of contamination by viruses and adventitious agents),” says Catherine Buchere, product manager Virus-based Therapeutics, Sartorius.

With process intensification, the aim is to increase the final product yield by optimizing the use of resources, whether it be a physical footprint, consumables, and/or time. Kopec points out examples of how processes could be intensified, which include perfusion operation with cell-retention devices reaching high cell densities, a shortened seed-train expansion, and continuous and integrated upstream and downstream processing.

Moreover, in addition to significant cell/media advancements as well as the momentum toward process intensification methods, Kopec observes that there are clear trends...
that continue to revolve around the ease of scale up, commercial flexibility, and advanced automation. "All of these promote much needed increases in development and processing efficiencies—especially for biotherapeutics, where a strong quality-by-design (QbD)/process analytical technology (PAT) approach will surely enable speed-to-market and higher success rates," he states.

**CURRENT STATUS**

The current status of cell culture processing owes its advancement to several influences, including cell-culture media considerations, the quality of raw materials, a push for sustainable processes, and concerns over inherent contaminants present in animal-derived materials.

Chemically defined media, as opposed to serum-based media (which can give rise to batch-to-batch variation issues), allow high cell densities in suspension cultures and reduce the risk of cells contracting human viruses, says Buchere. "Over the past two decades, major improvements in media composition, production strategies, and cell-line development resulted in the achievement of higher cell densities and product titers, leading to an overall reduction in production costs," Buchere states.

Furthermore, there is increasing customer interest in less complex media. "Complexity in media refers to the number of components and the complexity of the components themselves. A trend we are seeing is the development of a minimal set of well-balanced components to achieve a lean, robust, and flexible medium basis while maintaining highest performance in the cell culture step," notes Buchere.

With raw materials, meanwhile, variability is a key concern in the biopharmaceutical manufacturing process. Understanding the behavior of each raw material is crucial to reducing the risk of variation, Buchere adds. "Moving to chemically defined media is already an improved step, nevertheless, there are still some components that can introduce variation in the performance of the cell culture," she explains.

Buchere also explains that the source and production process for cell culture media would also be evaluated in terms of sustainability. "Many of the more common sources of culture media are not necessarily produced in a highly sustainable manner. The most popular media components, serum, is often produced from bovine and porcine sources, and production is energy-intensive and can result in significant emissions of CO₂ [carbon dioxide]," she says.

The quality and purity of biotherapeutics are influenced by many factors in the development and commercialization cycle, notes Kopec. These factors all play a significant role in the product’s ultimate success. "In recent years, we have seen a number of products on the market that enable a much better approach to cell-line development and media optimization," Kopec says. He points out that, for example, automated bioreactor systems (e.g., Ambr 15, Sartorius) offer "groundbreaking levels of efficiency and visibility to the process."

In the meantime, software-based scaling tools are now coming into play, which are helping the industry to eliminate much of the guesswork in the scale up of manufacturing processes, Kopec adds. "Continuous and comprehensive data collection and analysis equip process engineers with in-depth process understanding. Advanced sensors now deliver more precise measurements at every stage of the process, generating vast quantities of information. Seamless data connectivity is now critical to translating in-line monitoring into actionable, real-time insights derived from data analysis," he says.

Ultimately, leveraging data collected across the workflow leads to greater process knowledge and can help reduce failure rates and, thus costs, Kopec asserts. Process consistency is the key process output—achieved with a QbD scale-up approach and advanced automation—to fully enable smart process development.

**A BRIGHT FUTURE**

The growing use of automation during expansion to increase product consistency and reduce failure rate is a rising trend in the biopharma industry, Kopec adds. "Highly automated bioreactors will require integration from various sensors, software, and interconnectivity via digitalization technologies such as MTP (module type packages). Interconnectivity is also a steppingstone for future scalability by ensuring larger consistent yields with larger bioreactors," he says.

Any manually controlled process holds a high level of risk, low output potential, and difficulty monitoring critical process parameters and critical quality attributes (CQAs). Interconnectivity across the workflow, together with automation, will enable more control and a more consistent output, Kopec explains. "Bringing together inline sensors, continuous monitoring, and advanced real-time analysis will require 'next-gen' automated bioreactors to enable finer, holistic control of the process. This next level of automation will result in a tighter design space and pushing the process to maximum output," he states.

Kopec also notes that next-generation, advanced bioreactor systems and variants are now entering the market, and these will offer true “off-the-shelf” setup and operation. These systems are well designed for emerging biotherapeutic process modalities. “The next-generation single-use bioreactors will integrate the latest advances in QbD/PAT technologies, such as advanced sensors, software (for automation/data analytics/scaling), and plant-level integration,” he explains.

In addition, in the near term, Kopec expects that the biopharma industry will see strong momentum toward automated sampling for online CQA monitoring, which will help move the industry closer to real time release testing. Overall, there is heavy investment in the development of these technology integrations to support new biotherapeutic applications, Kopec observes.
Ongoing trends in the biopharmaceutical industry, such as faster speed-to-market and more efficient manufacturing, continue to drive development and use of single-use technologies, which are key components of flexible and modular processing systems. Compared to multi-use stainless-steel equipment systems, single-use systems (SUS) help capacity-constrained biopharmaceutical manufacturers use their existing space efficiently (1). SUS are well established in upstream processes and fluid handling; advances are being made in downstream processing operations, such as purification, filtration and separation, as well.

*BioPharm International* spoke with Stuart Tindal, PhD, product manager Separations, Sartorius, about new technologies and how Sartorius is addressing supply-chain limitations and other challenges.

**NEW TECHNOLOGIES**

**BioPharm:** What are the advantages of using SUS vs. reusable systems in downstream processes in particular?

**Tindal (Sartorius):** There are significant benefits of single-use vs. reusable systems in downstream processes. First, SUS provide a low-risk method for quick turnarounds between batches and products. And, because they eliminate cleaning and sterilization validation efforts and are used where bioburden and cross-contamination risks are highest, they are useful for clinical and low-volume, high-titer production. Secondly, customers are seeking efficient processes, and process intensification (with SUS as a part of that) leads to higher productivities, higher yields/recovery, less effort, less risk of failure, or less cost. It is these business and technical pain points that enhance the applicability and utilization of SUS in this area. Sartorius has seen those outcomes specifically with regards to next-generation treatments like mRNA [messenger RNA], cell/gene therapy for vaccines, and personalized medicine. Third, SUS contribute to the continuing desire for sustainability, which is driving single-use strategies to be accountable through fabrication, use, and disposal. Sartorius has a dedicated function focusing on strong collaboration between drug producers and material suppliers to achieve sustainability success and define suitable metrics.

**BioPharm:** Have you added any new technologies for single-use downstream equipment for clinical/commercial manufacturing?
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In October 2021, GEA introduced the single-use separator kytero for fermentation solutions and cell cultures. The GEA kytero uses disk stack technology for centrifugal separation, rather than filter-based harvesting. This separation method has increased efficiency for the clarification processing step and provides gentle processing, which prevents damage to products, such as mammalian cells, *Escherichia coli*, or gene therapies. Ruediger Goehmann, GEA Product Manager, says that biopharmaceutical manufacturers requested that GEA adapt its existing and well-proven stainless-steel disk stack technology, used in large pharma separators, to single-use technology for small batches. In the single-use version, all product-contact parts are to be replaced after use, which prevents cross-contamination without requiring cleaning and sterilizing. The friction-free GEA breezedrive allows biocontainment because there are no seals or bearings. The aim, says Goehmann, was to simplify the system and to create an efficient, safe and reliable design.

"Single-use systems are also often required when customers have a need to immediately produce or evaluate the required machine design," adds Markus Kuehberger, senior director Business Line Chemicals & Pharma at GEA. He says the separator is ready to use. "No clean-in-place (CIP) or sterilize-in-place (SIP) validation is necessary. No additional utilities, such as hot caustic or acid for CIP or clean steam for SIP, are needed."

Kuehberger says that the separator does not completely eliminate the need for filtration but can significantly reduce the amount of single-use waste. The first version of the equipment is useful for laboratories and small batches and has been successfully tested at rates up to 150 L/h. To address scale-up needs, which can be a challenge for single-use systems, GEA will develop larger capacities and plans to launch the kytero 2000 in the fourth quarter of 2022.

Sartorius has launched the third-generation Flexact Modular, a single-use automation platform that addresses an automation need in the current good manufacturing practice (CGMP) clinical/commercial market. This platform improves the efficiencies from manual single-use processing steps and reduces the risk of process deviations that are attributed to human error or failure in system communication protocols and connection to other digital infrastructures. Flexact Modular focuses on the normal flow filtration and fluid management batch process steps. In these downstream processing areas, product concentrations and volumes increase the ergonomic challenges for operator handling. The larger the scale, the stronger the need is for automation to reduce the total time and effort.

We are also addressing a specific downstream processing pain point of packed-bed column usage. Even with pre-packed options, the operation, handling, validation, and storage is a risk-heavy part of purification. The combination of a high-capacity affinity capture membrane and an optimized chromatography system, however, achieves productivity that can exceed packed-bed capture. Currently, the technology is available in smaller-scale multi-use, with clinical- and production-scale SUS coming soon. The combination of SUS and membrane technology promises to revolutionize the chromatography space, particularly for clinical manufacture. It’s a challenge to design a system to optimize the process—with faster valve switching times, low hold-up volumes, and appropriate flowrates. Our philosophy is that as far as possible, our SUS and multi-use systems are equal partners, particularly in terms of chromatography performance and quality of instrumentation.

**CHALLENGES**

BioPharm: Are supply-chain constraints a challenge for downstream single-use equipment? If so, what are the pinch points and what are some of the best practices for dealing with these?

Tindal (Sartorius): Industry wide, there have been supply-chain challenges because of COVID-19 and the continued ‘warp-speed’ need to support customers with assembling new solutions and equipment. Sartorius has been growing rapidly for decades; we were fortunate to identify many of these supply-chain pinch points pre-pandemic and thus were in the process of further sourcing and establishing supply mitigation strategies.

“Logistic processes should be qualified and use standard practices for transportation of frozen materials.”

— Stuart Tindal, PhD, Sartorius

Supply-chain challenges have taught customers and suppliers that the route to a more robust downstream processing
supply chain is standardization. Standardization, within and between product lines, across different facilities, and eventually industry wide, results in more agility to increase production rates while also better balancing lead times against shelf life when considering inventory policies. Standardization also allows us to better protect supply chains by providing significant leverage to implement effective dual/multi sourcing of components.

BioPharm: What are some other challenges for SUS in downstream processes, and what are the best practices you suggest for handling these challenges?

Tindal (Sartorius): There are several challenges in downstream processes including:

- **Process closure**: Ensuring no unwanted contaminants enter the process
- **Containment and preventing leaks**: Ensuring nothing unwanted gets out of the process and that it poses a threat to the operator or requires decontamination of the cleanroom
- **Detecting failures in integrity**: Including ‘holes’ in or out of the consumable (in the film, point of connection, weld) or through an in-process barrier (filter membrane or packed column) where the ‘holes’ are too big and may impact the integrity performance capability.

Self-contained consumables with diverse aseptic connections and disconnections can help ensure that the process is closed and contained. Integrity testing equipment can be used to test filters and SUS. Other commonly overlooked challenges often encountered in later stages are those around freezing, storage, transport, and thaw of bulk drug substance. These include the sensitivity of biologics to cryo-preservation and thawing, complexities and costs involved in the supply chain, limitations in scalability and safety, and addressing the environmental challenges posed around the refrigerant usage during the storage and shipping process. Sartorius has addressed these challenges with scalable and robust freeze and thaw solutions comprising systems and consumables. Our freeze and thaw portfolio includes plate freezing platforms providing fast freeze and thaw rates for sensitive molecules, preventing cryoconcentration effects while monitoring critical process parameters.

Logistic processes should be qualified and use standard practices for transportation of frozen materials. Our platforms include shipping solutions that are validated with common transportation methods for frozen materials according to International Safe Transit Association and ASTM-recognized standards.

**REFERENCE**


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**Tosoh Bioscience**

**Viral/Vaccine Purification Solutions**

**The Best-in-Class Resins for AAV/Gene-cell Therapy Purification**

**Ion Exchange and Hydrophobic Interaction Resins**

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The Lighthouse Effect: Using Technology to Improve Life Sciences Manufacturing

Lighthouse manufacturing techniques utilize technology and automation to streamline production.

Prior to the COVID-19 pandemic, the bio/pharma manufacturing industry had been relatively slow to embrace the ongoing digital revolution. But the pandemic forced the life sciences industry and drug developers to rethink their hesitation toward digitization to quickly produce and distribute new vaccines under unprecedented conditions. Now, technology is being used as a solution to improve efficiency and sustainability in life sciences manufacturing.

Those who have led the way are said to be creating the “lighthouse effect.” Just as actual lighthouses help sailors navigate dangerous waters, lighthouse companies serve as guiding lights for charting the course of an entire industry. For the life sciences manufacturing industry, becoming one of these luminaries relies on a mix of advanced technical capabilities and coming up with innovative applications for the technology. In the age of Big Data, artificial intelligence (AI) and digitization will play lead roles in achieving lighthouse effects.

Lighthouse manufacturing techniques utilize technology and automation to streamline production. Bio/pharmaceutical manufacturers can employ systems that optimize the allocation of resources to boost output, track productivity, and improve sustainability by using energy-efficient processes. But what does this mean from a facilities standpoint? Let’s talk about three key areas where lighthouse effects are enacting great change in the life sciences manufacturing industry.

MORE EFFICIENT BUILDINGS AND PRODUCTS

AI is increasingly being used by lighthouse corporations to find and eliminate inefficiencies in building operations. For example, smart building technology can monitor the temperature of the water being used in a building. It can then crunch the numbers to make determinations, such as raising the temperature of the boiler by five degrees will be more efficient overall because it will take less time and energy to heat the water to the average-use temperature. This sort of technology is called

GUL DUSI is a director for Linesight.
As more manufacturing processes become automated, the number of human employees needed in the building gets lower. The fewer people in a space, the less square footage these buildings will need. This makes it easier for companies to upgrade existing buildings rather than build new ones, as they can repurpose space that is no longer needed.

Lighthouse techniques apply to life science production as well. According to a World Economic Forum and McKinsey & Company case study, Novo Nordisk boosted output at one facility by optimizing production through the use of big data, advanced analytics, and AI (1). The manufacturing site used digital scheduling and work-management applications plus automated overall equipment effectiveness monitoring and digital performance surveillance to boost production capacity without expanding the facility. Managers could see the real-time status of production lines and equipment, allowing them to allocate resources, order supplies, and identify problems before they become severe. The technology also allowed managers to set realistic benchmarks regardless of work shifts or operators. The result was increased people efficiencies and a significant reduction in downtime.

**BETTER DATA EVALUATIONS**

The magic of AI comes from its ability to make sense of huge quantities of data, revealing patterns that might otherwise go unnoticed and allowing companies to process data in bulk much faster than by hand. This allows for the implementation of risk-based qualification to accelerate the process of getting facilities and manufacturing techniques approved by FDA. Life sciences manufacturers can conduct trials and studies at scale and format that data for submission to FDA.

Automation plays an important role in all of this as well, speeding up the process of working with all that data and getting it into an acceptable state. Because leading AI has the ability to learn from its own experience, these systems become more efficient as they work with more data and on more projects. Pharmaceutical giant Novartis is just one company using AI to help speed up the development of new drugs and therapies (2). Using algorithms, the AI scans images of cells treated with untested molecules to see what might be worth further research. This saves the company time and effort and gives it the best chance of finding innovative compounds.

All this newly usable data can reveal some interesting insights. To go back to the Novo Nordisk example from earlier, data insights will allow you to see the full carbon footprint of your operation, even though it involves everything from individual machines to distribution (2). It’s all data, and that means AI can make sense of it altogether.

A key to this is the edge data center, which gets its name from its smaller footprint that enables it to be built on the “edge” of urban centers—sometimes even within the same building as the facility using the data center. This proximity reduces the latency in sending data back and forth between the life sciences manufacturing facility and the data center, which makes a difference in the perceived performance of these sophisticated AI applications.

**FASTER PRODUCTION SCHEDULES**

Incorporating AI and analytics lets life sciences manufacturers build facilities and products faster. Much of this has to do with eliminating inefficiencies in every step of the manufacturing process. Having increased visibility into the supply chain makes it easier to coordinate phases of a construction project and helps achieve connections to other manufacturing facilities to improve supply chain efficiency. Again, this grants unprecedented visibility into considerations, like the overall energy use or carbon footprint of the production process.

Lighthouse techniques reduce supply chain issues by allowing bio/pharma manufacturers to see things at a network level and identify where things either work or don't work. This allows manufacturers to act proactively rather than reactively to ensure production schedules stay on track and to account for shortages or overages before they happen. AI can utilize data in other ways. It can enhance quality controls by searching for anomalies in production, allowing issues to be corrected early in a batch. It can predict which machines in the facility may fail, allowing for predictive maintenance and virtually eliminating unscheduled downtime.

Every industry has leaders who show others the way via the lighthouse effect. But companies who have yet to implement the lighthouse effects could begin the process today, including utilizing AI and digitalization. All it takes is the proper investment in technology and the right vision to see how that technology can create meaningful change. Thanks to the increasing availability and affordability of AI solutions, including off-the-shelf AI systems that can perform SBMS tasks, execute mass data evaluations, and better manage supply chains and production schedules, there is a low barrier to entry when it comes to creating a lighthouse effect.

**REFERENCES**

Plan Early: Optimizing Stability During Lyophilization

The need for sustainability and early considerations of a lyophilization strategy grow more pertinent on the back of growing biologics volume.

FELIZA MIRASOL

Lyophilization remains an integral step in the manufacturing process for certain biotherapeutics, as was demonstrated with the COVID-19 vaccines. Lyophilization is also important in traditional biologic manufacturing and for emerging therapies. However, there remains inherent risk in subjecting these biomolecules through successive freeze-thaw cycles, which call for best-practice procedures to ensure that product viability and stability are maintained during the lyophilization process. Furthermore, questions have arisen about the long-term sustainability of current lyophilization techniques as the development of new biologic and emerging therapy drug candidates continues to grow.

CHALLENGES WITH EMERGING THERAPIES

One big bioprocessing challenge posed by the lyophilization of emerging biotherapeutics, such as cell therapy, gene therapy, and nucleic-acid-based therapies (e.g., the mRNA-based vaccines), is a general impact on machine technology. The shift from small-molecule pharmaceuticals to biologics has also changed the manufacturing requirements because of the nature of the products, explains Jörg Rosenbaum, director product management at Hesse, Germany-based Optima Pharma.

“Biologics are fragile products that cannot tolerate heat and have a limited stability. Lyophilization is a very important process in biotherapeutics manufacturing to improve product stability,” Rosenbaum states.

Factors that have made the lyophilization of biologic drug products challenging include the equipment requirements. The equipment used must be advanced, user-friendly, efficient, and applicable from development to scale-up, notes Rosenbaum. The increasing demand for biologics requires smaller batch sizes and greater flexibility in manufacturing solutions, which necessitates frequent line and equipment changes, Rosenbaum observes. The requirement for smaller batch sizes and manufacturing flexibility is leading to a shift from large manufacturing areas to small and flexible footprints. As a result of the shift towards biologics, there is also a growing trend towards the use of single-use technology, he adds.

“The driving forces are not only cost reduction and improved production efficiency, but also the ability to process potent com-
pounds and produce smaller batch sizes,” says Rosenbaum.

Rosenbaum goes on to discuss some of the manufacturing challenges in the lyophilization of biologic drug product. “Freeze-dried and liquid drug vials for biologics are filled in a similar manner, but the different formulations present different manufacturing challenges,” he says.

Liquid products, for instance, require less time for development and therefore have shorter lead times. The lead time for lyophilized products accounts for the lyophilization cycle and the characterization of that cycle. Characterization is important because the parameters of the lyophilization cycle affect the production of a cake with high integrity, and the production of a cake without collapse, re-melting, or shrinkage requires additional development, Rosenbaum explains. “In both cases, it is necessary to understand the stability of the formulation, but for freeze-dried products, we need to develop the cycle through calorimetric measurements, refine the process parameters, and optimize the cycle. The freeze-dried product needs to be characterized and the stability profile needs to be established,” Rosenbaum states.

Meanwhile, a major technical challenge lies in the development work that takes place before a clinical batch is filled, as freeze-dried products require more preparation in selecting the right excipients, fillers, and cryoprotectants, as well as in cycle development. “It is also important to note that some of the COVID-19 vaccines are multi-dose and require the use of an evaluated preservative,” Rosenbaum says.

By way of example, Rosenbaum points out that messenger RNA (mRNA) vaccines use nanoparticle technology to increase stability, as opposed to the aqueous-soluble molecules typical of standard biologics. Recombinant protein vaccines may also require the use of an adjuvant to stimulate the immune response, and there are unique differences between live and attenuated or inactivated vaccines. “These differences require considerations related to plant classification and engineering controls, as live viruses must be separated from other types of vaccines. At the end of the day, COVID-19 vaccines are no more difficult than other biologics from a filling/manufacturing perspective. However, the real problem lies in managing the time that vaccines are out of controlled storage,” Rosenbaum cautions.

He does note that transferring liquid formulations to freeze-dried products can improve thermal stability and reduce the need for cold chain handling. There are already results showing that freeze-drying cycles can be developed and implemented that can be used to freeze-dry a COVID-19 mRNA vaccine.

**Questions have arisen about long-term sustainability of lyophilization.**

Meanwhile, Matthew Bourassa, process development manager at LSNE Contract Manufacturing, a PCI Pharma Services company, notes that, in the past 36 months, oligonucleotides and mRNAs have been among the fastest growing market segments (particularly for LSNE). “As the biologics market continues to mature and new products enter the clinic, LSNE’s techniques for minimizing line-loss continue to gain efficiency. [The company] has seen a significant increase in the number of companies developing RNAi [RNA interference] or siRNA [small interfering] products, and the cost of the oligonucleotide drug substance is high as well,” Bourassa says.

LSNE is currently working on lipid nanoparticle (LNP) formulations, which is a common formulation technology used in mRNA vaccines. Traditional critical quality attributes (CQAs) such as residual moisture, cycle time, and an elegant cake are important, but, additionally, because of the lipid component in the LNP, special consideration must be taken for potential reconstitution issues. LSNE is taking an iterative approach to developing a robust lyophilization cycle with optimized reconstitution characteristics, according to Bourassa.

**SUSTAINABILITY IN LYOPHILIZATION**

Given the fact that there is a large number of new biologics and emerging biotherapeutics currently in clinical development, the sustainability of the lyophilization process, for such products, is coming under greater scrutiny. Some industry participants have been looking towards solutions to keeping lyophilization sustainable.

There are potential pros and cons pertaining to the sustainability implications of lyophilization when it comes to certain aspects, such as packaging, according to Matt Hall, principal technical affairs manager, Corning.

“For example, removal of water from the drug product reduces the overall weight, which can reduce the energy required for shipping. In addition, freeze drying should significantly improve the stability of the drug product, allowing for room temperature storage and avoiding the energy needed to maintain a cold supply chain. Another potential sustainability benefit is reduced usage of expanded polystyrene insulation materials that are bulky and difficult to recycle,” Hall states.

The process of lyophilization does come with some potential negative implications in terms of sustainability, Hall observes. While the energy cost of the cold chain storage is avoided, the freeze-drying process itself can be energy intensive, he explains. “In addition, sterile diluent (and its associated energy costs for production and distribution) is still required to reconstitute the lyophilized drug. Finally, the use of fluorinated refrigerant gases could have negative impacts on the environ-
Hall enumerates the innovations below that can be used to improve sustainability of lyophilization. These innovations include, but are not limited to:

- New refrigerant technologies that reduce or eliminate the use of gases with a high global warming potential
- Development of pretreatments and/or simultaneous processes (e.g., infrared, microwave, etc.) that reduce the time to complete conventional freeze-drying cycles
- Development of process analytical technologies that accurately determine the endpoint of the drying cycle and potentially reduce additional time that is routinely used to ensure sufficient water removal
- Use of parenteral packaging that reduces the likelihood of vial breakage, which could result in a high loss of drug product, during the lyophilization process. Such parenteral packaging includes certain glass types used in vials (e.g., Valor Glass, Corning) that are treated in such a way as to enhance the protective properties of the glass (e.g., in the case of Valor Glass, the glass is ion-exchanged and externally coated, which provides up to 10x the strength of conventional glass vials).

Product quality is influenced by a number of factors, including the primary packaging components. Externally coated glass vials can improve quality by reducing the generation of glass particulate that can contaminate the product and the introduction of glass damage that can create cosmetic defects, which make vials more susceptible to breaking during the freeze-drying process. “Consistent vial geometry can also improve product quality by reducing the variability of the vial-heat-transfer-coefficient and its subsequent impact on the drying rate of product within a given vial,” says Hall.

Another approach that companies are taking to address the challenge of product stability and cold-chain management for biotherapeutics is by developing a lyophilized dosage form for that product. “The benefit of a lyophilized dosage form is to increase product stability at preferred storage conditions; for example, developing a lyophilized dosage form with refrigerated or ambient [temperature] for a liquid formulation, where previously -20 °C or -80 °C storage was required,” says Bourassa.

“A lyophilized product can dramatically reduce the product’s carbon footprint and the overall cost of cold chain management for parenteral products due to the lower shipping weight and ambient shipping temperatures,” Bourassa adds.

Increasing demand for biologics requires smaller batch sizes.

Meanwhile, newer refrigeration systems are designed to be particularly energy efficient. These new systems (such as those designed by Optima) achieve the defined temperatures in the ice condenser and set-up areas with extreme precision, emphasizes Rosenbaum. “With the F-Gas regulation [European Union Fluorinated Greenhouse Gases Regulation (1)] in Europe, for example, new framework conditions apply to the design of freeze-drying plants in regard to the refrigeration technology. Different solutions are possible to reach the required temperatures of approximately -100 °F/-70 °C at the ice-condenser and -60 °F/-50 °C on the shelves,” Rosenbaum explains.

The solutions being referred to earlier include LN2 refrigerant, which is a technically proven solution that has been known for years and is future-proof in terms of the F-gas Regulation, according to Rosenbaum. He explains that the investment costs in relation to the refrigeration system are lower here compared to the following solutions, but the consumption costs increase the more often the system is used. “This means that freeze-drying plants with LN2 refrigerants must be adapted to meet the operator’s operating scenario. This solution is suitable for new projects. However, with minimal effort, existing plants for climate-damaging refrigerants could also be converted to an LN2 system,” he states.

Meanwhile, for the use of refrigerants that are expected to be available in the medium term, such as R410A, and refrigerants available in the longer term, such as R448A, both refrigerants are non-flammable, but neither is completely environmentally friendly. Thus, refrigerants with a low global warming potential (compared to R404A/R507) can still be used in leak-tight, two-stage refrigeration systems. “There are two variations that can be considered: direct and indirect cooling of the ice condenser. From a technical point of view, the indirect cooling of the ice condenser makes the system future-proof. Here the refrigeration system is designed to provide indirect cooling of the ice condenser,” says Rosenbaum.

Flammable refrigerants can also be used at a later date by replacing the refrigeration system, Rosenbaum continues. It is not yet possible to say, however, whether the classic design—where the ice condenser is cooled directly—will require future design changes to the ice condenser to comply in the long term with the F-gas Regulation. “First and foremost, with this solution the investment costs are lower than with the solution referred to above. However, retrofitting could be technically complex or even technically impossible. Should a retrofit of the ice condenser be deemed necessary and technically possible, the total investment will be greater than for indirect cooling of the ice condenser, which will be implemented immediately. The operating costs for both variants are higher (approx. +10% to +30% compared to conventional freeze-drying systems),” says Rosenbaum.
Meanwhile, solutions for flammable, environmentally friendly refrigerants include developing another future-proof, environmentally friendly variant. In this case, the refrigeration system should be designed as a cascade system, for example. In addition, the indirect cooling of the ice condenser must also be performed via a second circuit. “Investment costs are higher than those for classic freeze-drying plants (up to +40% higher). Operating costs are also higher by [approximately] 30%,” Rosenbaum notes.

WHERE BIOMOLECULES ARE MOST AT RISK

From a pharmaceutical point of view, the thawing of the raw material (as in the case of proteins, for example) prior to formulation and filling plays a decisive role in determining where the biomolecule is most at risk. Concentration differences during the thawing process can negatively affect the stability of the drug substance, specifies Rosenbaum. During filling of the finished formulation into vials, factors such as pressure and shear stress due to pumping processes, among other things, can lead to aggregation of sensitive biotherapeutics. The choice of the right pumps as well as suitable tubing materials is therefore essential.

“During the freeze-drying process, special attention is paid to the freezing step. The cryoconcentration that takes place causes stress to the protein drug and can degrade its physical and conformational stability. Another essential step for maintaining the quality of the product is to find a right balance during primary drying between too conservative drying processes that increase production costs and too aggressive drying above the characteristic parameters \( T_g \) (glass transition temperature) or \( T_c \) (collapse temperature) leading to product loss,” Rosenbaum explains.

From a technological point of view, being able to determine a biomolecule’s vulnerability involves the design of the drying processes within the design space, Rosenbaum adds. With what he calls the ‘design space approach’, a bio manufacturer can develop an understanding of the boundaries within which freeze-drying for a certain product can be safely done. “The critical process and material attributes for the quality are unique to every product,” Rosenbaum says. “By specifying a design space, the conditions for a sustainable quality of the product are defined in advance.”

A threshold is the critical product temperature that is required before a collapse occurs, Rosenbaum explains. The second limit is the minimum controllable pressure of the plant. The course of the chamber pressure and the sublimation rate is dependent on the heat transfer coefficient of the vial and the product resistance, which determines the correlation between the controlled parameters and the product temperature. Changes in the design of the freeze-dryer as well as product deviations may alter the drying process and could lead to product loss, and irregularities in the shelf temperature or drying pressure can result in uncontrolled freeze-drying, he cautions.

BEST PRACTICE APPROACHES

Having a best-practice approach to the lyophilization of biologic drug product is a good way to optimize product stability during the lyophilization cycle. Approaching the problem early on in the drug product’s development cycle is one such best practice.

To develop a robust lyophilization cycle, special attention should be given in the early stages of development to comprehensively understand a product’s physical characteristics and thermal properties, says Bourassa. Bourassa explains that having a deep knowledge of the formulated product’s thermal profile is essential prior to developing a lyophilization cycle.

“The use of modulated differential scanning calorimetry (mDSC) and freeze-dry microscopy (FDM) identifies the physical characteristics of the formulated drug product, such as a product’s freezing point, glass transition, eutectic temperature, and collapse temperature, to tailor a lyophilization cycle that will produce a stable pharmaceutical product,” Bourassa states. LSNE’s Process Development team, for instance, will use a “sample thief” to collect numerous samples during development lyophilization runs. This allows the team to assess moisture content or residual solvents in real-time and ascertain an optimal secondary drying cycle and lyophilization process parameters, Bourassa explains.

Bourassa stresses the importance of taking proactive steps to ensure phase-appropriate development, which helps to speed up progress and minimize API or biologic drug substance loss. “If the clinical program is successful, clients may choose to spend additional time and money on expanded development. If time or budget is constrained, a lyophilization development program with fewer development runs for early clinical needs may be the best approach,” he says.

Bourassa adds that using a conservative lyophilization cycle and later optimizing once dose range studies are complete can save time and money in early clinical trials. “Progressing with an optimized cycle is vital as a company approaches Phase III/registration and process validation batches by greatly reducing risk during manufacturing and saving costs over the life of the product,” he states.

A number of techniques exist that are new to the study of freeze-drying. For instance, modeling and simulation are advanced techniques that can provide a useful understanding of the process itself. “Integrating the known product characteristics into the simulation will shorten the necessary trial-and-error development runs,” says Rosenbaum. “If the freeze-drying parameters are well defined, the whole process will achieve the best efficiency and robustness.”

REFERENCE

Improving Lab Operations
Recently released technologies aim to improve laboratory processes.

Evolutionary therapies and innovative drugs can largely be attributed to the research, development, and manufacturing work conducted by the bio/pharm industry. Contributing to that success, however, are the contributions of laboratory technology manufacturers.

As much as new therapeutics are continually discovered, researched, and developed, innovative laboratory equipment is continually being developed, improved upon, and introduced to the market. A primary goal of these lab equipment innovations is to improve the efficiency of the drug development cycle or unlock as yet unknown benefits for researchers. A summary of some of the most recent product innovations to hit the laboratory scene are highlighted below.

REFEYN’S SAMUXMP MASS PHOTOMETER
Announced in January 2022, Refeyn’s SamuxMP mass photometer is designed to be used with only basic training. Intended for use in adeno-associated virus (AAV) analytics, it has a mass range tailored for AAV analysis and provides accurate results in less than five minutes from sample loading to final result. Combined with low-operational costs and a small footprint, the SamuxMP enables routine quantification of empty/full AAV capsid ratios, even in smaller labs, to set a new standard in AAV characterization.

The SamuxMP is designed to overcome the drawbacks of the current analytical methods by enabling users to rapidly and cost-effectively determine empty/full capsid ratios for AAVs of any serotype at the bench using very low sample volumes and concentrations with minimal sample preparation. This is intended to enhance productivity and speed up workflows through more frequent analyses in-house, making R&D and process development of gene therapies and AAV-based therapeutics significantly more efficient (1).

BIO-RAD’S BIO-PLEX PRO HUMAN SARS-COV VARIANT NEUTRALIZING ANTIBODY ASSAYS
Bio-Rad Laboratories announced in December 2021 that it would be offering new Bio-Plex Pro Human SARS-CoV Variant Neutralizing Antibody Assays for use in measuring neutralizing antibodies. The product consists of a ready-to-use 96-well kit containing premixed magnetic capture beads, a detection converting enzyme (ACE)-2 receptor, a standard and positive control, and buffers that measure levels of neutralizing antibodies and percentage inhibition of the ACE-2 receptor binding the viral antigens coupled on the beads.

The assays are being offered in an 11-plex complete all-in-one kit format that consists of wild-type recep-
tor-binding domain and S1 and 9 variant antigens, customizable singleplex assays, and 2-plex Delta variant—such as Omicron—is included. This customizability may prove invaluable as mutant strains of COVID-19 continue to develop (2).

**SamuxMP makes R&D and process development of AAV-based therapeutics significantly more efficient.**

**BIOCHROMATO’S SMART EVAPORATOR C1**

In November 2021, BioChromato released data supporting the notion that its Smart Evaporator C1, designed for preparing microbial degradation culture media for analysis, can utilize a novel bioremediation technique to improve the detoxification process for persistent organic pollutants (POPs) that cannot be decomposed by natural processes in soil.

According to an interview the company had with an anonymous researcher, various advantages were found relative to rotary evaporators:

- The Smart Evaporator C1 can evaporate culture medium samples without azeotroping, saving a significant amount of time relative to rotary evaporators.
- Rotary evaporators are at risk of water contamination from the steam adsorbed from the water heating bath. The C1 instrument avoids this risk because it does not need water.
- Researchers no longer have to monitor the process to avoid solvent bumping—because the C1 instrument operates under normal pressure, samples can be left unattended (3).

**OPENEYE’S ORION ANTIBODY DISCOVERY SUITE**

OpenEye, in a partnership with Specifca, launched the Orion Antibody Discovery Suite, a jointly developed software, in December 2021. Orion is designed to identify diverse antibody sets with better properties for downstream therapeutics development. The product exclusively features Specifca’s AbXtract software, an antibody discovery module that uses proprietary artificial intelligence methods to analyze large amounts of sequence data.

OpenEye claims that Orion is the only cloud-native fully integrated software-as-a-service molecular modeling platform. Orion uses Amazon Web Services, which provides it with unlimited storage and computational scalability in tandem with its data sharing, visualization, and analysis tools (4).

**MILLIPORESIGMA’S COLORWHEEL FLOW CYTOMETRY ANTIBODIES AND DYE**

Announced in November 2021, MilliporeSigma’s ColorWheel Flow Cytometry Antibodies and Dyes present the latest advancements in cytometry profile technology. The product allows users to select antibodies and dyes for assembly in any desired combination, resulting in an output of mix-and-match antibodies and dyes analogous to a primary conjugated antibody.

According to MilliporeSigma, multiplexing in flow cytometry can be difficult because researchers must consider instrument configuration, antigen expression and dye brightness balance, and antibody–dye combination availability. In this regard, the ColorWheel is designed to overcome these constraints by making it easier to build a new multiplex assay for samples with varying expression levels of antigen.

Other notable features of the ColorWheel include:

- Flexibility to pair any antibody with any dye in a ready-to-use, convenient format
- Can be used in five minutes of hands-on time, minimizing necessary time and effort
- Preservative-free presentation that promotes sustainability and wider sample type compatibility
- Lyophilized product, enhancing stability and allowing for ambient shipping (5).

**OpenEye claims that Orion is the only cloud-native fully integrated software-as-a-service molecular modeling platform.**

**SARTORIUS’ SARTOLAB RF|BT 150–1000 VACUUM FILTRATION UNITS**

Sartorius introduced the new Sartolab RF|BT 150–1000 Vacuum Filtration Units in November 2021. Designed to offer faster and higher capacity filtration, the new filtration units also allow for enhanced physical stability for a wide range of sample types through a newly optimized center of gravity.

The RF|BT 150–1000 has an increased membrane surface area designed to facilitate optimal filtration. Additionally, there is an 0.45-μm polyethersulfone membrane in place of the 0.45-μm cellulose acetate membrane, which increases flow rate while keeping the same low-protein binding properties.
The new units can be directly used on the Sartolab Multistation for parallel filtration. Additionally, the new vacuum filtration units are available in three different pore sizes to meet the needs of most applications:

- 0.1 μm: mycoplasma removal
- 0.22 μm: sterile filtration of cell culture media, buffers, and reagents
- 0.45 μm: clarification of aqueous and viscous solutions (6).

**THERMO FISHER SCIENTIFIC’S ORBITRAP EXPLORIS MX MASS DETECTOR**

Thermo Fisher Scientific unveiled the Orbitrap Exploris MX Mass Detector at the 69th American Society for Mass Spectrometry and Allied Topics in October 2021. The new mass detector allows biopharmaceutical laboratories to implement multi-attribute method (MAM), an analytical extraction technique that can extract large amounts of different quality parameters of a protein via a single analytical approach.

In addition to MAM, the Orbitrap can perform intact analysis of monoclonal antibodies, conduct oligonucleotide mass determination, and carry out peptide mapping. According to Thermo Fisher, this instrument simplifies the transition of biotherapeutics from development to manufacturing and enables quality control customers to use the same method established earlier in a molecule's journey to commercialization. This design is intended to accelerate the overall biopharma development pipeline (7).

**CURIrx’S CURILYTICS PLATFORM**

CuriRx announced the CuriLytics Platform in September 2021. Designed to support the development of complex biotherapeutics, CuriLytics uses high-resolution mass spectrometry and various orthogonal characterization methods to characterize modern biopharmaceutical drugs, including:

- Recombinant proteins
- Monoclonal antibodies
- Bispecific antibodies
- Vaccines
- Antibody drug conjugates
- Oligonucleotides
- Gene therapy products.

Ultimately, the platform can identify quality attributes of protein candidates at the individual residue level, which can be used to provide context to effects brought about by changes to the process or production of the drug (8).

**BÜRkERT’S FLUID CONTROL SYSTEMS**

Bürkert Fluid Control Systems new scalable chemical disinfection system features a compressed air-operated dual-substance nozzle that provides homogenous and fine aerosol formation of hydrogen peroxide with minimal chemical and energy input.

The system is designed for applications such as sterilizing packages, cleaning high efficiency particulate air filters, or disinfecting rooms. In operation, hydrogen peroxide is pumped from a stainless-steel container to a liquid flow controller. Atomizing air is metered to the nozzle through a mass-flow controller, producing a fine mist. The measured material flows enable the control of disinfection time.

The modular preparation system can be customized to suit customer needs to include heaters, integrated flushing, safety devices, or control cabinet integration with programmable logic controllers (9).

**LASAIR PRO AIRBORNE PARTICLE COUNTER**

The Lasair Pro Airborne Particle Counter from Particle Measuring Systems, announced in July 2021, supports a range of applications, including clean-area monitoring and classification while meeting international cleanroom certification standards.

The instrument is designed to meet increasing data integrity and regulatory requirements, featuring integrated audit trail capabilities. Sampling activities can be programmed and managed locally or remotely. Collected data are securely saved and transferred to meeting data integrity-related standards such as 21 Code of Federal Regulations Part 11.

The instrument can store up to 10,000 data samples and can be configured for up to 100 users. Unlimited users can access a near field communication card (10).

**REFERENCES**

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A Customized Regulatory Approach to CMCs

Build into the chemistry, manufacturing, and control strategy the ability to pivot and be flexible should the course change.

MEG RIVERS

Chemistry, manufacturing, and control (CMC) strategies and requirements vary for different products, including small molecules, large molecules, and gene therapy products. Although approaches to CMC strategies differ, how does this factor in from a regulatory perspective?

BioPharm International interviewed Monica Commerford, head of regulatory affairs, viral vector services, pharma services, Thermo Fisher Scientific; Jesse Bishop, manager, regulatory affairs, viral vector services, pharma services, Thermo Fisher Scientific; Bram Lardée, client relationship manager product lifecycle management, ProPharma Group; Peder Edin, managing consultant, RA CMC EU, ProPharma Group; Roland Gustafsson, subject matter expert, quality, ProPharma Group; and Khanh Ngo Courtney, PhD, senior director, biologics, Element. These experts dive into key considerations for CMCs, audits, fast-track designations, and how a one-size-approach doesn’t fit all.

**KEY DIFFERENCES FOR CMC REQUIREMENTS**

**BioPharm:** CMC requirements vary for different products, including small molecules, large molecules, and gene therapy products. What are some of the key differences, and what are the best ways to approach each?

**Lardée (ProPharma Group):** Small-molecule active pharmaceutical ingredients are more robust and resistant against microbial contamination. Generally, small molecules are administered orally and, therefore, formulated accordingly into solid oral dosage forms, suitable for exposure to the harsh conditions in the gastrointestinal tract. Large molecules and gene therapy products are biological products that contain complex proteins or whole cells. These products must retain their structure and modification and are typically dosed via injection or infusion in a clinical setting. The best way to approach each category of products is to acknowledge these differences and combine the similarities in disciplines independent of drug product or process type.

**Courtney (Element):** CMC for large molecules, particularly gene therapy, is much more complex than for small molecules—specifically when it comes to the measurement of potency and process-related impurities. For a small molecule, U/HPLC [high and ultra-high-performance liquid chromatography] to show purity is suffi-
cient as a measurement of strength and potency. The next level in complexity is a large molecule, such as a recombinant enzyme. To show potency, U/HPLC is not sufficient, but requires an *in vitro* enzymatic activity and an *in vitro* cellular potency assay to show *in vitro* mechanism of action. For gene therapies, showing an *in vitro* mechanism of action is more complex and cumbersome as the assay must be able to demonstrate viral transduction followed by a cellular response. Demonstrating the clearance of process-related impurities is also more difficult for advanced therapeutics because there are more starting materials, complex upstream processes, and complex purification steps.

**Commerford (Thermo Fisher Scientific):** We have to remember that cell and gene therapy products still fall under regulations and licensure requirements for biologics in the United States. Therefore, CMC requirements would be similar for cell and gene therapy products as they would for the more traditional biologics (i.e., monoclonal antibodies). However, the licensure regulations in the United States are different than what is needed to approve small molecules (as small molecules and their manufacturing processes are not licensed).

**KEY CONSIDERATIONS FOR QUALITY**

**BioPharm:** From a quality/regulatory perspective, what are key considerations for CMCs?

**Courtney (Element):** Staging CMC activities by appropriateness is one of the key considerations for CMCs. Another key consideration is identifying critical quality attributes of the drug substance and drug product as early as possible in product development so that robust methods could be developed to monitor the quality of the product as the process is being developed. A third key consideration is to build into the strategy the ability to pivot and flexibility to change course based on clinical data or business decisions.

**Edin (ProPharma Group):** The CMC sections in a product dossier should indicate that the drug product is produced with a consistent quality throughout the development process and throughout the period the product is marketed to guarantee the safety and efficacy profile of the medicinal product. To demonstrate that the manufacturer is in sufficient control during manufacture of the drug product, all critical steps and parameters need to be evaluated for starting materials and the production processes during the development phase of the product and, subsequently, a quality control plan needs to be put in place. Additionally, the shelf-life and the usability of the final product need to be established. Extensive characterization of the drug substance and drug product are fundamental for any comparability program following any manufacturing changes. Control of impurities is critical, particularly those that are process-related to gene therapy products.

**Bishop (Thermo Fisher Scientific):** Matching the quality/manufacturing controls and the regulatory requirements to the phase of development is critical here. Clearly, patient safety should never be compromised, but starting with too many controls too early can cripple a program’s forward momentum and lead to delays in getting patients the life-changing therapies they need. When considering regulatory strategy and forward momentum, it’s also important to have a clear understanding of the increasing regulatory requirements through all phases because of the pitfalls that so many programs are experiencing when not looking ahead.

**REGULATORY ROADBLOCKS**

**BioPharm:** What might halt forward motion for CMCs for small molecules, large molecules, and/or gene therapy products in terms of regulatory steps? How can potential roadblocks be avoided?

**Bishop (Thermo Fisher Scientific):** No matter what the phase, it’s important to start with the end goal, analyze the regulatory requirements to reach that goal, and develop a long-term strategy to meet those requirements throughout the course of the program’s development. Roadblocks arise when you don’t ask the right questions of the regulators at the right time or don’t prepare for increasing requirements over the program’s movement through the phases. How do we avoid these potential roadblocks? Ask questions of the regulators, early and often. Take advantage of those opportunities whenever possible. Also, it’s important to develop checklists of all regulatory requirements in order to arrive at the end of the programs with all requirements met, instead of experiencing program delays due to having to go back to meet a requirement that was not properly planned for.

**Edin (ProPharma Group):** Old processes that do not meet current regulatory requirements, lack of critical data, and risk assessments might halt forward motion for CMC. Different regulatory requirements in different countries and lack of alignment between different authorities (US vs. EU [European Union] vs. JP [Japan]) could also be a hindrance. Other obstacles, especially for large molecules, could be insufficient comparability data to support any manufacturing changes (site, starting and raw reagents, adherent to suspension cell lines). Finally, it must be emphasized that marketed product[s] must always be supported by representative development data. Changes made in the development process can endanger meeting this requirement, which may result in significant delays and extra work. These roadblocks can be avoided by planning and performing comparability studies with validated analytics, having sufficient retains [retainer samples] of pre-change drug substance and drug product as well as...
post-change drug substance and drug product, and the ability to perform side-by-side comparability analysis. Necessary changes in the development process should always be evaluated for regulatory impact. The involvement of a regulatory CMC person during development—and even the planning of development—could be very helpful to prevent unnecessary delays.

**CMC AUDITS**

**BioPharm:** What do you typically encounter with audits for CMCs?

**Courtney (Element):** CGMP [current good manufacturing practice] compliance is becoming more rigorous and is being required earlier in the CMC process. Even if methods are not yet validated, they are being required to at least be sufficiently qualified. Furthermore, all software that generate[s] electronic records, such as Empower, OpenLab, or instrument-specific acquisition and analysis software, must be 21 CFR [Code of Federal Regulations] Part 11 compliant—particularly regarding audit trail capability and validated systems (1).

**Commerford (Thermo Fisher Scientific):** This is often looked at as an afterthought or planned for too late in the product’s development timeline. Manufacturing facilities should be in a continuous state of inspection readiness, particularly once the product application has been submitted to regulators. To prepare, the CMCs should be mock inspected by the appropriate subject matter experts. The goal for any mock inspection should be to ensure that the data [are] accurate, that the data [contain] the appropriate level of quality, that quality-by-design principles are built into the manufacturing process, and that the manufacturing process and site practices are aligned with the submitted application.

**Bishop (Thermo Fisher Scientific):** This is also the perfect time to look ahead at what questions can be anticipated from the regulators during the review cycle (or perhaps at the next submission) as the inspection for a product application and the review of it are linked. Some of these questions or information requests coming back from the regulators are going to be on a short time clock, and if there hasn’t been some thought and preparation for those questions, the program can be slowed down or halted.

**Gustafsson (ProPharma Group):** For CMC, we focus our expertise on audits of manufacturing sites, which significantly impacts GMP compliance. An important part of this is to make sure that process validations have been performed according to current standards, that the results are reflected in the master batch record, and that all subsequent changes are handled by a change control system. Furthermore, we encounter a focus on the QA/QC [quality assurance/quality control] release process to ensure that registered critical process parameters and critical quality attributes are within limits before batch release and measured with validated analytical methodology.

**FAST-TRACK DESIGNATION**

**BioPharm:** What can increase the likelihood that companies secure a fast-track designation from FDA or other regulatory bodies for CMCs?

**Lardée (ProPharma Group):** For fast-track designations, this is dependent on the necessity of the medical indication (unmet need). In addition, having a complete and logical technical storyline and communicating this as early as possible does help in convincing the competent authority. Above all, fulfilling an unmet need is most important.

**Commerford (Thermo Fisher Scientific):** Regulatory bodies (specifically, FDA) have a specific set of criteria that they consider when discussing (and ultimately agreeing to) a fast-track designation that include[s] the seriousness of the condition and demonstrates the potential to address an unmet medical need (2). For applicants considering this designation, early communication (even as early as the pre-IND [investigational new drug application] meeting) with the regulatory body is needed to discuss plans and approaches. Particularly, the FDA recommends submitting your requests “when the IND is first submitted or any time thereafter before receiving marketing approval of their BLA or NDA” (2).

**CMC TRENDS**

**BioPharm:** Do you foresee any trends for CMCs in the near future?

**Commerford (Thermo Fisher Scientific):** Within the next few years, as more and more cell and gene therapy submissions are moving to the market, we will likely see more strategic guidance from regulators as they are starting to compile the necessary quality and safety data from reviewing a diverse range of applications. This guidance could come in formal ways (e.g., guidance documents, industry meeting responses) or through informal means.

**Courtney (Element):** Analytics will become more automated. There will be more online data capture, such as metabolic or spent media information in bioreactors, or automated data analysis of downstream processes. Process development will become more platform based and streamlined, especially for similar modalities like specific AAV serotypes.

**Lardée (ProPharma Group):** Personalized medicines continue to gain, independent of drug product or process type … Finally, I foresee an acceleration in more strict and new standards for Eco+ productions and handling of biopharmaceutical waste streams. More efficient use of medication with further improvement of communication and information to end-users will be an important part of this.

**REFERENCES**

2. FDA, Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, fda.gov (May 2014).
Method Development in Demand

Experience is an invaluable asset for outsourcing partners, particularly as more challenging method development services are in demand.

FELICITY THOMAS

According to market research, the size of the outsourcing sector serving the pharmaceutical and biotechnology industries is expected to expand, reaching $99.4 billion by 2028 (1). Demand for outsourced services is being driven by several factors, such as high demand for biologics and small molecules, a lack of in-house expertise, and rising costs associated with in-house development capabilities.

To find out more about how demands have changed for outsourcing partners providing method development services and the trends affecting this sector, BioPharm International spoke with Jerry “Jr.” Mizell, senior director, Analytical Services, Metrics Contract Services.

CHANGING DEMANDS

BioPharm: Could you provide a brief overview of how the demands have changed over the years for outsourcing partners in terms of method development services?

Mizell (Metrics Contract Services): Nowadays, there is an increased demand for sound methods to be developed early in the product life cycle. More customers want rugged and robust methods in place as early in the development process as possible, and they want methods that require minimal changes as their programs advance to commercial phases.

Based on the experience of Metrics Contract Services, customers also want to develop quality control (QC)-friendly methods that help maximize laboratory efficiency in the commercial phase. Across various methods developed in recent years, dissolution, in particular, has been in the spotlight. A comprehensive approach to dissolution should produce a discriminating method that can demonstrate that an adequate drug product has been manufactured. Current customer expectations also demand a detailed dissolution method development report describing how the dissolution procedure was derived. This is especially important for new drug applications (NDAs).

COVID-19 DISRUPTIONS

BioPharm: How has demand of outsourced services for method development been impacted by the COVID-19 pandemic?

Mizell (Metrics Contract Services): While we haven’t experienced a direct uptick in development services requested because of the COVID-19 pandemic, we have experienced supply chain challenges as a result of it. The delays and disruptions to key supplies have made it imperative to execute method development in the most effective means possible to align with clinical timelines.
Choosing a method development partner with vast experience and a proven track record becomes invaluable to customers who need to deliver treatments to patients at speed, while also ensuring that key project deliverables are met.

**CALL FOR EXPERIENCE**

**BioPharm:** Have there been changes in expectations as to what an outsourcing partner should be able to provide or accomplish with method development services?

**Fu (WuXi STA):** Molecules are getting more complex, pipelines more diverse, and at the same time, increasing numbers of targets are on accelerated pathways. Put these factors together and there is a need for contract development and manufacturing organizations (CDMOs) that can handle integrated and accelerated pathways with a full suite of technologies from biocatalysis and flow chemistry through to crystallization and spray drying. Integrated models provide much greater flexibility and enable API and formulation teams to work side by side.

Phase-appropriate development is also often asked of many CDMOs, and this usually means running pathways sequentially. Another way timelines can be accelerated is by developing an ‘end-in-mind’ process strategy to seamlessly connect discovery, development, and commercial API needs from milligram to metric ton scale. But the CDMOs will need a large R&D team with the right expertise and a broad technology platform to ensure the most appropriate chemistry at every scale.

The final trend that is being seen and, in some ways is linked to the challenges of the pandemic, is the requirement of a partner who can ensure supply chain stability with a robust continuity business plan including multiple facilities available, technologies to avoid or minimize the use of scarce material, or even the ability to manufacture them in the event of shortages. This means forward-looking innovators are seeking backing by a contract partner that has a solid network of vetted vendors and a large chemistry organization and a diverse manufacturing and technology platform that can react and adapt quickly.

**BioPharm:** What other trends have impacted outsourced process development in recent years?

**Fu (WuXi STA):** Undoubtedly, bioavailability and solubility are increasingly common challenges and process characteristics are, therefore, a must for any outsourcing partner—they need to have the full suite of particle size engineering tools and expertise from crystallization, micronization, nano-suspension to amorphous solid dispersion. There has also been an increase in the need of highly potent APIs, which necessitates highly specialized facilities and expertise.

And, more recently, there has been a high demand for the CDMOs that can handle oligos, peptides, and various complex conjugates. Novel conjugates involving combinations of oligos, peptides, high potency payloads, linkers, and specific carriers are increasing, but the resources required are lagging worldwide.

One of the other major trends is that innovators are seeing the benefits of integrated networks with R&D and manufacturing teams in one location and, taking this a step further, having drug product formulation and manufacturing capability to be paired with the API project. These obviously bring tremendous benefits in reducing transfers—of materials or knowledge—and enable formulators and chemists to work closer and reduce time to market or milestone.

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**Mizell (Metrics Contract Services):** The outsourcing partner, or contract development and manufacturing organization (CDMO), should have a vast array of development experience in solid oral dosage formulations. This experience will allow for expedited development services, especially when challenging formulations are being developed. These challenging formulations may include API loaded on resin or beads and molecules that do not contain chromophores, requiring alternative modes of detections.

CDMOs with experience in charged aerosol detection, evaporative light scattering detection, and refractive index detection for challenging molecules can be the deciding factor in awarding a project. Outsourcing partners with mass spectrometry (MS) capabilities are also at an advantage when impurity issues arise and identification is needed. Cost can be a primary focus for some programs; however, quality assurance and the...
Outsourcing

ability to meet deliverable timelines are also very important qualities, which can often outweigh price differences.

PRESENT AND FUTURE TRENDS

BioPharm: What other trends have impacted outsourced method development in recent years?

Mizell (Metrics Contract Services): Over the past few years, there has been an increase in the development of poorly soluble small-molecule drug products, which can be extremely challenging when developing a dissolution method. This type of program is challenging because introducing two APIs into the same formulation and combining products, with significantly differing physical and chemical characteristics, means that method development can take on a new level of difficulty.

BioPharm: From a safety perspective, highly potent APIs (HPAPIs) introduce additional challenges, as developers want user-friendly methodologies in place without jeopardizing laboratory staff safety.

Mizell (Metrics Contract Services): There should be more and more Biopharmaceutical Classification System Class II and IV molecules being discovered for evaluation. Customers should seek outsourcing partners with extensive experience in dissolution development and alternative mode of detection in the event that a molecule does not contain a chromophore. Instrumentation must remain compliant with current industry standards to ensure method expectations are met.

There is also an expectation that future demands will call for methodology development for nitrosamine assessments, and the ability to meet FDA (and other regulatory bodies’) requirements for NDA filings and current commercial products on the market. This methodology requires MS, which if not currently available at a CDMO, may become a worthwhile investment to offer to customers. As with elemental impurities, this requirement will not go away and will only face increased scrutiny as time passes.

REFERENCE


bioPharm International accepts four types of peer-review papers that are considered: standard data-driven, novel research; topical literature or patent review; technical case studies/technical application notes; and science-based opinion papers.

Manuscripts for peer-review papers are accepted on an ongoing basis. Publication priority is given to papers in the order they are accepted for publication.

Submitted papers are initially screened by the editors, then submitted for formal review by a member of the editorial advisory board, who will review the article for technical interest and content in a double-blind review process. Article acceptance is conditioned on the reviewer’s approval. Once accepted for publication, a paper typically is published within three to five months.

Peer-review papers are published in the print and digital editions of BioPharm International, and on www.BioPharmInternational.com. Links to the online versions of peer-review papers also are featured in e-newsletters distributed to the publication’s audience.

To learn more about the peer-review submission process, click the Submission Guidelines link on www.BioPharmInternational.com.
Sustainable Biowaste Treatment System

Suncombe’s MicroEDS BioWaste Treatment System is a biologically hazardous waste decontamination unit that can process between 150 to 500 L of waste per day. The low-volume system is certified to ASME and ISO/EN standards for treating biosafety level 1, 2, and 3 waste through an innovative batch process that allows for the positive release of all collected waste.

Advances in the MicroEDS include thermal energy regeneration, low energy usage, and 100% positive release for treated waste and electronic records generation. The system is designed to operate at a thermal treatment parameter of 121 °C for 15 minutes, as well as variable temperature, time and f0 lethality settings, for specific requirements.

According to Suncombe, the new unit delivers at least 61% energy saving relative to prior models and can reduce energy usage and utility consumption by up to 75%. Additionally, based on average use, it reduces the carbon footprint by up to 1.68 tons of carbon dioxide each year.

Suncombe
www.suncombe.eu

Single-Use Separator

The GEA kytero single-use separator, intended for use in fermentation solutions and cell cultures, is equipped with GEA Westfalia Separator disk stack technology designed for maximum yield, high separation efficiency, and gentle product handling.

The GEA kytero combines the high performance of larger GEA stainless-steel pharmaceutical centrifuges with the benefits offered by disposable components that do not require cleaning. The technology relies on centrifugal separation, rather than filter-based harvesting, for increased clarification efficiency.

To prevent cross-contamination and hygienic cell harvesting, all elements that come into contact with the product, such as hoses and containers, are made of recyclable material and are replaced after use. The design of the aseptic connector system is intended to ease the process of exchanging single-use components. The mobile plug & produce unit also fits into any cleanroom.

GEA
www.gea.com

Single-Stage Clarification

The 3M Harvest RC clarifier from 3M Health Care uses a proprietary fibrous chromatography media to condense three process steps into a single-stage purification of recombinant protein therapeutics.

The clarifier provides monoclonal antibody recovery of more than 95% and can be used with cultures with different cell densities, high-packed cell volumes, and cell culture characteristics. The quaternary ammonium functionalized polypropylene fiber, and 0.2 µm PES membrane, provides scalable clarification from discovery to commercial manufacturing scale.

The clarifier introduces chromatographic separation earlier in the process to remove soluble impurities, resulting in cleaner effluent, the company reports.

3M Health Care
www.3m.com

Ready-to-Use Disinfectant Wipes

STERIS Life Sciences’ VestaSyde SQ 64 st Ready-to-Use Disinfectant Wipes are used to disinfect cleanroom surfaces. The wipes are part of a family of disinfectant products including concentrated and ready-to-use formats with the same quaternary ammonium active ingredient.

This product uses a system that combines cleanroom-quality wipes packaged with a separate internal pouch containing the quaternary ammonium active ingredient. The internal pouch allows for maximum chemical stability while still offering a method to saturate the wipes. By rolling the package of wipes, the internal pouch of liquid opens and quickly saturates the wipes. The wipes are low linting with a knitted polyester construction and ultrasonically sealed edges.

Each package of wipes is double-bagged and gamma irradiated to facilitate introduction into cleanroom areas. Every lot is USP sterility tested with complete lot traceability to meet quality assurance and quality control needs.

STERIS Life Sciences
www.sterislifesciences.com
section helps everyone (employees, auditors, clients, regulators) understand the overall quality system as it applies to your facility. The next section I would recommend be included is an organizational chart. The organizational chart should demonstrate the reporting hierarchy of the company to demonstrate the independence of the quality organization.

One of the most critical sections to include in your quality manual, in my opinion, is the section on management responsibilities. In this section, you should introduce the company’s management review responsibilities as well as the senior management titles that are responsible for overseeing the pharmaceutical quality system and the management review meetings. The next critical section to include is an overall description of the quality management system in effect at your company. In this section, you can describe your company’s approach to all the applicable systems utilized by your company for planning, documenting, implementing, and monitoring the activities that potentially impact product quality and patient safety. These processes included but are not limited to quality by design, quality risk management, corrective and preventive actions (CAPA), change control management, management of materials, and maintenance of facilities. In describing the quality management system, you should discuss how it relates to manufacturing, facilities and equipment, materials, packaging and labeling, and laboratory controls. If you outsource an activity, you should note that the activity is outsourced and your oversight responsibilities.

The last element of the quality manual is its approval. In my opinion, the quality manual should be agreed to and signed off by representatives from the various departments it governs. The final step in the process is to ensure that everyone, from senior leadership on down, is trained and understands the quality manual and how it relates to their job responsibility. If you follow this simple approach to constructing a quality manual you will have an easy-to-follow, comprehensive document that communicates the company’s commitment to manufacturing safe and effective pharmaceutical products.

REFERENCES
4. ICH, Q10 Pharmaceutical Quality System (ICH, June 4, 2008). ◆
Q: I work for a small start-up company and have been tasked with writing the quality manual for my company. I have searched but have been unable to find regulations that define what is contained in this document. Can you help?

A: The short answer is there is little guidance on what the actual content of a quality manual should contain. It is clear, when reviewing the regulations, there is an intent to have documentation regarding a company’s overall quality approach. In Europe, EudraLex Volume 4, Chapter 1, titled Pharmaceutical Quality System, section 1.7, states, “the Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the Quality Management System including management responsibilities” (1). The United States Code of Federal Regulations (CFR) doesn’t mention a quality manual but does mention a need for a quality policy in the medical device regulations. US 21 CFR 820.3 states, “Quality policy means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility” (2). And in section 21 CFR 820.20, the regulation states a “Quality policy. Management with executive responsibility shall establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization” (3). The best source for what you should include in your quality manual comes from the International Council for Harmonisation (ICH) in the ICH Q10 document titled Pharmaceutical Quality System (4). Section 1.8 of this document states, “A Quality Manual or equivalent documentation approach should be established and should contain the description of the pharmaceutical quality system. The description should include: (a) The quality policy (see section III (2)). (b) The scope of the pharmaceutical quality system. (c) Identification of the pharmaceutical quality system processes, as well as their sequences, linkages, and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner. (d) Management responsibilities within the pharmaceutical quality system (see section III (2)).” Just to be clear, the quality manual applies to the entire company and not just the quality department, similar to how the term quality culture is not referring to the culture of the quality department but the entire company’s approach to culture.

Because the quality manual governs the entire company, it is advisable that it be constructed with representatives from various functions in the company. This collaboration helps ensure the overall purpose and scope of the document is representative of the company’s philosophy. A simple purpose statement might say something to the effect, “The quality system described is intended to ensure the facility is compliant with [list regulations] and serves as the basis of the Quality Systems that apply to [list company name], products, and current good manufacturing practice (CGMP) activities.” The scope statement can be just as simple and state something to the effect that the quality systems described apply to all products, personnel, and manufacturing operations to ensure products meet the requirements for safety, identity, strength, and purity.

Another section to consider adding is a section of definitions. It is my experience that each company/facility utilizes their own acronyms. Any special acronyms being used at the facility should be defined in the definitions section along with common acronyms such as CGMP, FDA, EU, SOP, etc. Having a definition...
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