Pharma Looks Ahead to 2022

Development
- Excipients for Taste
- Solubility Challenges

Manufacturing
- Single-Use Technologies
- Facility Design

Analytics
- Biologics Testing

Quality/Regulations
- Quality at Manufacturing Facilities

Outsourcing
- State of the Industry

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IN MEMORIAM

Michael J. Hennessy, Sr., was the beloved chairman and founder of MJH Life Sciences, parent company of *Pharmaceutical Technology*. Hennessy spent his career turning his passion for building businesses and creating jobs into a run of successful ventures and brands. Following his graduation from Rider University in 1982, he started his career in medical publishing as a sales trainee. In 1986, Hennessy became chief operating officer of Medical World Business Press, which was part of the launch of medical newspapers and other media products.

Hennessy launched Multimedia Healthcare, LLC, in 1993 and built a portfolio of award-winning clinical journals. In 2001, Freedom Communications, Inc., acquired Multimedia Healthcare, about the time that Hennessy was pioneering a new approach to print and digital publishing with Intellisense, LLC (now part of MJH Life Sciences).

To build a comprehensive multimedia and education platform, Hennessy added additional companies and capabilities to the MJH Life Sciences portfolio. In February 2008, Hennessy acquired the rights to the journals *Pharmacy Times* and *The American Journal of Managed Care*, both recognized in their respective markets as authoritative, trusted media platforms that provide essential information to a large audience of healthcare professionals.

In 2019, MJH Life Sciences made its largest acquisition to date when it acquired the Healthcare and Industry Sciences divisions of UBM Medica, nearly doubling the size of the organization and adding legacy titles such as *Medical Economics* and *Pharmaceutical Executive* to the already impressive portfolio. This acquisition made the organization the largest independently owned medical communications company in North America. In addition to acquisitions, Hennessy organically developed ancillary in-house agency divisions with Proximyl Health, Truth Serum NTWK, and MJH Global Medical Affairs.

Later in 2019, Hennessy elevated his own role to Chairman while naming his son, Mike Hennessy, Jr., to assume the leadership role of the organization and carry on the family legacy. Under Mike Jr’s leadership, the company enhanced its global potential by entering into a long-term partnership with BDT Capital Partners, LLC in November 2021.

Due to his broad business and educational experience and understanding of the challenges facing New Jersey, Hennessy’s counsel and insight had been sought by several organizations, including his alma mater Rider University, where he served on the Board of Trustees and was elected to the executive committee. In addition to being active in state and national politics, Hennessy also had a long record of service at the local level, where he was a strong advocate for veterans and environmental issues.

Hennessy was preceded in death by his wife, Patrice Hennessey, who bravely battled cancer for almost 10 years until her death in January 2020. Hennessy donated $4 million (€3.5 million) to Rider University to expand the Science and Technology Center at their alma mater. The Mike & Patti Hennessy Science and Technology Center is set to be completed in 2022.

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Innovative and high-quality medicines have been approved over the last year, which the analysts have predicted could make US$4.55 billion (€3.97 billion) in annual revenue in the next five years. The drugs highlighted are reasonably similar with the exception of tirzepatide, therapies that have been picked out are adagrasib from Mirati Therapeutics and Zai Lab, faricimab from Roche and Chugai Pharmaceutical, lecanemab from Eisai and Biogen, donanemab from Eli Lilly and Company, tepezelpatam from Amgen and AstraZeneca, tirzepatide from Eli Lilly and Company, and vutrisiran from Alnylam Pharmaceuticals (4). The therapeutic targets for these treatments range from Alzheimer’s disease to cancer and eye disease to asthma, and the majority of the drugs fall under the classification of biologics. Projected sales for all of the drugs highlighted are reasonably similar with the exception of tirzepatide, which the analysts predicted could make US$4.55 billion (£3.97 billion) in sales by 2026 (4).

Only time will tell as to whether or not these promising medicines will indeed be the next ‘blockbusters’.

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Felicity Thomas
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EDITOR’S COMMENT

Hot Picks for 2022

Despite the continued turbulence from COVID-19, the bio/pharma industry experienced another good year for drug approvals in 2021. The latest available figures from the European Medicines Agency (EMA) showed that 2021 marketing authorizations were granted to 82 therapies, 14 of which were for generic medicines and seven of which were for biosimilars (1).

However, a drug that has been hitting headlines and was highlighted as ‘one to watch’ by Clarivate in 2021 (2), aducanumab from Biogen and Eisai, has not gained a favourable decision from EMA (3). Main reasons for the refusal of the marketing authorization of the drug included the fact that the effect of amyloid beta reduction in the brain and clinical improvement from Alzheimer’s has not been established, conflicting study results, and insufficient proof of safety (3). The three remaining drugs from the four highlighted in Clarivate’s 2021 report (2), bimekizumab, relugolix, and vericiguat, all gained marketing authorization in the European Union.

Pick of the bunch in 2022

For 2022, Clarivate has highlighted seven late-stage treatments that its analysts expect to reach blockbuster status (i.e., earn US$1 billion (£873 million) or more in annual revenue) in the next five years. The therapies that have been picked out are adagrasib from Mirati Therapeutics and Zai Lab, faricimab from Roche and Chugai Pharmaceutical, lecanemab from Eisai and Biogen, donanemab from Eli Lilly and Company, tepezelpatam from Amgen and AstraZeneca, tirzepatide from Eli Lilly and Company, and vutrisiran from Alnylam Pharmaceuticals (4). The therapeutic targets for these treatments range from Alzheimer’s disease to cancer and eye disease to asthma, and the majority of the drugs fall under the classification of biologics. Projected sales for all of the drugs highlighted are reasonably similar with the exception of tirzepatide, which the analysts predicted could make US$4.55 billion (£3.97 billion) in sales by 2026 (4).

Only time will tell as to whether or not these promising medicines will indeed be the next ‘blockbusters’.

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Dual-Shaft Mixer with High Shear Rotor/Stator

ROSS has incorporated a high shear rotor/stator into its Dual-Shaft Mixer to meet more intense shearing and homogenization requirements. Rather than including a typical high-speed disperser blade, the mixer comes equipped with a rotor and slotted stator mixing head, also called a homogenizer, for more advanced deagglomeration and emulsification capabilities. The product also features a two-wing anchor that promotes bulk flow and uniform batch temperature.

The ROSS Model CDA-25 (pictured) includes dry-running Double FlexiLip seals on both agitator shafts, making it appropriate for vacuum operations up to 29.5” Hg. This model also features a portable mixing vessel with a heating/cooling jacket.

Charles Ross & Son Company
www.mixers.com

Digital Integration Platform

Scitara’s Scientific Integration Platform (SIP) is a cloud-native infrastructure designed to realize the full benefits of digital transformation. SIP establishes a flexible, adaptable framework that facilitates a fully connected laboratory and an in-situ configurable platform. Its flagship technology, the Scitara Digital Lab Exchange, forms an independent, vendor-agnostic integration layer.

SIP enables laboratories and science-based organizations to access the advantages of data mobility, independent of any digital platforms that have already been deployed. It automates scientific data exchange across various endpoints and interfaces existing various informatics platforms, as well as instrument-specific analysis systems.

Scitara Corporation
www.scitara.com

Next-Generation Cas9 Proteins

Thermo Fisher Scientific’s Invitrogen TrueCut HiFi Cas9 Protein is designed for research applications that require highly precise genome editing, such as the engineering of chimeric antigen receptor (CAR)-T cells and the creation of cellular models for disease discovery.

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Thermo Fisher Scientific
www.thermofisher.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
Regulating Digital Therapeutics

DTx manufacturers are taking advantage of the new regulatory flexibility, afforded by the COVID-19 pandemic, to pilot new products and generate real-world evidence to support regulatory filing and reimbursement.

The Digital Therapeutics Alliance (DTA) defines digital therapeutics (DTx) as products that deliver: “evidence-based therapeutic interventions that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimise patient care and health outcomes” (1).

Acceptance of DTx has grown rapidly over the past couple of years, particularly during the COVID-19 pandemic, as they can support patients in the remote management and treatment of a range of medical conditions including anxiety and depression. Importantly, they can be used as a standalone therapy or in conjunction with more pharmacological interventions or in-person therapy, and enable data to be collected, processed, and analysed, and then tailored to an individual’s medical needs.

In Europe, DTx regulations are fragmented and disparate (Table I). For instance, in the United Kingdom, DTx are classified by the National Institute for Health and Care Excellence (NICE) based on their functions and then stratified into evidence tiers based on the potential risk to the user (2). Conversely, in Italy DTx are classed as medical devices and must pass International Organization for Standardization (ISO) standards to ensure they are compliant with safety requirements. They are categorized according to their risk from level 1 being low risk for health and level 4 high-risk, which can have irreversible effects and impacts on health and/or mortality; the risk category defines the clinical data requirements and approval process (3).

Regulatory changes

DTx are covered by European Union (EU) regulation 2017/745 on medical devices, which came into force on 26 May 2021 (4). The EU Medical Device Regulation (MDR) resulted in a more stringent pre-market security mechanism, provides greater regulatory oversite from notified bodies, and provides additional rules on clinical evidence and post-market surveillance. It established new risk classification for in-vitro diagnostic (IVD) medical devices as well as improving transparency and traceability of devices.

The new EU MDR should help to simplify the exchange of data on medical devices and improve data collection and post-market surveillance to reinforce end-user confidence in DTx solutions. However, Class I products have been upgraded and now require notified bodies designated by EU member states to assess them before a Conformité Européenne (CE) mark is granted; previously manufacturers provided self-declaration for these products. The requirements for pre- and post-market clinical data have increased and expert panels will now scrutinise all Class III and some Class IIB high-risk devices to ensure the safety and efficacy is supported by robust clinical data. This may increase the data burden for DTx developers and potentially increase the approval time to market.

A key objective of these regulatory changes is to ensure a high standard of safety and quality of digital health products while providing patients with quicker access and reimbursement to these innovative solutions. However, the EU MDR contains no specific provisions for DTx and further clarity on the subdivision into risk classes, the approach to be taken by notified bodies concerning regulations applicable to DTx would be useful and enable companies to determine the most appropriate route to market based on the risk–benefit each product brings.

In the United States, the Food and Drug Administration (FDA) has published draft guidance regarding changes to premarket submission of digital health technologies. This guidance includes software as a medical device (SaMD) and focuses on basic and enhanced risk devices and provides greater clarity on Software Requirement Specification (SRS) and Software Design Specification (SDS) regarding their intended use, functionality, safety, and effectiveness (5).
Belgium, and the United Kingdom, a B2P reimbursement self-insured employer health plans, whereas in France, the Netherlands, DTx manufacturers have directly targeted with differing degrees of success. In Germany, Ireland, and business to consumer (B2C), and business to payer (B2P) reimbursement models including business to business (B2B),

date, DTx manufacturers have implemented a variety of essential if DTx are to become universally adopted. To

While these regulatory changes are encouraging, the

The next hurdle is reimbursement

The non-profit organization, DTA was established in 2017 and has played a critical role in raising the profile of DTx. The organization engages with stakeholders and has helped to define and categorize DTx (6) and to facilitate the establishment of standards, code of ethics, and best practices as well as advocating on regulatory and reimbursement. Investment in DTx continues to grow, and a plethora of solutions are now under development within a broad range of conditions to help target unmet medical needs (7).

DTA raising the profile of DTx

The non-profit organization, DTA was established in 2017 and has played a critical role in raising the profile of DTx. The organization engages with stakeholders and has helped to define and categorize DTx (6) and to facilitate the establishment of standards, code of ethics, and best practices as well as advocating on regulatory and reimbursement. Investment in DTx continues to grow, and a plethora of solutions are now under development within a broad range of conditions to help target unmet medical needs (7).

The next hurdle is reimbursement

While these regulatory changes are encouraging, the development of a reimbursement framework is also essential if DTx are to become universally adopted. To date, DTx manufacturers have implemented a variety of reimbursement models including business to business (B2B), business to consumer (B2C), and business to payer (B2P) with differing degrees of success. In Germany, Ireland, and the Netherlands, DTx manufacturers have directly targeted self-insured employer health plans, whereas in France, Belgium, and the United Kingdom, a B2P reimbursement model has proven successful.

Germany is embracing digital health, and other European countries are closely watching this space (8). In December 2019, Germany implemented the Digital Healthcare Act (DGV), to enable the reimbursement of prescribed DTx on a national level (9). To gain reimbursement, manufacturers must demonstrate evidence on safety, functionality, quality, data security and data protection, and an overall effect on improving patients’ care (10). On 9 April 2020, the (Digitale Gesundheitsanwendungen-Verordnung (DGV) or Digital Health Applications Ordinance was enforced to regulate the procedure and reimbursement eligibility requirements of digital health applications by statutory insurers (11).

As of January 2022, 28 digital solutions are available for reimbursement and are now listed on the Federal Institute for Drugs and Medical Devices (BfArM) (12).

In Europe, there are encouraging signs that countries are adopting more centralized pathways to regulate DTx but further clarification is needed to drive future innovation and enhance patient access to a broader array of life-changing digital health solutions. Given that Germany has taken the lead on introducing a legal framework for certification of digital apps to achieve DTx status and reimbursement. It will be interesting to see what approaches other European countries implement over the coming months.

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The year 2021 has been transitional for the most part, with many stakeholders of the bio/pharma industry getting used to the ‘new normal’ or post-pandemic working life. Industry continues to drive innovation across the board, with continued efforts to tackle COVID-19 and a large number of approvals for a range of products.

Potential big changes in pharmaceutical legislation, however, are on the cards for Europe (1), as the European Commission (EC) continues working on its pharmaceutical strategy for the region, which was adopted in 2020 (2). The reformation of the pharmaceutical legislation is foreseen to be implemented by the end of 2022 and will be the first time the European Union’s rules on how drugs are made, approved, and sold have been comprehensively reviewed in 20 years (1).

Expectations and an obvious theme
For Jürgen Höning, pharmacist, senior director, Regulatory Business Intelligence at PharmaLex, the expectations for the year have been surpassed. “Although the pandemic has tremendously influenced the social and economic environment, the pharma industry has demonstrated that by having established robust process it has been possible to maintain the supply chain,” he says. “Furthermore, it has been shown that how medicinal products for the treatment of COVID-19 and related diseases were developed in a short time using creative and holistic approaches and in compliance with regulatory requirements.”

“The obvious theme for 2021 has been the turnaround of COVID-19 vaccines, magnifying trends already seen before and showing that promising new technologies can actually hold their promise, and that it is possible to optimize drug development to speed up delivery,” states Christian K. Schneider, MD, head of Biopharma Excellence and chief medical officer (Biopharma) at PharmaLex.

A surprising trend from 2021 has been the rapid adoption of digital technologies in clinical trials, Schneider notes. The use of such technologies has enabled the decentralization of readouts in clinical trials through mobile phone applications, he adds. “Finally, we’ve seen more companies diversifying their portfolios and investing in therapies for rare diseases so that advanced therapies, and in particular, gene therapies—which were deemed experimental and risky when I was involved with the European Medicines Agency’s Committee for Advanced Therapies some 10–12 years ago—take centre stage,” Schneider continues. “Cell therapies, by comparison, may have slipped behind a bit—but will catch up.”

An obvious theme for 2021 has been COVID-19, but the next 12 months will see industry and its people experiencing further change.
The year’s expectations were unsurprisingly centred around COVID-19 for Martin Lush, global vice president, Health Sciences, NSF International, who revealed that despite there being some successes for the industry over the year there were also some disappointments.

In terms of achievements, the pharma industry has surpassed all expectations in turning around safe and effective vaccines at ‘high’ speed and has coped with COVID-19 disruptions remarkably well, he emphasizes.

However, the fragility of the supply chains, as demonstrated by the pandemic, has persisted with continuing drug shortages occurring, and governments have failed at unifying efforts to make the whole population safe as is being proven by the Omicron variant. “We are not safe until we are all safe,” Lush adds. “This can only be achieved by a global collaborative focus on getting as many needles in as many arms as possible, starting with Africa. Africa will remain a petri dish for COVID-19 for decades to come. More variants are mutating away as we speak. Two things are certain for 2022: more disruption and more uncertainty. If I were a CEO, I would be obsessing about how I look after my people and how I become really agile.”

Gabriela Marton, director of Regulatory Affairs, Quality and Compliance at Arriello, also agrees that 2021 progressed as anticipated, due to the pandemic and resulting focus around vaccines development. “[2021] was a year in which all the important players in the biological pharmaceutical industry strove and, in some cases, succeeded in developing their own vaccines against the SARS-CoV-2 virus,” she says. “Those that had already achieved this in the previous year, meanwhile, continued with the task of gathering safety data to support the vaccination scheme.”

Furthermore, 2021 bore witness to restructuring of Big Pharma, in the guise of acquisitions and partnerships to support biotech business growth, thanks to the high demand for medicines to treat diseases in specialist therapeutic areas, such as oncology, autoimmune, metabolic, hormonal, cardiovascular, neurological, and inflammation and infectious, Marton states. “I would say that this is a continuation of trends seen during the past five years, but with a faster pace due to the pandemic,” she notes.

**Disconnects and promising aspects**

During the course of 2021, face-to-face events started taking place again after an unprecedented hiatus due to the pandemic. In attending a pharma conference, Lush revealed that despite feeling better informed on his departure, he was also highly concerned as delegates were seemingly discussing quite different topics and trends to those that were presented by the industry experts during the event.

“In short, the experts were focused on the science whilst those at the coal face were focused on their people,” Lush says. “[The workers] are worried about the possibility of massive attrition and the war for talent. They want to know more about organizational agility (via simplification), so they can pivot at the drop of a hat. They are having sleepless nights about managing, leading, and motivating their teams in a world gone crazy. They want to become expert ‘risk-based’ decision-makers. They want guidance on fast and effective change management. They want to make their organizations more risk smart and less risk-averse—but they do not know how to achieve this. The disconnect between the experts and the workers is now causing me sleepless nights!”

However, there will also be promising potential in digital technologies, according to Höning, who believes that technologies, such as artificial intelligence (AI), digital transformation, and cloud technology, will facilitate the translation of languages and provide industry with an open platform for discussion. This aspect will, in turn, accelerate drug discovery and development, as well as allow the decentralization of clinical trials, he states.

Additionally, personalized medicine will be a prominent trend in 2022 for Höning, who states that these medicines will help tailor options for patients and optimize the effectiveness of treatment and hence improve patient outcomes. There will also be implementation of the “lessons learnt during the pandemic,” Höning continues, which will afford the industry smoother approval and decision processes.

A continued focus on biotech, automation, and AI development will happen over the course of 2022 as a result of the high demand in certain therapeutic areas and the need for faster ways to collect and manage data, adds Marton. “Many big pharma companies will continue down the path of externalising services for small molecules and/or known molecules maintenance, to keep their focus on novel molecules,” she explains.

There is the additional prospect of the European market gaining more interest from start-ups from the United States and small companies that have a modest portfolio of innovative products thanks to the evolving legislation in the region allowing accelerated approvals, Marton continues. “The pandemic highlighted how quickly changes can be triggered, and I expect this rhythm to be maintained,” she says.

“The emergence of pre-competitive industry consortia is promising. During the pandemic, we have seen smaller consortia forming around co-development, and now with new technologies, we’re seeing a growing desire by companies to join forces so that they don’t duplicate effort via individual development programmes,” Schneider highlights. “We’re starting to see evidence of regulatory agencies working together more, which I hope will lead to greater convergence of regulatory...
The European industry is facing a number of challenges, which may prompt a fresh look at other regulators’ frameworks towards increased harmonization and reduced complexity.

Regulatory revisions
As mentioned earlier, the EC is seeking to overhaul the pharmaceutical legislation for Europe by the end of 2022. As a part of the changes, Schneider specifies that it would be good “to see the cost/benefit of a drug or therapy (the payer’s role) addressed in the same uniform way as risk/benefit (the regulator’s role) in Europe.” Under the current rules, reimbursement is a complex issue due to the fact that each member state of the EU makes its own decision on this matter, Schneider adds. As a result of this complexity, there can be much negotiation and, hence, delay in access to medicines, he explains.

“I’d also like to see novel methodologies finding a more permissive and open climate, so that there is faster regulatory action not just for advanced therapies and small and medium-sized enterprises, but also for academia, companies of larger sizes, and those working with other therapies,” Schneider says. “A review of incentives is needed: how much negotiation and, hence, delay in access to medicines, he explains.

“The pandemic showed that there is a need for fast evaluations, authorization, and decision-making, which the previous, 20-year-old legislation couldn’t provide for,” Marton emphasizes. “What I would like to see changed is the way that national authorities across the EU implement EU legislation. I would clearly want to see that done faster and more clearly, so that we avoid a long and ambiguous transition period. I would like to see more guidance from national authorities on how to fulfil local requirements.”

“The rules of maintenance of marketing authorization, especially the variation system, are complex and not currently easy to navigate,” adds Höngig. “And so, a facilitation of such rules would be welcomed.”

However, Höngig cautions that any revisions should build upon the existing legal acts that have already been implemented over the past two decades and proven to be a good basis for pharmaceutical legislation. “The revision should ensure a reliable EU regulatory system which is attractive in a competitive global environment with fast decisions and transparent approval times allowing for flexibility and lean maintenance procedures,” he says. “A revision of the variation system would lead to a more efficient procedure. Furthermore, the revision should take into account the technical development of the last decade and should foresee future developments.”

Schneider is encouraged by the fact that Europe is aware of the need for international regulatory convergence, which will help the EU become a more attractive market as it will be easier to navigate for companies with treatments already approved in other territories. “Patient centricity and empowerment are other big themes, and we’re seeing regulators becoming more directly involved here,” he notes. “For rare diseases, [patient centricity] is particularly important as a patient’s appetite for risk might differ from their doctor’s or a regulator’s, for example.”

Further issues that will be better addressed with closer collaboration of regulatory bodies and patient groups include the use of placebos and the issue of clinical trial readouts being subjective and possibly not standing up to regulatory rigour, Schneider confirms.

“Medicinal product research, development, and manufacture is a global industry, and the EU needs to help ensure that it remains attractive to both new start-up companies and Big Pharma. Most generic medicinal product manufacturing has already moved outside the EU with the resulting supply chain vulnerabilities,” Gough stresses. “If the EU gets the revised legislation right, the impact on industry should be positive, but if it just adds more complexity and restrictions, it will be very negative as the industry will continue to migrate to more agile regions.”

What the future may hold
European bio/pharma is a source for innovation and development for novel medicinal products, Höngig asserts, with many EU countries home to well-equipped manufacturing sites for bio/pharmaceuticals that are proven to manufacture high-quality, safe, and efficient products. However, more recently the vulnerabilities of the supply chain have become apparent,
mainly as a result of discontinuation of supply of important active ingredients or the needed finished products manufacturers in certain Asian regions, he specifies.

“The reasons for [these issues] range from a lack of raw materials, insufficient quality, price increases, problems in logistics, and political decisions,” Höning says. “In order to become less dependent on these numerous imponderables, and to be able to guarantee EU consumers a fair and necessary supply, pharmaceutical companies will relocate production or parts of it to existing manufacturing sites in the EU or will set up new manufacturing sites.”

Existing non-harmonized reimbursement procedures are of particular concern for Höning, who believes that in many EU member states, procedures are not fit for purpose and forming part of the underlying reasons as to why production is forced out of the region. “Certain regulatory flexibility will contribute to more security of supply,” he confirms. “Creating unnecessary regulatory and financial burdens for the industry will not contribute to a solution.”

The pandemic has clearly shone a light on some supply chain issues, concurs Schneider, not least of all the issues of shipping ‘fragile’ products, such as messenger RNA vaccines, across distance. “For gene or cell therapies—individually manufactured and with a very short shelf life—we see patients needing to come to the medicine, rather than the other way round. Either this requires a very rapid and solid supply chain, or the creation of special centres near hospitals where patients can readily access the treatments they need,” Schneider emphasizes. “An appropriate regulatory framework could help enable this.”

For Marton, a number of changes that have already been evident in the bio/pharma industry over the past five years will force companies to approach their business differently. “As mentioned, the pandemic highlighted the potential for and impact of accelerated development and approval; then there’s the growing emphasis on specialist therapeutic areas,” she says. “In addition, newly-implemented clinical trial legislation will come in to support companies’ growing interest in new and innovative products.”

In Marton’s opinion, 2022 will more than likely be the year when companies will need to define their direction and targets for the future. “Legislation will bring the need for greater transparency across the supply chain and product stocks, so we can expect to see companies preparing to implement the new rules, with execution over the following years,” she adds.

When predicting what awaits the industry for 2022 and beyond, Lush reveals that COVID-19 disruption is here to stay. How disruptive the virus may be, however, will depend upon the work of the governments around the world, he asserts. “One thing is for sure—the virus is not wasting time,” Lush adds. “Pasteur famously said, ‘the Microbe will always have the final word’. We have the science and the pharma industry to prove Pasteur wrong, but we just need the political will. The ability to pivot at short notice will be key, which requires simple systems, fast (bottom-up) decision-making, and a world-class change management system to keep track of everything.”

More drug shortages will be on the cards as China and India continue to prioritize meeting domestic demands, Lush continues. “Reshoring manufacturing to improve resiliency sounds great in theory—but will take years to accomplish. Supply shortages will be with us for some time,” he says.

Post-pandemic clearance of the backlog of regulatory audits will require a more nuanced (hybrid) risk-based approach, according to Lush, which could potentially affect compliance levels. “Within the next 15 years, medicines based on mRNA platforms and technology will account for 30–35% of approved meds and turn the traditional vaccine business model on its head,” Lush adds.

Pricing pressures will ramp up as governments attempt to pay for increasing healthcare costs with very little money, Lush remarks. As a result, companies will need to simplify and reduce costs or watch margins evaporate, he specifies. Governments will also increase pressure on sustainability issues. “Sustainability ‘words’ must turn into actions,” Lush stresses. “One of the major contributing factors to this pandemic is climate change. Shockingly, the pharma industry generates 11–12% more carbon emissions than the automobile sector.”

In addition to these trends, Lush expects there to be massive growth in in-vitro diagnostics and combination products as industry “moves from a treatment-based ‘disease care’ system to a ‘prediction and prevent’ healthcare system,” he notes.

Finally, Lush iterates the importance of ‘the people’ in 2022. “When asked ‘what it takes to manufacture high-quality medicines consistently,’ my great friend and mentor, David Begg, responded, ‘It is all about the people—stupid!’ Before we make medicines, we must make (and look after) our people,” Lush summarizes. “We have to rethink our recruitment and retention strategies to make our workforce more diverse in every regard. We need more rebel thinkers and fewer clones. We cannot solve many of the challenges we face with old thinking. Of course, you do not have to do any of this—survival is not compulsory.”

References
For oral dosage products in which a bitter API does come in contact with saliva and taste buds in the mouth, different sweeteners are often used depending on the dosage form, Guy says. For instance, Elizabeth Tocce, AD&I scientist, Pharma Solutions at IFF, points to the use of sweeteners, often in combination with texture modifiers, in orally dissolving tablets (ODT), chewable tablets, oral thin films, and sachet formulations that stay longer in the mouth.

“Taste modification using flavours and other additives is more complicated, though,” Guy comments. Even so, it is often needed. “In many cases, and for very bitter high-dose drugs in particular, just changing the organoleptic properties is not sufficient, and other methods to create a physical or chemical barrier around the drug particles, such as microencapsulation and complexation, are used,” Tocce explains.

The method employed largely depends on the API characteristics and the intended dosage form, agrees Krizia M. Karry, head of global technical marketing for BASF Pharma Solutions. “Poorly water-soluble APIs with adequate dissolution rates (i.e., BCS [Biopharmaceutics Classification System] II APIs) tend to be micronized and compressed into tablets. At low dosages, adding flavours or sweeteners can suffice to ensure palatability as most tablets are not meant to disintegrate in the oral cavity, but flavours will not suppress bitter tastes,” she says. At high drug loadings and for orodispersible products, Karry adds that film coating with methacrylate copolymers that are insoluble at saliva pH is the most effective technology.

If the unpleasant taste is related to grittiness or chalkiness in chewable tablets, ODTs, or suspensions, a common method is to use finer grades of the APIs and excipients, according to Tocce.

Liquid prescription drugs are particularly popular in the EMEA (Europe, the Middle East, and Africa) market, where there is a preference for the dosing flexibility and a perception...
that they offer rapid relief, according to Karry. In North America, meanwhile, liquids are mostly offered for over-the-counter cold and flu medications. In most of these liquid formulations, she observes that highly concentrated sweeteners and flavours are typically employed to mask the bitter API taste. In formulations where multiple APIs are combined including some that are bitter or where product shelf-life is of concern, however, Karry observes that insoluble polymers are used to envelop API particles and allow their suspension in the continuous liquid phase.

For liquids, other options if sweeteners aren’t sufficient, in addition to microencapsulation and complexation, include using an insoluble form of the API and adjusting the pH of the solution to lower the API solubility, according to Mahmoudi. She adds that viscosity enhancers and texture modifiers are also used. Alternatively, taste and appearance issues with liquid formulations can be overcome by containing them in soft or hard capsules.

Wide range of excipient choices

Many different types of excipients are used to improve taste and appearance. Because the most common taste challenge is the bitterness of APIs, sweeteners, both natural and artificial, are the most commonly used taste-modifying excipients. Beyond compounds such as sugar, mannitol and sucralose, actual flavouring agents (orange, mint, etc.), flavour-maskers, particularly bitter-maskers, texture modifiers (co-processed microcrystalline cellulose and guar gum), and polys are used. Complexing agents such as cyclodextrins and ion-exchange resins are often used for improving the taste of liquid formulations and orally dissolving dosage forms, Mahmoudi states.

“Depending on the formulation, different approaches to taste and flavour modification are needed,” Guy says. In fast-dissolve forms, short intense flavour bursts are needed, while in longer lasting products such as chewables, longer-lasting flavour effects are needed.

Hydrophobic (ethyl cellulose) or hydrophilic (hydroxypropyl methylcellulose, polyvinylpyrrolidone) polymers, lipids, and sweeteners can be used as coating materials, alone or in combinations, to modify both taste and appearance, Mahmoudi adds.

In addition to preventing an unpleasant taste, Guy notes that some coatings may also include pore-formers to help promote dissolution of the drug substance to meet standard immediate-release requirements for the API. “In such formulations, a careful balance must be achieved between taste-masking and efficacy. It is therefore a rich area of development given the complexity of drug particles and granules, varying solubilities, the need to often achieve a specific location of delivery (enteric needs for instance), and excipient compatibility concerns,” he comments.

For appearance, colour is most widely used to differentiate products and mask undesirable product properties.

For appearance, colour is most widely used to differentiate products and mask undesirable product properties. For solid dosage forms, colour is applied within coatings. For liquids, water-soluble dyes are generally employed.

Ultimately, Guy contends that the choice of excipients for taste and appearance improvement comes down to the preferred dosage form and the external factors that can impact the effectiveness of the choice, which include excipient compatibility, resistance to mechanical influence (granulation and tabletting), solubility, stability, etc.

Impact of need for patient-centric formulations

Because taste and appearance are important factors influencing the patient experience, it is essential for formulators to understand the preferences of different patient populations for drug formats and, within those preferred formats, taste and appearance qualities that will encourage good medication compliance. “Different patient groups based on their ages, disease states, cultures, and demographic locations may require certain taste, flavour, texture/mouthfeel, and drug product appearance properties, such as tablet size, colour, and shape for solid products and the viscosity and grittiness of liquid formulations,” Tocce asserts.

Flavour companies, adds Guy, are today much more attuned to patient and consumer preferences by gender, age, and other factors. “This information can and does help formulators and brand/product managers to make smarter decisions for taste and appearance as it relates to the intended patient or therapeutic group,” he says.

In particular, Guy notes that the need to create fit-for-purpose formulations for ageing populations and paediatric patients has put pressure on appearance as it relates to the size of oral solid dosage forms. For instance, important research conducted by academics and members of the European Paediatric Formulation Initiative has revealed that young children are more accepting of small or mini-tablets.

“Such a patient-centric approach definitely benefits patients, but it does present manufacturing challenges,” Guy states. “For example, it can be difficult when producing tablets that are 2 mm in diameter or smaller to achieve good flow through production equipment for APIs and excipients, which in turn impacts the ability to achieve good content uniformity and acceptable taste,” he says.

From a personalized medicine standpoint, it is also important to understand specific age-related elements of physical condition that might impact drug performance and the appropriate excipient choices. “For paediatric medicines, factors to be considered include
Karry, the formulator should ensure dose formulation. Usually easier to taste-mask a low-dose must also be considered; it is than irregularly shaped particles. The spherical particles are easier to coat specifically, Mahmoudi notes that the approach for taste-masking shape of the API can influence solubility determine which excipients, she states. Mahmoudi agrees. The characteristics of the API and the desired properties of the final product directly impact excipient selection, she states.

The first consideration, though, Guy emphasizes, is therapeutic benefit and efficacy, followed by safety, ease of use for the patient, and manufacturability. "We need to understand the target drug product profile when selecting a taste-modifying agent/approach to ensure drug performance is not negatively affected," Mahmoudi agrees. The extent and type of unpleasant taste associated with the API (bitter, sour, irritating) and its aqueous solubility determine which excipients will be appropriate. "It can be more challenging to cover the poor taste of a highly water-soluble API than that of a less-water-soluble active," Mahmoudi says.

In addition, the particle size and shape of the API can influence the approach for taste-masking and appearance improvement. Specifically, Mahmoudi notes that spherical particles are easier to coat than irregularly shaped particles. The dose must also be considered; it is usually easier to taste-mask a low-dose formulation.

In film-coating approaches, adds Karry, the formulator should ensure complete drug solubilization and absorption to achieve optimum bioavailability. "Doing so is especially important for reverse-enteric polymers, as they should quickly dissolve in the acidic stomach media to allow drug diffusion out of the coated core and absorption in the small intestine. Fast polymer solubilization is critical because the tablets and pellets have a short residence time in the stomach, and these polymers are not soluble in non-acidic media. In other words, if the film does not dissolve in the stomach, it will not dissolve anywhere else in the body and as such, the drug will not diffuse out of the protected core," she explains.

Appearance factors such as shape and colour can play a role in determining the correct identification and/or correct dosing material (syringe or spoon, etc.). In some cases, a certain format can address appearance concerns. For instance, Guy points to single-unit doses such as stickpacks as a potential means for enhancing identification through improved naming and ‘branding’ of the unit itself. He does stress, however, that care must be taken to ensure that these adult/senior-friendly products are child-resistant.

Experience and knowledge of patients best guides
For some excipients, such as those designed to improve API solubility, formulators have developed predictive algorithms that facilitate more rapid formulation development. Taste and appearance are more challenging, however, because often these qualities vary from one individual to another.

"Structuring data from humans and how they respond takes a great many data points and statistical analysis and remains subject to less-well-understood error knowledge. While augmented intelligence approaches can certainly help formulators make better choices sooner rather than later, there are too many unknowns, and the need for structured data is too overwhelming for good models to work at this point," says Guy.

The fact that there is no one method that can address taste and appearance properties in every oral medication makes predictive approaches difficult, Mahmoudi agrees. She does note, however, that evaluating literature reports and patient and caregiver surveys has revealed some general “dos and don’ts” that should be followed to achieve desirable taste and drug appearance.

Age is indeed one of the most important factors guiding excipient selection.

For example, Mahmoudi says that the use of a coating on tablets is preferred among older patients because it can help to optimize both medication identification and taste. “Elderly patients generally take multiple medications, and having tablets that are visually appealing and easy to identify and handle, such as with a score line for easy breakage and optimized dimensions and shapes that address dexterity issues, is important,” she explains.

“There are more preferences towards brightly coloured tablets and identification based on shape and colour for different indications to avoid medication errors,” she adds.

Karry disagrees with Guy and Tocce with regard to the ability to predict bitterness and believes the process for identifying if an API is bitter has rapidly progressed in the past few years. She points to BitterDB, a free database available to formulators with more than 1000 naturally bitter and synthetic compounds and the use of machine learning algorithms trained with known bitter API molecules that can predict the bitterness of new compounds. “Based on these predictions and additional physiochemical API properties, pharmaceutical formulators can proactively plan for their choice of taste-masking technology,” Karry contends.
The use of electronic tongues, however, has not been successful to date, says Karry, and the process to test and optimize taste-masked formulations continues to be reliant on trained human panels. E-tongues are expensive instruments based on capacitance sensors that are used to rank the bitterness of formulations, but have been shown to exhibit no correlation to the results obtained by human taste panels (1).

The use of human test panels presents its own set of challenges.

A new formulating challenge
The use of human test panels presents its own set of challenges, including a new one that has recently arisen. A study published in 2017 by Dagan-Wiener et al. showed that 66% of drugs in clinical and experimental stages at the time were classified as bitter compounds (2). The situation remains the same today, according to Karry. Many of the drug candidates under development today, however, are different because they have much smaller differences between their therapeutic and toxic doses (NTI-drugs), she says. "For these drugs, recruiting healthy volunteers for taste panels and ensuring no side effects after evaluation of test formulations has become more complicated," Karry remarks.

New technologies of note
Currently, conventional film coating and the addition of sugars, flavours, and sweeteners remain the common approaches to taste masking, but numerous other taste-masking techniques have been developed to address this challenging task, according to Mahmoudi. "Microencapsulation, high shear mixing, freeze-drying, fluid-bed coating, and spray drying have been successfully used to modify taste and making various dosage forms," she says.

In fact, Karry notes that there is a move away from the use of flavours and sweeteners to mask bitterness because studies have shown that sucrose sweetened medicines are associated with increased dental issues in children. Addition of acids to generate sour liquid formulations rather than bitter medicines, meanwhile, affects tooth enamel and causes dental erosion.

"For these reasons," Karry says, "film-coating approaches are increasingly used for taste masking of bitter compounds. Commonly used polymers include methacrylate copolymers such as Kollicoat Smartseal or Eudragit E-PO since they are insoluble in saliva (pH 6.2 –7.4), but readily soluble in the stomach."

Hot-melt extrusion and 3D printing for personalized medicines are emerging pharmaceutical technologies that Mahmoudi believes can be efficiently used to mask the taste of very bitter APIs. In particular, Mahmoudi notes that 3D printing is a powerful technique with the potential to enable the design of visually appealing tablets with modified taste.

With respect to advances in excipient technology, Mahmoudi points to the introduction of several taste-masking polymers with pH-dependent and independent solubility, new excipients such as co-processed microcrystalline cellulose (MCC) and guar gum, colloidal MCC, and many different flavours and taste-masking agents developed by excipient manufacturers as being tremendously beneficial in modifying taste and drug appearance.

For Guy, the use of taste-masking agents as ingredients, rather than simply applying a coating as a physical barrier, is transforming flavour and flavour perception.

"Such an approach has allowed us to tackle ‘off-notes’ in products, particularly in nutraceutical formulations. Specifically, combining bitter-maskers with an appropriate flavour combination helps to reduce or even eliminate off-notes to a background level that is tolerable," he says.

Orally disintegrating and dispersible solid-dose formulation have increased in popularity in recent years, creating challenges for taste masking and appearance. "It can be difficult to navigate the possible excipient choices and strategies that will ensure the desired product performance, for which there are numerous requirements and constraints," Guy observes. "Facing challenges is not unfamiliar territory, though, and formulators do have an extensive and growing toolbox of excipients that can be applied for these and other novel oral dose forms," he concludes.

Always remember: patients are people
When formulating any type of drug and using excipients of any kind, including for the modification of taste and appearance, the safety, regulatory acceptance, and daily allowable intake of each excipient must clearly be considered in addition to process and cost, according to Mahmoudi. "Beyond that, patient-centric drug design is paramount. There are great taste-masking excipients/texture modifiers and techniques that should be considered from the early formulation development steps when pursuing patient-centric solutions," she says.

In addition to ensuring safety and efficacy, Guy reiterates that the most important thing formulators must do for any drug product is to ensure that the patients and care-givers that will be using/administering the medicine will not be afraid or put-off by the nature of the drug. "It is essential to have and apply good people knowledge and consider different formulation options for different patient populations as dictated by their differing needs. Patients are people, and that must always be top of mind," he insists.

References
Tackling the Big Issue of Solubility

Poor solubility remains a big issue for drug development and, as such, is driving innovation in approaches and use of novel technologies to help overcome the associated challenges.

Felicity Thomas

Increasingly, poorly soluble compounds are forming part of the development pipeline, driving greater innovation in ways to overcome the associated challenges these compounds give rise to. To learn more about solubility and bioavailability considerations in drug development and innovations in the field, Pharmaceutical Technology Europe spoke with Kyle Smith, president and COO of Aprecia, and Jim Huang, PhD, founder and CEO of Ascendia Pharmaceuticals.

Still a big issue

PTE: Could you provide some insight into the issue of poor solubility/bioavailability and how it impacts bio/pharmaceutical formulation, both currently and into the near future?

Smith (Aprecia): Up to 40% of commercial products require solubility/bioavailability enhancement for sufficient exposure to achieve therapeutic action (1). For compounds in development, it is estimated that up to 90% require solubility/bioavailability enhancement (1). Development of products to achieve required solubility and absorption presents a critical challenge to clinical dosage formulation and process development, which can add significant time to early formulation development work. Furthermore, scientific rationale, quality-by-design, and quality risk assessments become more critical when trying to formulate poorly soluble compounds, as they are necessary to define the functionality, reproducibility, and assurance of consistent performance related to efficacy and safety to patient.

Huang (Ascendia): Poor solubility/bioavailability is still a big issue for drug discovery and development in a high percentage of small molecules and a portion of peptide and large molecules. Low solubility causes poor oral bioavailability and insufficient drug loading for parenteral dosage forms, which cause issues in generating enough drug plasma concentration that is required for drug toxicity and efficacy evaluation in preclinical and clinical studies.

Common approaches

PTE: What formulation approaches are employed to overcome solubility/bioavailability challenges?

Huang (Ascendia): Using our practice and experience at Ascendia Pharma as an example, typical approaches for solubility and bioavailability enhancement includes salt formation, micronization, solution, micelle, lipidic solution, complex formation; advanced technologies to address the challenge include nanoemulsion formulation, amorphous solid dispersion, and nanosuspension; new technologies, such as amorphous nanoparticles and lipid nanoparticles, have been proved useful for certain challenging compounds.

Smith (Aprecia): A number of approaches can be explored based on the API’s inherent physicochemical nature. Some current approaches include micronization of API, nanoparticles of API (obtained via ball mill, cryomills, jet mill, and Nanoform’s Controlled Expansion of Supercritical Solutions [CESS] technology), cocrystals, complexes, prodrugs, solubilization (lipids, oils, surfactants, absorption enhancers, etc.), and amorphous solid dispersions (e.g., hot melt extrusion, high pressure dispersions [DisperSol], spray-dried dispersions, drug layering on substrate). However, many of these approaches require a larger design space and/or minimal exposure to process stress to ensure optimal solubility/absorption is achieved.

Novel techniques

PTE: Could you highlight some novel techniques and how...
such techniques or disruptive technologies, such as three-dimensional printing (3DP), can provide formulation advantages when approaching poorly soluble compounds?

Smith (Aprecia): 3DP can offer many advantages, such as rapid formulation prototypes, fast-to-clinic and to-market via expedited timelines for clinical supplies and commercialization, a reduced development time, improved stability due to less aggressive processing conditions (e.g., less heat, water activity, pressure, particle deformation), and dose flexibility. Additionally, the technology is inherently suitable for process condition monitoring and advanced process control; there is the option for flexible controlled drug delivery if it is required, and it is a mature technology that has been proven for commercial product good manufacturing practice (GMP) manufacturing. Further to these benefits, the technology can provide unique branding and commercial imagery possibilities and a unique and pleasant patient experience that aids with compliance. It can be used to create easy-to-administer and swallow products that allow patients to overcome dysphagia, and is suitable for use when formulating drugs for most patient age groups.

Essentially, 3DP can expedite formulation development, potentially allowing clinical supplies with minimal excipients or solid oral dosage forms with substantially higher API content, which can be a limitation of conventional tablets or capsules related to swallowable size limitations. To take advantage of these benefits, Aprecia is partnering with technology companies, including Glatt and Nanoform, to develop novel dosage forms that help to overcome many of the challenges associated with conventional manufacturing.

Huang (Ascendia): Novel technologies such as 3DP may prove to be useful for orally disintegrating dosage forms for certain patient populations, who have difficulties with swallowing traditional oral solid dosage forms, as well as for drugs that need fast absorption and to bypass first pass metabolism. When evaluating a new technology, a tailored approach would be practical because every compound has unique properties, its own specific patient population, intellectual property strategy, dose amount, and manufacturing cost requirements, which may impact the selection of technology for use in dosage form development.

“New technology platforms provide opportunities for formulation and process development.”

—Kyle Smith, Aprecia

Novel excipients

PTE: Are there any limitations with the current availability of excipients that might hinder formulation of poorly soluble compounds? Might the new pilot programme for novel excipients drive innovation?

Huang (Ascendia): New excipients that improve solubility and bioavailability are certainly very welcome for use in dosage form development. However, expensive long-term pharmacology and toxic effects of novel excipients have to be evaluated using animal models before [the US Food and Drug Administration] FDA can approve them for use in humans, which could be a barrier to exploration of novel excipients for use in drug development.

Smith (Aprecia): A broad range of excipients used in approved products are available that provide broad functionality to support novel approaches for solubility and bioavailability enhancement. This approach can potentially provide intellectual property advantages. In general, and in the interest of time to market, complexity, and cost, the preference is to use materials already approved for pharmaceutical use within the maximum amounts established by the FDA. Novel pharmaceutical-grade excipients can be utilized when necessary but require additional testing to meet FDA regulatory requirements.

The future is here

PTE: What does the future hold for formulators in terms of poor solubility and bioavailability?

Smith (Aprecia): The future is here! Up to 90% of new compounds for formulation and process development require solubility/bioavailability enhancement. In addition, over half of new compounds are eligible for accelerated registration pathways. New technology platforms provide opportunities for efficient and effective formulation and process development to move compounds quickly through Phase Ia and Ib so ‘go/no-go’ decisions can be made quickly. With earlier decisions, resources for failing candidates can be quickly redeployed to other programmes.

Enabling Phase Ia and Ib product development programmes to be robust enough to move quickly into Phase II, Phase III, and commercial without reformulation or redesign of the manufacturing process is a key driver for technology innovation. In addition, continuous processing provides a further opportunity for eliminating the risks and costs associated with scale-up and technology transfer of conventional batch processes.

Huang (Ascendia): For most of the compounds in development, traditional technologies in combination with nano-based technology should be able to address solubility and bioavailability issues. New technologies and processes, such as amorphous nanoparticles, are worth exploring for certain types of compounds.

Reference

Continued process verification (CPV) for a cleaning validation (CV) programme begins once the validation study is complete. Planning for the CPV needs to be considered, however, as the cleaning validation is planned. Otherwise, the necessary parameters for the CPV might not be captured in a way to allow the smooth transition from the CV study to the CPV programme to maintain the validated state of cleaning.

Validating cleaning in a pharmaceutical manufacturing facility is a regulatory requirement (1–4). In regulatory guidance documents, programme basics, regulatory expectations including prerequisites, and acceptance criteria are reviewed along with the strategy for selection of the product(s) and equipment to validate. Although cleaning validation (CV) execution is described in general terms, guidance documents are limited to describing what to do, but not how to do it. The more recent the guidance update (2), the greater level of specific expectations are included.

The guidance documents include general instructions on how to proceed once cleaning validation is completed. The validated state of cleaning is to be monitored using ongoing testing of the cleaning process to demonstrate continued control of cleaning. This linear approach to cleaning validation resulted in the cleaning maintenance part of the programme being slowly neglected, resulting in programmes that fell out of compliance. The concept of lifecycle control of manufacturing process validation (5) addressed the shortcomings of the linear approach to process validation using Stage 3–Continued Process Verification (CPV). Using a similar approach, an ongoing programme to collect and analyze cleaning parameter data can be applied to cleaning validation. Although the lifecycle approach better addresses the post-validation cleaning programme, it still leaves the details up to the individual facility. And the concept of CPV is not mentioned until after the initial validation is complete.

Waiting for the completion of cleaning validation to address CPV will prove problematic as to how to document, gather, and trend the appropriate cleaning process data, critical process parameters (CPPs), hold times, and campaign lengths to clearly demonstrate continued control of the validated cleaning process. CPV is a factor to be considered as the cleaning validation strategy is defined. Addressing cleaning parameters for the long term needs to be addressed as part of the cleaning strategy. Otherwise, there might not be a viable mechanism to capture and trend ongoing cleaning parameters. The CPV strategy should address
what cleaning parameters to check only for compliance and what parameters to check for compliance as well as to track and check trends.

**Background**

To understand the issues of addressing CPV after completion of cleaning validation, start by considering the requirements for cleaning validation:

- The hardest-to-clean product(s)
- The lowest cleaning limit
- Equipment grouping
- Product/equipment matrix
- CPPs
- Demonstration of acceptable and consistent cleaning
- Dirty equipment hold time (DHT)
- Clean equipment hold time (CHT)
- Campaign length.

There are alternatives for establishing the products and equipment to execute cleaning validation, but a grouping strategy is accepted by the regulatory agencies (1–4) and is the most practical approach. A hardest-to-clean product for cleaning can be established using solubility of the formulation API, but this approach ignores excipients and practical experience. A more rugged approach is to look at the cleanability of the formulations using a three-prong methodology (6): formulation composition, personnel experience, and formulation cleanability.

The cleaning limit should be established for every product (6), and the lowest cleaning limit should be the target for the cleaning validation study. Equipment needs to be grouped for validation so that one piece of equipment is representative for the entire group. The product/equipment matrix, which contains the equipment train for each product, is used to decide the most efficient cleaning validation strategy to cover all products and equipment groups.

The product and equipment selection must be made before cleaning validation can commence. The cleaning data to demonstrate acceptable and consistent cleaning as well as the critical cleaning parameters (CCPs) (e.g., time) are captured during cleaning validation execution. The agreed upon DHT, CHT, and campaign length are targeted prior to execution and then confirmed during execution. The CCPs, DHT, CHT, and campaign length can be conveniently captured in the cleaning validation study protocol documentation along with the product and equipment being validated.

Once cleaning validation is successfully completed and a final report documented, the controlled, validated state needs to be maintained.

**Continued process verification**

**Product and equipment.** To ensure a smooth transition, a flexible plan or protocol to address CPV should be in place as the cleaning validation study draws to completion. The CPV plan should be drafted by the same team that implemented the CV programme and should address all the captured parameters and their ongoing status. The worst-case product, cleaning limit, and equipment grouping will not be affected unless a change is made to the validated state. Changes could include: a new product or a new piece of equipment is introduced; a change is made in a product manufacturing process or equipment configuration; or a product or equipment is retired from service. Any change should go through the change control system and an assessment made as to whether an additional CV study is required. The assessment should include an update of the original product or equipment assessment documentation. The assessment and document update should fall on the CV representative to the Change Control Committee.

**Critical cleaning parameters.** CCPs were established during cleaning development and are those parameters that have a direct impact on the level on cleanliness from the cleaning process. A clean-in-place (CIP) cleaning cycle records all cleaning parameters and issues a report at the conclusion. A manual cleaning procedure is a more problematic situation as far as identifying and recording CCPs. During development, it can be shown that detergent concentration and water temperature are not critical. Personnel can be trained and qualified for consistent cleaning. Minimum cleaning times can be established, and specific cleaning tools can be identified. During CV of a manual procedure, the CCPs can be recorded by an observer to corroborate the cleaning outcome. However, post-CV recording of CCPs falls on the personnel cleaning the equipment, which is problematic for someone wearing wet, soapy gloves and could lead to CCPs being captured immediately after cleaning.

Trending of CCP data is even more challenging. The CCP data must be extracted from the cleaning checklists, entered into a logbook or database, and trended over time.

**Acceptable and consistent cleaning data.** The CPV plan should include periodic testing of equipment after cleaning to demonstrate continued control of the validated cleaning. The frequency of the testing should be risk-based with the rationale clearly defined in the CPV plan. Factors that might increase testing frequency include manual cleaning methods vs. CIP methods; low cleaning limits; and CV data that passed but are close to the acceptable residue limit (ARL); all of which increase the risk of subsequent cleaning failures. Capturing and trending CV and CPV data is probably the clearest demonstration of continued control of equipment cleaning in the facility. All data should be trended to demonstrate consistency of cleaning. The challenge here is to update and maintain the CV database. Data processing and trending could fall on the personnel assigned to perform sampling or testing. An alternative would be to mirror the effort used to trend in-process manufacturing data.

**Dirty hold time.** DHT is established in the CV protocol execution. The end of manufacturing activity is recorded in the product batch record. After a designated DHT, the beginning of cleaning is recorded in the cleaning record or checklist. The executed CV protocol captures both times.
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and determines the effective dirty hold time. DHT is captured for the three validation runs, and the longest of the three is designated the validated DHT based on the equivalency of all CV data. A single DHT, which is applied to all equipment for all products, is applied going into the CPV stage of the cleaning lifecycle.

Post-validation, capturing and relating the two times with the established DHT becomes more problematic. The two times and DHT are in separate documents, and personnel filling out the manufacturing batch record do not see the cleaning record, while personnel cleaning the equipment do not have easy access to the manufacturing batch record. The established DHT is reported in the CV final report, and because the DHT is a cleaning parameter, the end of manufacturing time and established DHT need to be readily available to personnel performing the subsequent cleaning.

There are several options how to capture, maintain, and trend DHT data. A logbook kept with the equipment is the most straight-forward solution. The validated DHT is known and is recorded in the logbook header. The date and time of completion of manufacturing activity are entered each time the piece of equipment is used. At the beginning of cleaning, the date and time are recorded, the DHT is calculated and confirmed to be less than the established DHT.

A second alternative is to capture the DHT at the beginning of the equipment cleaning checklist or record. This would ensure that the DHT is captured but makes trending more difficult in that there is no centralized documentation of the DHT data in a logbook.

Attempting to trend the DHT data is more problematic, because collating DHT data from logbooks for all equipment or individual cleaning records is resource intensive. The best option is to periodically download the DHT information into a database for ongoing trending.

If an electronic manufacturing batch record is used and the equipment cleaning information is captured electronically, then DHT data can be captured. Trending of electronically captured DHT would have to be programmed to download and trend, but once implemented, would not require continued personnel involvement.

The value of the logbook option is limited because the records are paper-based and all entries and data analysis are handwritten. However, the advantage is that the logbook stays with the equipment and compliance is more readily confirmed.

Trending of DHT data provides another level of control to the CPV programme. If DHT times increase over time, trending could indicate a problem with scheduling equipment cleaning or manpower resource issues, which could be addressed before a DHT excursion by extending the DHT.

Alternatively, depending on how the equipment is handled at the end of manufacturing, it could be argued that DHT is not critical (7). If the equipment is scraped, vacuumed, and wiped down with solvent (e.g., 70% isopropyl alcohol) to minimize the amount of product residue left on the equipment, then the DHT might be a non-issue because the equipment would be rid of most residue and would already be dry. This strategy would minimize the API released into the wastewater stream during cleaning and limit exposure of personnel during cleaning.

Clean hold time. The issues for tracking and trending CHT are comparable to the DHT issues. CHT is established in a separate CV protocol execution. The end of cleaning activity is recorded in the cleaning record or checklist. After a designated CHT, the beginning of manufacturing is recorded in the product batch record. The executed CV protocol captures both times and determines the effective CHT. The CHT is captured for the three validation runs, and the longest of the three is designated the validated CHT based on the equivalency of all CV data. A single CHT, which is applied to all equipment after cleaning, is applied going into the CPV stage of the cleaning lifecycle.

The options to capture, maintain, and trend CHT data parallel those for DHT. For the logbook option, it might be able to capture both the CHT and DHT in the same logbook and trend quarterly. Downloading and trending the DHT and CHT from a logbook for every piece of equipment is labor intensive.

CHT criticality could also be minimized during validation (7). If CHT is established for an extended period (e.g., > 45–60 days), then equipment held in the same controlled conditions can be used up to the validated CHT.

For clean equipment held outside the manufacturing area, a standard policy of recleaning any equipment being brought into the manufacturing area is customary.

A second option to minimize concern for CHT post validation is to routinely rinse or wipe the equipment with 70% isopropyl alcohol immediately before use. This action further mitigates risk of bioburden proliferation during the CHT.

Trending of CHT data also provides a level of control to the CPV programme. If CHT times increase over time, trending could indicate a problem with scheduling of manufacturing batches or manpower resource issues, which could be addressed before a CHT excursion by extending the CHT through a protocol execution.

Campaign length. The maximum campaign length is established in the CV protocol execution. The number of batches manufactured and the length of time to manufacture are captured both on the equipment logs and the protocol. The campaigns are executed three times for validation, and the longest campaign length is designated as the maximum campaign length based on comparable cleaning data.

Post validation, the batch campaign length is known based on scheduling and equipment use. However, the length of time to manufacture a campaign is not typically noted and would normally only be unduly extended due to mechanical equipment issues. And while bulk hold times
are considered for manufacturing process validation, the potential effect of increased campaign time on the subsequent cleaning is not considered. One option is to have the equipment card designed to include a check of the maximum campaign parameters, both number of batches and number of days. The campaign data can be periodically downloaded into a database for ongoing trending.

**Non-compliance.** The risk of not complying with validated parameters is low as long as the validated parameters are readily available, limited in complexity (e.g., one DHT value of 10 days for all equipment), and the parameters are recorded contemporaneously. If there is a non-compliance with any parameter, it should be immediately recognized and addressed before a non-compliant situation develops. For example, if the DHT is exceeded, testing after cleaning can be arranged after cleaning to verify a successful level of cleaning before the cleaned equipment is used again. Additionally, if this type of occurrence could be addressed proactively and a protocol documented and approved prior to equipment cleaning, the cleaning data might be used to lengthen the DHT for the cleaning process. Any delay in recording data increases the risk of non-compliance.

**Non-compliance investigation.** If a non-compliance for a cleaning parameter is only recognized after the equipment is reused, an investigation is necessary. If a critical cleaning parameter (time, temperature, detergent concentration), DHT, or campaign length is non-compliant, then the equipment might not have been sufficiently cleaned, and carry-over into the next batch is possible. A risk assessment should determine the level of risk of the non-compliance. The higher the cleaning limit of the cleaned API, the lower the risk of unacceptable carry-over. Conversely, an API with a low cleaning limit increases the risk of an unacceptable carry-over.

If not already established, a visible residue limit (VRL) of the cleaned API should be determined (8, 9). If the VRL is lower than the cleaned API cleaning limit, it provides a clear indication that the visually clean equipment was sufficiently cleaned and further batch investigation might be avoided.

The cleaning records and equipment log need to be checked to verify the extent of the non-compliance and what subsequent batches are potentially impacted. As necessary, the subsequent batches should be tested for the presence of the carry-over API, which might require some analytical method development and validation. Personnel should be interviewed to determine the root cause and corrections implemented.

**Compliance verification vs. trending**

Verification of cleaning validation parameters on an ongoing basis is critical for maintaining the validated state of the cleaning programme. If a parameter is exceeded, then action must be taken to correct the non-compliant condition. The value of trending some cleaning validation parameters might not be as obvious. Certainly, trending cleaning data in the form of swab sample or comparable data results adds value in that it provides an ongoing picture of the consistency of cleaning and the level of risk for a potential cleaning failure in the future. But once cleaning validation is complete, cleaning data are not generated after every equipment cleaning. Based on the risk of a cleaning failure, the frequency of swab testing can decrease, and the lower frequency of cleaning data points presents a periodic snapshot of cleaning rather than a continuous record of equipment cleanliness. In addition, relying solely on cleaning data for CPV is akin to solely relying on release testing for manufacturing process control, which is not acceptable to the regulatory agencies.

Therefore, other cleaning parameters that continue to be captured after every post-validation cleaning become more indicative of continued cleaning verification. They include CCPs (times, temperature, detergent concentration as necessary), DHT, CHT, and campaign length. Along with a visual inspection performed by qualified personnel, trending of these parameters individually might not provide assurance of CPV, but taken together, provide a picture of a cleaning system that continues to be in a state of control.

**Conclusion**

Tracking and trending CPV parameters are necessary to demonstrate that a cleaning validation system is maintained in a state of control. Options are available, but the easiest path forward is often the more labor-intensive approach. Consideration for long-term use of CCPs, cleaning swab test data, DHT, CHT, and campaign length should be taken during the CV planning phase rather than waiting until CV is complete, to ensure a robust ongoing CV programme.

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Deployment of single-use technologies (SUT) has accelerated over the past few years as manufacturers adopt SUT at the commercial scale. The spike in demand has exacerbated an existing shortage of employees trained in the handling, installation, and use of disposable production systems. Knowledge transfer regarding how to use SUT must be achieved in a rapid and scalable manner to enable the workforce to operate good manufacturing practice (GMP)-compliant, aseptic, single-use bioprocesses successfully and reliably.

A collaborative investigation of the specific training requirements around SUT and key aspects of adult learning led to the joint development of an integrated SUT training approach by Lonza Pharma and Biotech and Pall Corporation. The programme relies on digital technologies, such as virtual classes, enhanced digital videos, and virtual reality, but also includes face-to-face courses and hands-on learning. The result is an effective, accelerated training programme with reduced time spent in cleanrooms.

In this two-part article series, the authors begin by exploring the reasons for the SUT training gap. Part one addresses why SUT training is crucial to biopharmaceutical manufacturing. Part two outlines the fundamental aspects of training related to adult learning principles, the value of digital and virtual learning elucidated, and an approach to training.

Addressing the Training Gap for Single-Use Technologies

Workforce training is crucial for biopharmaceutical manufacturing.

Michael Moedler, PhD, is head of Training at Lonza Biologics Operations Visp, and Helene Pora, PhD, is vice-president of Technical Communication and Regulatory Strategy at Pall Corporation.

From clinical manufacturing to full commercial upstream/downstream with fill/finish production. This move to SUT is occurring at a time when several drugs whose clinical batches were manufactured using SUT are receiving fast-track approvals and scaling almost immediately to commercial production.

Given the highly regulated nature of the pharmaceutical industry, including requirements for training of manufacturing staff according to current GMPs (CGMPs), effective and efficient training is essential. It imparts safety and quality as well. It has, in fact, become crucial to the continued, successful expansion of the industry considering that more than 40% of new hires over the next five years are expected to support bioprocessing operations (1).

Achieving the appropriate level of training during a period defined by rapid expansion combined with accelerated implementation of SUT solutions is creating challenges for many biologic drug and vaccine manufacturers.

GMP-compliant training methods

According to CGMP regulations, training is compulsory and must be properly documented to achieve compliance. New employees must receive adequate training to become competent to fulfil all tasks associated with their jobs. Despite the importance of ensuring employees have the knowledge required to perform their jobs safely and effectively, gaps in employee and contractor training remains one of the frequent observations that drug manufacturers receive in GMP compliance inspections by regulatory authorities (2).

There are several causes for the existence of training gaps. A general challenge is the need to get to the clinic and the market as quickly as possible. Training is planned, but with time of the essence and employee turnover combined with workforce shortages, companies easily find
themselves putting training off until there is “spare” time on the production line—a situation that is unlikely to occur any time soon.

In some cases, training gaps can be linked to the recent arrival of new equipment or the implementation of new manufacturing processes and/or introduction of products. Comprehensive employee training is essential under these circumstances to ensure reliability of supply and to stay fully compliant.

SUT-specific training challenges

Single-use systems are now widely used for all bioprocessing unit operations in the manufacture of biologic drug substances and drug products, including critical steps, from lab to commercial scale. Despite the extensive effort made by SUT vendors to ensure the integrity of their single-use systems and components, as illustrated in Figure 1, improper handling once the SUTs are in the hands of the end user can easily cause damage, leading to leakage/breakage of sterile barriers of SUT equipment and causing contamination and loss of product (3).

Most established commercial bioprocessing facilities were initially designed around the use of stainless-steel equipment for all aspects of manufacturing and waste disposal. Operators are familiar with these conventional processes, which largely involve making non-sterile connections and sterilizing assemblies afterwards.

In single-use processes, operators must unpack, visually inspect, and install large biocontainers as well as make sterile connections right first time, then disassemble and dispose the used biocontainers. This sequence of operations (see Figure 2) is clearly more complex with numerous manual operations than what is required for processes performed in permanent stainless-steel equipment. In addition, single-use materials become vulnerable once removed from the packaging; therefore, special precautions must be taken.

Operator training regarding the installation and use of SUTs is essential to ensure aseptic or sterile operation as well as avoiding damage that can lead to leaks, contamination, and ultimately to batch failures.

In a 2021 survey of biologics manufacturers conducted by BioPlan Associates, single-use biocontainer (bag) breakage was found to remain a key concern and one of the top three reasons preventing more widespread use of SUT (1). This concern is reasonable, given that integrity failure of single-use systems can have major consequences on safety, quality, delivery, and cost, negatively affecting employees and patients.

The same BioPlan Associates survey further found that operator error was considered one of the top causes of batch failures. Survey respondents said that approximately 4.3% of commercial batches and 3.5% of clinical batches at their facility were lost annually to operator error (1). Overall, it has been reported that approximately 50% of all deviations can be attributed to human error (4).

Any failures at commercial scale, in particular, are serious and costly. Leakage of a single-use bag was reported by BioPhorum (a global collaboration of biopharmaceutical industry leaders and subject matter experts) to cost from US$50,000 (€44,000) to more than US$20 million (€17.5 million) depending on the type of bag and the material it contains (4).

The expenses associated with single-use bag leakage can be numerous. Reprocessing is often not possible, and product marketing and sales can potentially be disrupted, which can be disastrous, both for patients and drug companies. Costly
Training alone will not solve all the challenges posed by the rapid adoption of single-use technologies in bioprocessing. History has shown that improving the design of SUTs and components and driving for more standardization both contribute substantially to reducing failure rates (6).

One of the first issues to address is the complexity of current SUT workflows and the need to design new workflows that better integrate with other bioprocess operations. Some areas that can be improved include organization of systems storage areas; materials interlocks; inspection area designs; and mobile equipment. These workflows can then be incorporated into training programmes.

Joint efforts by suppliers and end users under the auspices of BioPhorum have led to the development of good concepts geared toward performing root-cause analyses of SUT failures and new training tools (4). The development and deployment of effective training methodologies, however, has not yet been achieved throughout the industry.

When thinking about effective and fast SUT training deployment in the biopharmaceutical industry today, several important aspects must be taken into consideration:

• Most of new employees have limited or no experience in practical biopharmaceutical manufacturing.
• Training must be more self-directed when there are travel restrictions.
• Training must be available in several languages.
• Accessibility of actual installed single-use systems and cleanroom suites is limited.

It is important only to place operators in real situations once the discovery phase and initial training on basics and fundamentals are completed. Specially designed training rooms and practices will be required for this initial introduction to SUT handling.

In addition to training on SUT handling, it is essential to ensure that operators also fully understand the rules and procedures for maintaining aseptic conditions throughout a given bioprocess.

In the second part of this article, the authors will take a deeper look at key considerations for SUT training and the blended approach developed that shifts the “one-size-fits-all” training paradigm by combining digital and virtual learning with face-to-face hands on training.

References
The Need for Speed: How Operation Warp Speed Shifted the Pharma Industry

A new focus on speed to market creates challenges for facility design and construction.

Christa Myers
is a process chemical engineer for CRB.

During the COVID-19 pandemic, speed-to-market in drug manufacturing went from important to “mission critical”—and that is not changing anytime soon. CRB conducted a survey of 500 life and biopharma leaders, and when survey respondents ranked their pre-pandemic business drivers, speed-to-market came second-to-last. After the pandemic began, however, it shot to the top of the list of must-haves for drug developers (1).

This newfound focus on speed brings along some challenges. So what has the industry learned over a year and a half of “warp speed” vaccine development? How can those lessons impact drug discovery and manufacturing timelines? And what does the need for speed mean for the future of capital planning and project delivery in the pharma industry? To find out, CRB asked survey respondents how they plan to keep up with the pace of change and overcome obstacles. The following sections discuss some key takeaways.

Managing supply-chain risks
The pandemic brought the fragility of the supply chain to the forefront for many facilities. During the United States government’s push for vaccine development and manufacturing (dubbed Operation Warp Speed)—and partly because of it—capital projects struggled to acquire adequate construction materials and equipment. Then, as facilities shifted into startup and operation, teams were tasked with sourcing chemicals, commodities, personal protective equipment, lab materials, and other supplies amidst scarcity. Supply shortages and late deliveries plagued almost every project.

The industry, however, is proving to be nimble. In fact, 85% of survey respondents aren’t experiencing challenges as frequently as they were before the pandemic. It seems that drug companies and their project delivery partners have developed new and flexible strategies to navigate and de-risk their approach to resources, such as phased delivery.

Look ahead. The main key is putting those strategies in place early in the delivery process, so that companies can secure access not only to building materials during construction but also to the manufacturing resources that are necessary for startup and operation. These proactive strategies will help industry meet today’s project delivery demands, despite ongoing interruptions in the global supply chain. One of the more interesting supply chain shortages for the industry is the availability of glass for vials for parenteral products. There is an unmatched pressure on this part of the supply chain currently that is affecting all injectable products. It is even difficult to source non-production samples for machine design. This is driving innovation and is forcing drug delivery devices to change. Many companies that had shelved more novel injection devices are looking again at their research to be able to distance themselves from this glass shortage (1).

Take a phased approach. Companies of all sizes are now trying to establish relationships with the consulting, design, and construction partners they’ll need to meet their speed-to-market goals. Project delivery partners are still in short supply. The key to addressing this shortage is to find partners capable of keeping schedules on track by establishing a phased project delivery approach. A flexible partner can tailor their delivery roadmap to align with both the manufacturer’s target milestones and their own available resources, which could mean breaking the overall business case into discrete packages. For example, if the goal is to have a facility with four production lines running at full capacity in five years, for example, a partner could develop a plan to design and launch two production lines in the short term, while leaving spare capacity for future expansion. This strategy addresses a manufacturer’s goals in a way that’s realistic, controlled, and in tune with available resources and supply chain activity.

The digital future
The pandemic eliminated the luxury of time. It was no longer logical to wait for every piece of information before taking projects forward. CRB’s clients who...
Manufacturing

participated in Operation Warp Speed found that all of the various project components—design, engineering, construction, and vendor coordination, as well as all of the owner concerns—had to move forward in lockstep.

**Leverage online tools.** One of the secrets to success amidst accelerated timelines was fully leveraging online tools to coordinate activities and prevent pileups. Once social distancing came into play, face-to-face interactions were replaced with video calls. At the same time, teams made fuller use of programs to organize all project documents so everyone could comment or write on the drawings and sets simultaneously, and in-progress drawings were made available for early review. Additionally, video production equipment was leveraged to offer an overview of progress in real time and even perform equipment testing. Operations and maintenance personnel could be in one part of the world reviewing and testing equipment in a different part of the world, multiple time zones away.

At the same time, the design, engineering, and architecture teams leveraged various building information management and virtual design and construction programs to coordinate closely with trade partners and installation crews. This tactic allowed construction to begin much sooner than by using traditional delivery methods.

**Use of automation.** Social distancing changed the way manufacturing and lab spaces and the need for automation are perceived. Dissatisfied with traditional manual labour methods and galvanized by the need for personnel protection and uninterrupted production, many project leaders are turning to faster and more secure, of artificial intelligence and machine learning to build smarter, more secure, and future-ready manufacturing centres.

**A surge of interest in CDMOs**

Perhaps contract development and manufacturing organizations (CDMOs) have never shone brighter than during Operation Warp Speed. Even before they were faced with the urgent need for available capacity for vaccine candidate manufacturing, CDMOs were already expanding to serve unmet needs in the industry. When the unprecedented speed and scalability needed for COVID-19 vaccine production was identified, this capacity was relocated. More manufacturers of different COVID-19 vaccines are currently planning and building capacity. There is also planning to ensure future pandemics can be managed with research and development, and fast implementation for rapid manufacturing deployment. CDMOs also continue to add capacity to support manufacturing for earlier unmet needs.

Large companies are best positioned to limit their reliance on outsourced manufacturing. For one thing, they are more likely to have the capacity and the capital to vertically integrate certain operations—such as the critical fill/finish step. Startups, however, are especially dependent upon leveraging CDMOs because they are typically operating with less capital, less infrastructure, and a great deal of pressure from investors to get product to market as fast as possible. That’s likely why 73% of survey respondents from this group plan to rely on contract manufacturing organizations and CDMOs exclusively when it comes to production (1). But companies face a significant challenge: demand currently outstrips supply, and many contract manufacturers have prohibitively long lead times. In short, startups are competing for a few outsourced manufacturing slots.

**Form strategic partnerships.** The main solution to limited manufacturing opportunities is to work with a consulting partner who can help them accelerate the process of finding, prequalifying, and negotiating with appropriate and available contract manufacturers. A good partner will go even further, though, helping startups review their business case with alternative options in mind. If a drug developer faces a five-year wait for capacity with their CMO of choice, for example, but they could build a small-scale manufacturing operation in just two years, they may come out ahead; the value of getting their product to market three years sooner could more than offset the cost of constructing and operating their own commercial facility. And if they design future flexibility into that facility—by integrating multimodal equipment platforms, for example—they could be at an even greater advantage, particularly as they grow and diversify their product portfolio over time.

**Develop a long-term plan.** As they mature, many drug developers will choose to bring manufacturing under their own control, but this takes both time and capital. It’s therefore important to start with the business case first or the “why”. This not only brings value and innovation throughout the duration of the project, it also provides flexibility for many years to come. A relentless focus on the business case is key to controlling cost and schedule, reducing risk, and maximizing value. To succeed, these manufacturers will need a flexible, phased approach to project delivery that can withstand the pressures and turbulence of a market in constant motion without losing momentum. It is crucial to think about a speed-to-market strategy holistically and not simply in terms of getting to the next phase. Looking ahead to late-stage clinical or to good manufacturing practice manufacturing will help drug developers stay ahead of obstacles. The earlier that risk management practices can be integrated into plans, the more effective these plans will be in the long run.

The pandemic and its accompanying acceleration of vaccine manufacturing required drug manufacturers to rethink the way the industry operates as a whole. Moving COVID-19-related projects from kick-off to commercial manufacturing in record time required an enormous, coordinated effort, both from those inside the pharma industry and from the general public. And now, all things considered, it seems warp speed is the new cruising speed in life sciences manufacturing.

**Reference**

Biologics Testing Highlights Need for Analytical Skills

There is need for training personnel in various analytical skill sets for biologic drug substance testing.

Feliza Mirasol

The complexity of biologic drug substances requires specialized analytics and the training to do the analyses. It is not enough to know how to run the assays, but also how to interpret the data to give meaningful clinical value to the analyses. To gain insight into methods with which biologics drug substance testing results must be analyzed and interpreted as well better understand the challenges inherit in dealing with complex biological molecules, Pharmaceutical Technology Europe spoke with Khanh Ngo Courtney, senior director of Biologics at Element, and Mahesh Bhalgat, chief operating officer of Syngene International.

The need for skill sets

PTE: Is there currently a lack in lab personnel with the specific skill sets to interpret data from biologic drug substance testing? If so, what skills training is in most dire need?

Courtney (Element): More and more, we are seeing that the characterization and routine testing of biological therapeutics, particularly of advanced therapeutics such as gene and cell therapies, require advanced analytical techniques combined with a thorough understanding of biology, which requires specialized lab personnel. For example, enzyme-linked immunosorbent assay (ELISA) is becoming a less effective way to quantify host cell protein (HCP) clearance due to emerging data showing that antibodies generated against the HCPs do not provide sufficient host cell proteins coverage. Hence, a more comprehensive analysis of HCPs is required. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) is emerging as a needed analytical method to quantify and characterize HCP clearance. Finding talent who could develop and perform a robust, chemistry, manufacturing, and controls (CMC)-appropriate, quantitative LC–MS/MS method for HCPs is challenging.

Similarly, biological therapeutics require an in-vitro cellular assay to show potency during characterization and for release and stability testing. The design and development of the appropriate cellular potency methods, including the method for read-out, require personnel who understand the mechanism of action of the therapeutic, and how to exploit the cell biology toolbox to show in-vitro efficacy of the drug in a robust and CMC-appropriate manner. The appropriate skill set required to perform this type of work is not easy to find in one individual.

“The major challenge lies in interpreting data for its significance when it lacks large data sets generated over a period.”

—Mahesh Bhalgat, Syngene

Bhalgat (Syngene): Biological drug substance testing is rapidly evolving, and new platforms and technologies are being used for testing purpose to suit the needs of the assays and drug mechanisms. While many labs and lab personnel are technically sound, there is still a lack of understanding and decision-making on the use of analysis models for biological product characterization and for the mechanism of action (MoA) studies. We find the greatest shortage in laboratory personnel is scientists trained on the statistical designs, analysis, and validation of the qualitative assays.

Additionally, there is a lacuna in getting professionals with biologics analytical training, especially in the structural and functional characterization areas. Apart from the physicochemical area, there is a need to strengthen the knowledge base on analytical ion exchange chromatography and N-glycan analysis for glycosylated biologics.

Interpreting and analyzing the data

PTE: What have been some of the major challenges in interpreting and analyzing data generated from drug substance testing of biologic APIs?

Bhalgat (Syngene): Drugs, including APIs and biologics, must be manufactured in compliance with
appropriate quality standards. Some of the major opportunities associated with analysis and interpretation of data from testing of biologics include product- and process-related impurity identification and analysis, which is always challenging due to the specialized nature of testing; assay changes during stability studies due to noncovalent interaction-driven oligomer formation; and HCP analysis of in-process samples.

The major challenge lies in interpreting data for its significance when it lacks large data sets generated over a sustained period. Since monitoring and analyzing the trend of the data is important for biologics and other drugs, we apply quality-by-design (QBD) approaches for ensuring data interpretation and comparison needs are met.

Courtney (Element): The heterogeneity of the biological molecule impacts how methods are developed, data are generated, and interpreted. Large molecules are tens, if not hundreds, of thousands of small molecules chemically interacting with one another to form tertiary structures, which translate to function. Yet, not all the molecules in a solution of the drug substance are going to be exactly the same—they vary in the amount of post-translational modifications such as glycosylation, phosphorylation, and other chemical modifications as well as endured damages, such as amino acid deamidation, reduction, and oxidation. All of these chemical modifications together impact the structure of the biological molecule, its function, and how it interacts with other molecules in the cell and how it behaves in analytical methodologies.

PTE: What methods or approaches have thus far been successful in generating clinically meaningful data and analyses of that data?

Courtney (Element): Meaningful data in the clinic require that the appropriate biomarkers are selected, and the methods for detecting and quantifying said biomarkers are robust and sensitive. The Meso Scale Discovery (MSD) and Quanterix immunological technologies are common methodologies and have been successful in the analysis of clinical samples. LC–MS/MS, if available, remains a powerful tool for the analysis of clinical data for its sensitivity and robustness in detecting and quantifying not only large molecules, but small-molecule biomarkers.

“Current methods all have their own pitfalls.”

—Khanh Ngo Courtney, Element

Bhalgat (Syngene): In clinical research, obtaining meaningful data is built on several factors. Best practices that have been successful in generating clinically meaningful data and have aided the interpretation/analysis of the generated data include drug-specific pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity assays, rather than generic/off-the-shelf kit assays or methods. Validated methods are also required in assuring assay performance, as per expectations for the set dosage, administration route, and intended clinical interventions. In addition, a careful review of the clinical trial protocol early in assay development, including a two-way dialogue between the clinician and the bioanalytical scientist, helps in setting up fit-for-purpose methods for the relevant trial. Finally, paying special attention to the performance of the method for a particular trial subject population, their age, disease state, ethnicity, etc., helps in generating reliable data.

Meeting industry’s needs

PTE: Where is there the most unmet need in term of analytical solutions for complex and challenging biologic drug substance testing?

Bhalgat (Syngene): The bioanalysis of biologics requires the ability to use many different approaches, so there are many unmet needs. For instance, there is a need for high throughput automation and practical biostatistics for complex and challenging biologic drug substance testing. Meanwhile, immunoassays for biologics are labour-intensive and people-dependent. The move to much more automated technology for conducting sensitive and specific immunoassays is a clear opportunity. There is also a need for the availability of assays for biophysical characterization in the presence of various process matrices, host-specific, HCP assay, and non-destructive assay to understand the tertiary structure of drugs at the atomic level (for example, cryo-electron microscopy or single-molecule fluorescence techniques are yet not available for industrial use). Additionally, due to lack of proper guidelines, and there are differences in regulation across different geographies resulting in the development of varying approaches to testing products.

Courtney (Element): Highly complex biological drug substances, such as genetic information in the form of viral or nanoparticle encapsulated therapeutics (e.g., lentivirus, adeno-associated virus [AAV], nanoparticles), are extremely difficult analytically due to the heterogeneity in the quality of the drug substance. One example is the analytical challenge of separating and quantifying fill-amounts of viral particles (i.e., empty vs. partial vs. full). When AAV or lentiviral APIs are produced, the drug substance solution will comprise partially of viral particles containing the correct number of copies of genetic information, particles with too much material, particles with too few, and particles containing no material at all. Having the analytical capability and technology to obtain resolution between these different molecular compositions of the drug substance is still an unmet need. Current methods all have their own pitfalls. Analytical ultracentrifugation is expensive, not robust, and requires a significant amount of sample. Transmission electron microscopy is time-consuming and lacks quantitative power. High-performance liquid chromatography has poor resolution. Finding the right analytical solution for the intended purpose is unmet need for many quality-defining methods for advanced therapeutic molecules at the moment. PTE
J. Schniepp, distinguished fellow at Regulatory Compliance Associates. “I think many of the observations regarding insufficient quality are directed at this phenomena of companies producing products that are regulated and not understanding those regulations,” she says. Compounding pharmacies also got attention by the agency in 2021, with failures in aseptic and sterile manufacturing procedures a common notation on Form 483s (8–10). Some other common types of citations found in warning letters are listed in Table I.

Schniepp also sees the typical quality problems continuing in the future, including insufficient investigations, a lack of data integrity controls, not having adequate standard operating procedures (SOPs), and not following SOPs. “These issues have been responsible for the majority of observations in the past, and there is no reason to suspect that industry has solved these issues. I think one of the reasons for this situation is the industry doesn’t necessarily change their approach to certain key functions even as products and processes become more sophisticated and outpace a company’s ability to revise documents to keep pace with the product changes,” she says.

One of the common FDA observations in warning letters is the lack of adequate response to FDA 483 notices. “Effectively responding to a 483 and/or warning letter requires familiarity with processes, systems, and data because a proper response should address how you are going to fix the situation observed, how you are going to prevent the situation observed from recurring, and why the situation observed did not impact the patient safety/product quality of the product that was released before the situation was corrected,” says Schniepp. “I think many people forget to include this historical look back. Without this historical perspective, a response will never be sufficient.”

The pandemic created many challenges in 2021 for both pharmaceutical manufacturers and regulatory organizations. The quality of pharmaceutical products continued to be a focus, but many facility inspections were postponed in 2020, and US Food and Drug Administration (FDA) officials evaluated their inspection programmes during the pandemic and issued guidance for remote monitoring and other virtual activities (1–3). From March 2020 through March 2021, FDA conducted 821 mission-critical inspections (49 for human drugs, 10 for biologics) and 777 prioritized domestic inspections (106 for human drugs, 53 for biologics) (4).

In Europe, there were fewer regulatory inspections in 2020 than in previous years (5). Siegfried Schmitt, vice president, Technical at Parexel, feels the limit on in-person inspections might have a long-term impact on the expertise of quality personnel. “The current pandemic limits the opportunities for in-person meetings, visits, and travel. These have proven to be important elements of professional development, particularly for budding quality professionals, as these allow learning and experiences that cannot be conveyed through virtual/electronic means. This may limit the pool of experienced and seasoned quality and compliance experts in years to come,” he says.

These challenges have made the already difficult task of inspecting facilities more problematic. Regulatory agencies, however, worked to get back on track in 2021 (6).

Regulatory trends
The pandemic created another complication for regulators: a flurry of companies claiming to sell products to treat or prevent COVID-19. A good number of FDA warning letters listed on FDA.gov in 2021 appeared to be directed at facilities manufacturing hand sanitizer or other COVID-19-related products that were adulterated (7). Quality problems occurring within these companies entering the market showcase some of the problems regulators see in quality departments, according to Susan Haigney.

Quality Still a Priority
As regulators balance pandemic tasks and rethink procedures, quality at manufacturing facilities is still a priority.

Contin. on page 33
Outsourcing’s Race Toward Novelty

Recent developments in the outsourcing industry include a focus on early development services, biosimilar production, and RNA technology.

Bio/pharma is a fast-paced industry that is continuously innovating via new technologies and techniques. The determination of what, if anything, should be outsourced throughout the development, manufacturing, and commercialization process is subject to various interlocking factors that necessitate thoughtful consideration. What an outsourcing company can specifically offer over in-house offerings or cheaper competitors is crucial. Consequently, many outsourcing companies seek to adopt new technologies that can set them apart from competitors.

**Early development solutions**

Small drug companies own a large portion of the overall drug candidate pipeline, but they typically require more assistance throughout the early process to successfully bring their drug to market. Inexperience in regulatory filings, trial design, and other early design elements can doom a drug before development.

According to Jeetendra Vaghjiani, senior director of clinical development and strategic marketing at Lonza, emerging biotech companies are reliant on contract development and manufacturing organizations (CDMOs) because of their development and manufacturing capacity, expertise, and flexibility. These can prove pivotal in successfully bringing candidates to clinical trial, placing increased importance on end-to-end CDMO services (1).

In a similar vein, companies that can provide drug discovery solutions for these same, inexperienced start-ups looking to advance their product are also attractive. As companies enter the bio/pharma industry, CDMOs that can demonstrate repeated success in finding promising candidates will continue to get hired.

Armin Spura, CEO of Crown Bioscience, stated that a major advantage of outsourcing drug discovery is access to specialized technology and expertise. Because of the high attrition rate associated with drug development, the better your preclinical programme, the stronger the position you can establish in terms of programme design and patient identification (2). If one can improve their preclinical process with a CDMO, they will ultimately improve their chances of approval.

**Biosimilar production**

In recent months, biosimilar production has seen a boon in development. Following the Biologics Price Competition and Innovation Act in 2010, the US Food and Drug Administration (FDA) had approved just 30 biosimilars through 2020 (3). However, FDA announced the approval of the first interchangeable biosimilar insulin product, Mylan Pharmaceuticals’ Semgle (insulin glargine-yfgn), in July 2021. Since then, FDA has approved multiple biosimilars, such as Boehringer Ingelheim’s Cyltezo (adalimumab-adbm) for Humira (4) and Samsung Bioepis’ Byooviz (ranibizumab-nuna) for Lucentis (5). This situation presents a unique opportunity for the commercial viability of interchangeable biosimilars. However, because of the relative scarcity of approvals over the past decade, companies looking to capitalize on this new market are likely to require specialized knowledge to get through the approvals process.

Kelli Phillips, associate director of ImmunoChemistry at PPI Laboratories, noted that because contract research organizations (CROs) routinely support biosimilar product submissions to regulatory agencies, said agencies understand the current best practices expected by said agencies (6).

**mRNA Services**

Messenger RNA (mRNA)-based therapies took centre stage following the release of the Pfizer-BioNTech and Moderna COVID-19 vaccines. The development of these vaccines was built on over 50 years of foundational research into mRNA (7), but it is only after the release of mRNA vaccines that we have seen this rapid expansion in demand.

Moderna outsourced some production of its COVID-19 vaccine...
To CDMOs like Lonza, one of the world’s largest pharmaceutical services companies. Shortly thereafter, demonstrating one’s ability to provide some form of mRNA service became a hot commodity. In the past six months alone, large CDMOs, such as Samsung Biologics and Lonza, have advertised massive expansions of their mRNA manufacturing capabilities, which has been mimicked by various smaller companies scrambling to keep up (8, 9, 10).

The race to receive lucrative partnerships is on. While the industry is still in the infancy of this boom, as mRNA capabilities become a utility tool in drug development, CDMOs will attempt to present themselves as the best option for development and manufacturing.

References
5. PharmTech, “FDA Approves Biosimilar for Treatment of Eye Disease.”

As regulatory agencies work to combat COVID-19, facility inspections, either performed in-person or remotely, will continue to be one of the tools regulators use to ensure the safety of medicines. Inspections also provide pharmaceutical companies with the information they need to produce the most effective and safe products possible.

References
10. FDA, Form FDA 483, ACRX Specialty Pharmacy Inc, issued 23 July 2021.

Table I. Common trends in US Food and Drug Administration (FDA) warning letters in 2021.

<table>
<thead>
<tr>
<th>FDA comment</th>
<th>Date</th>
<th>FDA issuing office</th>
<th>Facility location</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>“It is a prohibited act under section 301(e) of the FD&amp;C Act (21 U.S.C. 331(e)) to refuse to permit access to or copying of any record as required by section 704(a).”</td>
<td>10/12/21</td>
<td>CDER</td>
<td>Portland, OR</td>
<td><a href="https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/healthmeds-lnc-614848-09292021">https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/healthmeds-lnc-614848-09292021</a></td>
</tr>
<tr>
<td>“We note that, while your firm is registered with the FDA as a manufacturer of GTC drug products, your website indicates your firm is also involved in pipeline operations and fracturing, also known as fracting. Fracturing operations typically involve multiple chemicals that could be harmful to patients if they were to contaminate drugs, such as your hand sanitizers.”</td>
<td>10/5/21</td>
<td>CDER</td>
<td>Midland, TX</td>
<td><a href="https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/trial-chemical-solutions-lc-616672-09292021">https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/trial-chemical-solutions-lc-616672-09292021</a></td>
</tr>
<tr>
<td>“Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d)(1)).”</td>
<td>9/21/21</td>
<td>CDER</td>
<td>Malaysia</td>
<td><a href="https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/truechemical-solutions-lc-616672-09292021">https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/truechemical-solutions-lc-616672-09292021</a></td>
</tr>
<tr>
<td>“Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.166(a)).”</td>
<td>8/31/21</td>
<td>CDER</td>
<td>Turkey</td>
<td><a href="https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/gulsah-unitem-kozmetik-sanayi-anonim-sirketi-611591-05132021">https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/gulsah-unitem-kozmetik-sanayi-anonim-sirketi-611591-05132021</a></td>
</tr>
<tr>
<td>“Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).”</td>
<td>8/24/21</td>
<td>CDER</td>
<td>Japan</td>
<td><a href="https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/truechemical-solutions-lc-616672-09292021">https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/truechemical-solutions-lc-616672-09292021</a></td>
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</table>

CDER is Center for Drug Evaluation and Research. CFR is Code of Federal Regulations.
**ASK THE EXPERT**

**Good Manufacturing Practice on Demand?**

Siegfried Schmitt, vice president Technical at Parexel, discusses the difficulty of operating non-GMP and GMP quality systems in the same facility.

**Q.** We have been manufacturing speciality chemicals for many years. Some clients have asked us to manufacture intermediates and drug substances for them in compliance with good manufacturing practices (GMPs). We are very interested to do so, but how do we manage two quality systems (GMP and non-GMP) within the same facility?

**A.** It is understandable that you wish to have a non-GMP quality system for your speciality chemicals business and a GMP system for pharmaceutical intermediates and drug substances, as these have a direct bearing on the cost of goods. Companies can certainly operate more than one quality system; the difficulty however is to operate them within one and the same facility. In short, I have never seen it work. Let us look at some of the reasons for this.

Your personnel will need to be trained in the respective quality system. Following a particular system requires more than training; it needs repeat experience (i.e., learning on the job). Having to switch between two rather different systems would be like having to cook over a campfire today and to prepare the same meal in a professional kitchen tomorrow. This is confusing, to say the least. Where GMP-trained and untrained staff work in close proximity, there is always a chance that untrained operators are called for help, thus creating a risk to product quality and compliance.

Your equipment must be suitably qualified, calibrated, and maintained to meet GMP requirements. Especially during times of high demand, the temptation is all too real to use unqualified equipment due to production pressure and looming deadlines. Or, if there is no clear physical segregation between non-GMP and GMP equipment, the probability to erroneously use unqualified equipment (in manufacturing or the laboratory) is unacceptably high.

You may require the same raw materials for pharmaceutical product manufacture and for other goods, yet in differing qualities (i.e., different specifications). It requires a very robust dispensing and documentation system to prevent any accidental use of raw materials with the incorrect specification. It is, however, not merely the use of the correct material that is of concern. You also need to consider the risk from accidental cross-contamination from non-GMP materials. Such materials may have unknown impurities, which may be difficult to detect and remove during cleaning.

Unless you have dedicated GMP and non-GMP equipment, there is a real risk of accidental cross-contamination.

Where things go wrong most often where more than one system is in operation is with documentation. GMP requires not only good documentation practice, but also must meet the strict requirements for data integrity. It matters for GMP products who performed the task, documented the task, and documented it contemporaneously. Yes, mistakes happen with GMP documentation too, but these errors need to be corrected in a controlled manner. GMP processes need to follow documented, controlled procedures and instructions, whereas non-GMP activities don’t. It is human nature to follow the path of least resistance. Thus, there is a real likelihood that staff may not want to bother with onerous procedures, particularly when there is a high workload and pressure to meet deadlines.

In summary, it is conceivable to have more than one quality system, but it is nigh impossible to operate them alternating or in parallel within one and the same facility. Physical and organizational segregation is a necessity, or deviations and costly mistakes will be encountered almost inevitably. PTE
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