The Shape of Dosage Forms

Development
Phage Therapy

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In April 2020, a clarion call by Outsourced Pharma set a major goal in "A Declaration of Drug Independence." This call sought to “… dedicate ourselves to the goal of reducing US dependency on foreign sources for drug materials, intermediates, substances, and finished products to 50% or less by the end of the year 2025" (1).

In hindsight, this looks prescient, especially as war in Europe now joins the pandemic to threaten access to essential medicines. What looks less than prescient was the frequently quoted response in May 2020 from the Pharmaceutical Research Manufacturers of America (PhRMA) whose core reply amounted to, “but now is not the time for sweeping changes to the pharmaceutical supply chain that could cause disruptions” (2). Even taken in context, it’s a paradoxical statement.

Eric Edwards, CEO of Phlow, is focused to rebuild the critical industrial base that’s been lost over decades, “to be able to manufacture these essential medicines end to end, from chemistry all the way to the finished dosage form so that we can get it to the patients at the bedside.” Phlow emphasizes continuous manufacturing processes to "allow chemical reactions to run on a much smaller scale, over and over again, until an entire volume of an active pharmaceutical ingredient is produced, [which] has significantly lower labor requirements [as it’s highly automated]. Then you have to get it into that finished dosage form, and we’re starting by focusing on sterile injectable drugs. The reason we’re focusing on sterile injectable drugs initially is because the majority of drug shortages in America are sterile injectables” (3).

There are still reasons to hold on to optimism. Various aspects of continuous flow manufacturing, now adopted at higher rates, allow for increased production while maintaining reasonable cost conditions. There have also been investments made on national strategies, from BARDA and BioMADE and with genuine leadership shown from the National Institutes of Health, National Institute of Standards and Technology, and FDA. But using all our logic while avoiding half measures will be required to get close to the outlined goal. One of the upsides of being a conservative industry should, theoretically, have been holding on to control more firmly.

Our exciting new podcast series Drug Solutions explores this topic in depth this March through a lively discussion with Dr. Fernando J. Muzzio, Distinguished Professor, Chemical and Biochemical Engineering, Rutgers University and Frederic Kahn, VP Sales, Wave length Pharmaceuticals. Both are well respected from many years of excellent and devoted service to our industry.

References
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As someone who helped invent and patent several types of biomedical instrument, I feel a traitor for writing the following: our market has unsurpassed need for fast, accurate analytic tools. While I can certainly see why some will resist or equivocate in response, this is absolutely an opportunity and not censure.

It’s not just that messenger RNA (mRNA) needs to be of genetic impurities like truncated transcripts or incorrect DNA template, or that wrapping it in lipid nanoparticle formulation for delivery creates more complex analytical challenges. Other recently created, small-molecule less celebrated drug formulations also had a need for new or more powerful analytic tools. Plazomicin (marketed as Zemdri), a novel aminoglycoside effective against gram negative bacteria, required novel modes for development and manufacturing, but it also benefited from a specialized analytic tool, the QMS plazomicin immunoassay (1), for measuring quantities in human plasma while treating complicated urinary tract infections, for which it was FDA approved.

As written elsewhere, there is now also an overarching business imperative to deliver products by continually breaking previous speed record barriers. Once the rewards for increasing patent lifetimes by being earlier to market became tangible, this has provided sustained business impetus to accelerate every aspect that could potentially slow deployment and delivery, hence parallel and redundant capacities and the investment in buildings, manufacturing equipment, and now analytic tools.

When married to increased drug novelty and rising complexity, requirement to have actionable data this hour, not this week, month, or quarter, further deepens this unmet need. In pharmaceutical analytics, this might well be just what the doctor ordered. Don’t get me wrong, I am delighted capillary electrophoresis has made a reappearance, and we’ve imported various stripes of particle size analysis from material sciences. But I keep a weather eye for novel analytic tools that might fill in that gap.

When readers send descriptions about good methods they’ve personally used, we’ll find a way to incorporate them in our coverage. That really should add intensity and drama to analytics, and a dash of new character!

Reference

Send your thoughts and story ideas to: cpsivey@mjhlifesciences.com.
2022 PDA ANNEX 1 WORKSHOP

Are You Prepared for the Annex 1 Revision? Get Ready with the 2022 PDA Annex 1 Workshop.

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New England Biolabs (NEB) Luna Probe One-Step RT-quantitative polymerase chain reaction (qPCR) Mix with uracil-DNA glycosylase (UDG) enables sensitive, linear, real-time detection of target RNA sequences in a room temperature-stable format. When measured in NEB’s “dot in boxes” scoring method—a high-throughput data visualization tool that provides quality scores for qPCR outcomes—the LyoPrime Luna outperformed many competitor products and strongly matched the company’s liquid mix, according to the company.

The lyophilized mix contains murine RNase Inhibitor, deoxynucleoside triphosphate, and a passive reference dye. It incorporates thermolabile UDG, which is well-suited to RNA workflows, as well as deoxyuridine triphosphate to reduce carryover contamination risk between reactions.

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The device can be combined with the Inert Gas Regulator, which acts as a regulated pressure interface between the RHGen and an external gas supply to allow inert gasses into the chamber. This allows the RHGen to replicate unique environmental conditions. It can also be used in conjunction with light microscopy, Raman, Fourier transform infrared, and X-ray for further sample characterization.

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A Rocky Road Ahead for Commissioner Califf

Jill Wechsler

Califf will face challenges that include COVID-19, opioids, and user fees.

The heightened political debate that delayed his Senate confirmation, plus continued challenges created by the COVID-19 pandemic, ensure that Dr. Robert Califf’s tenure leading FDA will be much more contentious than his previous stint. His Senate confirmation process was punctuated by sharp queries from both sides of the aisle about access to COVID-19 tests and therapies, agency policies for speeding new drugs to market, and FDA’s role in facilitating access to both long-acting opioids and to medicine to induce abortions, as the politicians sought to make points with constituencies leading up to mid-term Congressional elections in November.

That partisan tone was apparent in January 2022 as the Senate Health, Education, Labor & Pensions (HELP) Committee voted to advance his nomination as FDA commissioner by a close 13 to 8 margin (1). Final Senate approval by an historically narrow 50–46 vote came only after the White House and Califf’s supporters lobbied hard to gain sufficient support, a success that is very different from Califf’s 89–4 approval back in 2016. Four Democrats and independent Bernie Sanders opposed the nomination, citing Califf’s close ties to industry and his failure to halt access to opioids. Califf won the vote of Sen. Elizabeth Warren (D-Mass) and some others by agreeing to extend ethics restrictions on his future involvement with industry.

Califf will benefit from the experience of Acting Commissioner Janet Woodcock, who will remain at the agency as his principal deputy commissioner. Only six Republicans voted for confirmation, led by HELP Committee ranking Republican Richard Burr of North Carolina, who championed the appointment of his fellow Carolinian as a knowledgeable scientist and experienced policymaker. Most Republicans preferred to rail against FDA’s recent decision to remove curbs on prescribing and dispensing medications that induce abortion at early stages of pregnancy.

Approvals and access
Califf’s first order of business is to support the development and approval of drugs, vaccines, and diagnostics vital to taming the ongoing coronavirus pandemic. FDA’s recent decision to delay consideration of a COVID-19 vaccine for very young children indicates that many difficult scientific and legal issues remain on the agency’s agenda. Califf will benefit considerably from the experience and assistance of Acting Commissioner Janet Woodcock, who as agreed to remain at the agency as his principal deputy commissioner (2).

An immediate challenge for the commissioner is to revisit and clarify the risks and benefits of the agency’s accelerated approval (AA) programs and to ensure completion of required confirmatory trials. Califf promised such an effort to several uncertain Senators concerned about FDA’s approval of and access to the Alzheimer’s drug Aduhelm and about a proposal from the Centers for Medicare and Medicaid Services (CMS) to limit prescribing Aduhelm to patients participating in clinical trials. If adopted, the Coverage with Evidence Development requirement could apply to similar Alzheimer’s treatments moving through the R&D pipeline, which has raised fears of discouraging further research in the Alzheimer’s field by both patient groups and biopharmaceutical companies. The situation has fueled debate over FDA’s reliance on limited evidence in assessing new products under the AA process and the scope and timing of postapproval confirmatory studies. Meanwhile, the Department of Health and Human Services (HHS) inspector general is investigating the Aduhelm approval decision by the

Jill Wechsler is Pharmaceutical Technology’s Washington editor, jillwechsler7@gmail.com.
Center for Drug Evaluation and Research (CDER) and whether reviewers behaved properly in weighing the risks and benefits of the therapy.

**Patient advocates want FDA to increase diversity in medical product research and to advance treatments for rare diseases.**

Patient advocates also want FDA to increase diversity in medical product research and to advance treatments for rare diseases, improved antibiotics, and safer gene and cellular therapies. Pressure to help control the high cost of prescription drugs will continue to drive FDA support for developing complex generic drugs and biosimilars. FDA has taken action against scores of clinics and operations promoting unapproved COVID-19 treatments, many presenting serious health risks to consumers.

**Vast responsibilities**

Oversight of drugs and medical products is only one of many hot-button issues for FDA’s leadership to track and tackle. There is pressure to clarify rules governing e-cigarettes amidst concerns about flavored products luring young people into tobacco use. FDA also has to address serious health problems arising from contaminated food and seafood, including significant volumes of imported products. The safety of cosmetic products, dietary supplements, sunscreens, and other non-prescription products raise additional complex issues, many described in FDA’s annual report for 2021, which outlines these and several other high-priority regulatory programs (3).

Amidst all these programs, probably the most consequential assignment for FDA’s leader is to win Congressional support for agency funding and resources. This year that entails the timely approval of new user fee agreements on drugs, generic drugs, biosimilars, and medical devices as part of a larger legislative package that must be passed by Sept. 30, 2022. Califf comes to the job with valuable experience in these areas, which he will need to manage the many controversial decisions and heavy political pressures ahead.

**References**

Technological advances are helping shape the dosage forms of the future.

It is well-known that oral solid dosage (OSD) forms remain the market leader, with recent research estimating the market size to be worth nearly $8.5 billion by 2027 (1). “OSD forms such as tablets and capsules continue to be popular dosage forms in the healthcare sector being the preferred delivery system due to them being patient friendly,” confirms Anil Kane, PhD, MBA, senior director, global technical scientific affairs, pharma services, Thermo Fisher Scientific. “However, the number of biologics and large molecules is growing, and this is also seen in the increase in the demand for sterile injectable dosage forms.”

Impactful trends
For Cornell Stamoran, PhD, vice-president of Strategy and co-chair of the Catalent Applied Drug Delivery Institute, a key trend impacting drug dosage forms has been the increasing complexity of drug formulations. “[This increasing complexity has been] driven by strong pipeline growth of newer modalities and mechanisms, the need for targeted delivery, and bioavailability-challenged compounds, along with more frequent use of formulations and dose forms to enable patient self-administration, or reduce the complexity of treatment regimens,” he says. “We have also seen important progress in gene therapies using adeno-associated viral (AAV) vectors and lipid nanoparticles to deliver messenger RNA (mRNA).”

“A key consideration in my view is that, with the ever-increasing diversity and complexity of novel therapeutic modalities and APIs that must be injected to achieve efficacy, the need for sterile medicines will see a corresponding rise,” states Hanns-Christian Mahler, CEO of ten23 health. It is likely, he continues, that as a result of this trend there will be a drive towards easier-to-administer (or self-administered) medicines via devices, for example, which should improve compliance and overall therapeutic success.

“Ever-changing industry dynamics in recent years have had a considerable impact on the development and use of dosage forms for drug delivery,” specifies Jnanadeva Bhat, head—Formulation R&D (Pharma & Nutra), ACG Group. “One such change has been the improvement of existing products which can offer significant advantages, such as better therapeutic efficacy, whilst at the same time minimizing development expenses and timelines.”

As a result, Bhat continues, there has been an increase in the drug dosage form portfolio in general for the industry. Additionally, more research is being performed on larger and more complex entities and biologics so that challenges, such as solubility and bioavailability issues can be overcome, he states. “Low solubility molecules have been a major dosage form development challenge,” Bhat says.

However, Bhat points out that OSD forms have remained a stable trend with continuing popularity over the years. “There is continuous competition and
cover story: drug dosage forms

research in this area of pharmaceutical dosage forms to be ahead of the race, and also to reach a greater segment of the population," he states. "In particular, capsules have a multitude of benefits in terms of easier development and administration. The significant demand we are seeing right now creates room for more innovations across product lines."

"There is a strong desire to move from injectables to simpler oral administration; this would provide opportunities for life-cycle management as well as patient-centricity, especially in enabling technologies to allow oral delivery of biologics," emphasizes Ali Rajabi-Siahboomi, vice-president—chief innovation officer, Colorcon. "The oral route remains the gold standard. It considers patient convenience and self-administration, in addition to dose accuracy and speed of manufacturing of tablets for oral route."

"In 2020, oral solid products accounted for nearly 40% of the 53 novel drug products approved by the Center for Drug Evaluation and Research (CDER) (2). And of the 21 newly approved OSD products, 14 were tablets and seven were capsules," remarks Kane. "In 2021, the total number of approved drugs was 50, of which 52% (26 products) were injectable dosage forms and 46% (23 products) were OSDs (15 tablets and eight capsules), (3)."

Stamoran concurs that OSD forms are preferential, certainly for innovator small-molecule drugs, but for biologics there is strong growth in infusion delivery. "Across both small- and large-molecule injectable launches, the use of prefilled syringes and autoinjectors is increasing," he adds. "Also notable is a growing focus on dose forms that are most appropriate for pediatric and geriatric patients, driven in part by the increased expectations of regulators."

A trend that has been exceptionally prevalent in 2021 is the fast launch of vaccines to combat COVID-19, which have progressed from bench to use in billions of patients at incredible speeds, Kane stresses. "A direct impact of the pandemic is the increase in demand for sterile injectable dosage forms for vaccines in vials. There are many other vaccines and injectables in development, as well as clinical trials that have resulted in increased demand on capacity for sterile injectable formats," he says.

Another major trend has been the increasing complexity and risk of the drug product supply chain, asserts Thomas B. "Brad" Gold, PhD, vice-president, Pharmaceutical Development, Metrics Contract Services. "Fall-out from the pandemic, as well as other geopolitical dynamics will continue to impact the reliable supply of the many elements critical to finishing and dispensing drugs to patients," he adds. "Managing the longer lead times necessary for obtaining critical excipients and primary packaging for example will continue to challenge contract manufacturers and have the potential to impact market timelines."

"Many new chemical compounds have high potency and are sensitive to environmental conditions like moisture, oxygen, and heat, as well as potential interactions with other formulation components or gastro-intestinal environments, causing them to undergo oxidation, hydrolysis, or another degradation path," emphasizes Rajabi-Siahboomi. However, advances in computing power and new capabilities in artificial intelligence (AI) are providing opportunities for accelerated innovation in drug dosage design, he specifies.

Technological advances

"Technological advancement is supporting ongoing drug development and the manufacturing innovation needed to sustain it," continues Gold. "For example, we are seeing continuous improvement to critical processing approaches and techniques, especially handling complex and increasingly potent compounds. Equipment manufacturers are responding with system designs that integrate containment technologies to control operator exposure and prevent other issues like cross contamination."

Moreover, as manufacturing technologies evolve, manufacturers are afforded the opportunity to introduce new and improved processes and production efficiencies, which are supported through the technology’s ability to gather process data, Gold adds. "The more data these systems provide the more useful the feedback is at improving robustness and determining if the process capable of being validated in the first place. Best practice is calling for the increased application of process analytical technologies (PAT) for example, to support continuous improvement," he says.

"Digitization and automation can provide accurate and efficient support," agrees Rajabi-Siahboomi, who explains that it is possible to use technological advances, such as AI, to be able to screen and identify molecules that can be progressed further through development. "AI screening has a high potential for undruggable sites—the term ‘undruggable’ is used to describe a protein that is not pharmaceutically capable of being targeted; recently, however, substantial efforts have been made to turn these proteins into druggable targets. The resulting new compounds have high potency and may potentially be unstable," he says. "AI will enable better insight into identifying target proteins."

Additionally, Rajabi-Siahboomi notes that three-dimensional (3D) printing technology is gaining momentum within industry, for the purposes of solid dosage manufacture. "3D printing allows the production of tablets with more than one active substance characterized by different properties and with different dissolution profiles. It has good potential, depending on the production method, as it can provide unique patient-centric dosages and improve stability by producing individual dosage forms that can be presented to patients in a short time," he states. "This technology is still in development with some success in the nutraceuticals market and limited approvals in phama."

For Bhat, there are two ways in which technology has helped to shape dosage form evolution. "One aspect is related to operations and manufacturing, and the other is related to the research and development of novel dosage forms," he says. When considering the former—operations and manufacturing—Bhat reveals that through the various innovations in equipment and techniques it has been possible to accelerate processes. "Automation improvements have also been aimed at continuous manufacturing, maximum production yield, and minimum losses," he adds.
In terms of dosage form innovations, there are numerous novel ways to deliver, manufacture, and formulate therapeutics, Bhat continues. “For example, prefilled syringes and automated injectors for injectable dosage forms are accurate, reliable, and convenient. They reduce the need for medical supervision and facilitate easier self-administration,” he specifies. “In the case of oral delivery, nanotechnology in formulation development has emerged with many advantages in terms of increased efficacy and bioavailability of drug molecules. Thus, continuous innovation and evolution can reduce or bridge the gap between demand and developmental challenges in dosage forms.”

There have been significant advances in drug delivery thanks to innovation in materials science and manufacturing processes, explains Stamoran. “For example, development of new softgel capsules now allow these dose forms to offer inherent enteric protection and extended-release formulation,” he says. “We have also seen innovations in functional coating technology, non-glass alternatives for injectables, and new excipients, which can enhance a drug’s performance or even shift treatment regimens to less invasive routes of administration.”

Furthermore, process innovations are enabling development progression, such as the improved scale of production for therapeutic proteins thanks to breakthrough cell-line development, Stamoran points out. “Additionally, equipment and process innovations have enabled critical scale-up increases for AAVs in the field of gene therapy, while the potential implementation of continuous manufacturing in both API and dose form manufacturing also continues to progress,” he adds.

According to Mahler, it can appear that there is limited innovation in the area of sterile products, as a result of the reliance of pharmaceutical products on prior use to ensure safety and regulatory compliance. “Lyophilization remains the drying method of choice for products that require drying; primary containers are typically made of glass; there aren’t really any novel formulation excipients,” he notes.

“At the same time, technology has advanced very significantly,” Mahler asserts. “And whilst innovation may not be apparent at first sight, it surely is on the second: the understanding of stabilization mechanisms has significantly grown, we now understand the role of some excipients like polysorbates in the formulation, we understand the various interactions between the process and the formulation and the packaging components. Hence, development of sterile medicines has become much more informed, enabled by analytical technologies.”

Kane believes that there will be a notable change in the dosage forms under development thanks to technological advances and improved understanding of processes. Areas of particular interest for Kane are biologics in OSD forms and the oral delivery of human microbiome and probiotics.

“Increased knowledge of technology and processes such as lyophilization, cryo-protection, targeted drug delivery, [and] in-vitro simulation models coupled with unprecedented recent developments in materials such as surfactants, permeation enhancers, polymers, muco-adhesive materials, and so on, are propelling advances in these areas and are likely to make oral delivery of biologics, microbiome, and probiotics a clinical reality,” Kane says. “Advances in specialized processes such as spray drying and lyophilization will help formulating peptides, oligonucleotides, enzymes, and proteins into stable solid or liquid states that can be formulated into capsules or tablets.”

**Impactful solutions**

Prominent technological advances, such as AI, additive manufacturing, blockchain, and other Industry 4.0 technologies, are impacting various aspects of drug development confirms Rajabi-Siahboomi. For example, AI is providing industry with more efficient ways of isolating potential clinical candidates and continuous manufacturing is offering cost and time-efficient production of therapies, he states.

Extrusion technology is an invaluable resource to help developers enhance material properties so that innovative manufacturing techniques, such as 3D printing, may be employed, Rajabi-Siahboomi continues. “Hot melt extrusion (HME), which enhances material properties, is emerging as a key technology for the continuous manufacture of drugs within the pharmaceutical industry. One notable advantage is the ability to produce a variety of formulations, such as solid dose forms, which improve drug bioavailability,” he says.

“Also, inline PAT tools can be integrated with the HME process to support a quality-by-design (QbD) approach to continuous manufacturing,” Rajabi-Siahboomi explains. “HME extrusion has been shown to molecularly disperse poorly soluble drugs in a polymer carrier, increasing dissolution rates and bioavailability. The most common difficulty encountered in producing such dispersions is the stabilization of amorphous drugs, which prevents them from recrystallization during storage. Advances in both materials and equipment have increased the development of equipment and chemicals for specific use with HME.”

Digitized solutions that can provide useful information, such as digital pills, smart pill, smart medicine, and on-dose authentication, are considered to be of importance by Kane. Digital pills—where an ingestible sensor is embedded in a pill—can be used for the provision of data on the administration of the therapy as well as the physiological condition of the patient, he explains. “Ingestible sensors in smart oral drug delivery dosage forms such as tablets and capsules will revolutionize diagnostics, clinical monitoring, data collection, and data analytics in the health care industry,” Kane adds.

“Smart medicines are a digitized form of traditional medicines. There are typically two components required to digitize a medicine—a target and a sensor,” Kane continues. “With smart medicines, the target is applied directly to the medicine via a coating or ink, and the sensing device (a cell phone application) is used to read the medicine and convert the signal into a digital format in a matter of seconds.”

On-dose authentication technologies can help to monitor patients and their administration of a therapeutic regimen, as well as ensure the medicine is authentic. The technology incorporates...
identification, such as bar codes and spectral images, on the dosage form, Kane specifies.

“A variety of formulation and manufacturing strategies are supporting more accurate, controlled OSD delivery to improve efficacy and patient outcomes,” emphasizes Gold. By way of example, he highlights how mini-tablets are emerging as a format that can provide an increased patient-centered dosing experience. “Configurable in single- or multiple-unit oral forms, mini-tablets have enormous potential to promote dosing flexibility and target dose forms to meet the unmet needs of different patient populations, like children or patients who have trouble swallowing,” Gold says. “Because of their size, usually less than 3 mm or less, these forms can be used to accomplish a number of oral drug delivery strategies.”

The most impactful dosage form technology for Anita Solanki, lead—White Papers, Formulation R&D (Pharma and Nutra), ACG Group, has been fixed-dose combinations (FDCs). “Combining two or more drug molecules can offer improved efficacy, as opposed to increasing the dose of a single drug—this is known as the synergistic effect,” she specifies. “To sum up, minimized drug resistance, maximized patient centricity, and the synergistic effect are the advantages for FDC in drug delivery.”

“For small molecules, the most significant changes in the time I have been involved in drug delivery are the advances in characterizing and addressing bioavailability challenges for oral delivery, which have become increasingly prevalent in the industry’s pipeline compounds,” states Stamoran. “Starting with better assessment tools to predict bioavailability characteristics, to a more comprehensive technology toolkit to solve the issues noted, the path to addressing these challenges today is far easier than in the past.”

In the case of large molecules, Stamoran highlights three developments as being most impactful: “the advances made in design, manufacture, and use of AAVs for gene therapy, including increasing understanding of patient safety-related factors of high-dose therapies; the large-scale clinical validation of lipid nanoparticle-based delivery of mRNA (COVID-19 vaccines); and the emerging opportunity for linkers and a site-specific bioconjugation technology, with a wider therapeutic window and improved manufacturability of antibody-drug conjugates,” he says.

**Trends for the future**

“There is a conspicuous move in the direction of personalization and customization of treatment for the coming decade. 3D printing techniques are important in the field of pharmaceutical applications because of the possibility of faster formulation of tailor-made medicines which can be employed in personalized treatment,” notes Solanki. “Patient-centered dosage forms could be developed via 3D printing. Not only personalized dosage forms, but also different drug combinations, shapes, and release patterns can be achieved with 3D printing technologies.”

Inhalation as a drug delivery route is undergoing extensive research and will remain a hot topic for the future as it is no longer restricted to respiratory disorders alone, remarks Solanki. “Capsules based dry powder inhalation formulations are one of the preferred choices, because of their affordability in comparison to other inhalation dosage forms. Inhalation device and product combination will make sure that an unskilled patient receives the intended effect, whilst also being easy to handle and carry,” she says.

Gold expects there to be two trends in particular that will be influential on dosage forms and formulation over the course of the next decade. He believes that medicinal chemists will be increasingly able to understand the genetic resistance (or lack thereof) to certain compounds and that it will be possible to rebuild lost tissue, treat joint and bone pain, and many other diseases and conditions, thanks to advances in autologous and allogenic regenerative stem cell therapies.

“The continuing evolution of emerging modalities will continue to push delivery technology innovation needs, to deliver to specific targets, enhance safety profiles, and ensure manufacturability and patient usability,” stresses Stamoran. “Sustainability continues to grow in importance, both in terms of raw material production/green chemistry, and the operation of development and manufacturing activities. Finally, there are active legislative proposals in the [United States] that may establish an FDA pathway for new platform technology review, providing a smoother route for rapid adoption of innovation.”

Smart medicines and, more specifically, on-dose authentication, will be trending in the future, according to Raja-Jabi-Siahboomi. Through these novel technologies, not only is it possible to deter counterfeiters, but it is also possible to help patients engage better with their medicines, he specifies. “In other words, ‘smart’ medicines not only bring authentication closer to the patient but also help them feel more comfortable with how they take the medicine,” Raja-Jabi-Siahboomi states. “Non-adherence is a huge challenge for healthcare systems and patients may have many reasons for not taking their medicine. All patients can benefit from greater information and support that ultimately improves safety and adherence.”

For Mahler sustainability should be a primary consideration. “My perception is that many companies have excused a lack of product sustainability focus with the need to treat the patient(s). In my view, both aspects should not be mutually exclusive,” he summarizes. “Cradle-to-grave considerations for modern dosage forms are required to be embedded early in development. And this should and has to go way, way beyond CO₂ emission calculations and offset.”

**References**

Bacteriophages could be crucial weapons in the fight against antibiotic-resistant bacteria.

Treatment of bacterial infections with bacteriophages (phages)—viruses that enter bacterial cells and rapidly multiply, quickly rupturing the cells and destroying the bacteria—has been known to be effective since the early 1920s. The advent of broad-spectrum antibiotics led to a halt in phage therapy research, however, except in Eastern Europe, particularly Georgia, and to some extent France (1).

Bacteria, meanwhile, have developed resistance to many antibiotics, and new “superbugs” that cannot be treated with even the most powerful antibiotics are increasingly common. There is real potential that the world could enter a post-antibiotic era in which giving birth or getting a simple cut could present a serious risk of death. The situation is exacerbated by the fact that antibiotics have long since been commoditized, and most major pharmaceutical companies halted their antibiotic development programs in favor of investments in more lucrative areas such as oncology. Few new antibiotics drugs have been approved as a result.

Consequently, the need for alternatives to traditional antibiotics has become urgent. In addition to leading to the development of novel chemical approaches, the current threat of antimicrobial resistance is driving renewed interest in phage therapy. A lack of appropriate infrastructure and specific regulatory framework are two main challenges to the realization of marketed products. Fortunately, developers of phage-based treatments expect these hurdles to be surmountable in the medium term, with several candidates in or soon to enter clinical trials.

Drug resistance not the only driver
Fighting bacteria that are resistant to current antibiotics is what most people see as the main driver of interest in the development of phage-based therapies. For Alexander “Sandro” Sulakvelidze, president and CEO of bacteriophage developer Intralytix, there is another important factor: growing understanding of the human microbiome and its role in health and disease.

“The microbiome field is exploding, with a lot of bright minds working in the area. People are establishing links between microbiome composition and diseases ranging from those having obvious bacterial etiology (e.g., infectious and gastrointestinal diseases like bacterial dysentery) to disorders that are not typically associated with bacterial infections, such as obesity, cancer, and others,” Sulakvelidze explains. “That means that with bacteriophages we not only have the potential to manage drug-resistant infections, but also a tool that may be able to beneficially modulate the microbiome to address both infectious and noninfectious diseases,” he states.

Indeed, the human microbiome comprises hundreds of bacterial species, and maintaining the right balance of “good” and “bad” bacteria in the gut microbiome helps maintain health through multiple mechanisms including modulation of inflammation and regulation of protective gastrointestinal functions, according to Sulakvelidze. “Lytic bacteriophages are superbly suited for gentle and targeted fine-tuning of the microbiome by killing their specific targeted bacterial pathogens without disturbing the normal microflora—a unique biological property that is increasingly explored for developing novel tools for microbiome modulation and research,” he observes.

Different mechanism of action
While broad-spectrum antibiotics are attractive because they can be used to treat a wide range of bacterial infections, they also do not discriminate between “good” and “bad” bacteria. Dysbiosis and secondary infections (e.g., fungal infections, inflammatory bowel disease, reactive arthritis, etc.) can occur as a result, complications that have not been observed with phages (1). Phages could also be ben-
As a result, while bacteria can become resistant to antibiotics, the mechanisms involved are very different from the one against phages. “The resistance that bacteria develop to antibiotics does not affect their resistance to phages, making these two approaches complementary,” Sulakvelidze observes. Indeed, often phages can be effective against bacteria that have developed resistance to antibiotics. There have been several case reports of the effective emergency treatment of patients for which conventional antibiotics have failed (1).

Specificity a two-edged sword
The specificity of phages is advantageous because it does not result in the death of desirable bacteria. It is, however, one of the reasons that phages fell out of favor after the introduction of antibiotics. For phage therapy to be effective, it is necessary to know which bacterium is causing the infection, which is not the case for broad-spectrum antibiotics, according to Sulakvelidze. It can take time to identify the specific phage or cocktail of phages that will be effective, time that some patients may not have, particularly in cases where phages are used as a treatment of last resort (1).

Antibiotics creating problem and inhibiting alternative solutions
Another difficulty facing the advance of phage-based therapies is the fact that the medical infrastructure that exists for the treatment of bacterial infections in most of the world has been designed around antibiotics (2). From susceptibility testing kits to the sophisticated machinery required for high-throughput testing and the training of hospital and clinical personnel, everything is geared toward antibiotics, Sulakvelidze comments.

“The business model for phages is very different from that for antibiotics, which creates a whole range of challenges from manufacturing and distribution to diagnosis and identification of the right phage treatment for each patient,” says Sulakvelidze.

The need for alternatives to traditional antibiotics has become urgent.
For Grégory Resch, head of the laboratory of bacteriophages at the Center for Research and Innovation in Clinical Pharmaceutical Sciences at Lausanne University Hospital, Switzerland, one of the biggest challenges is the complexity around producing many different specific phages under good manufacturing practice (GMP) conditions, which contrasts with the existing access to broad-spectrum antibiotics. He also notes that patenting phages is not as obvious, because many of them can easily be isolated from the environment.

Phages are manufactured via fermentation using the bacteria that serve as the natural host of the phage in question. The phage reproduces, killing the bacteria. The phage must then be separated from the dead bacteria and purified, as the dead bacteria and other contaminants can cause undesired immune responses. Fortunately, advances in fermentation technology and downstream processing have enabled successful, large-scale production of high-quality phage-based products, according to Sulakvelidze.

Production challenges, although they are being addressed, are further complicated by a lack of an established regulatory framework for the approval of phage-based therapies. The absence of a clear definition for bacteriophages, common and validated dosage protocols, and the length of phage treatments, for instance, creates uncertainty with respect to the development of clinical programs (2). On the positive side, however, many of the disadvantages of phage-based therapy relate to infrastructure and knowledge gaps that can be resolved as the field progresses.

Even so, Sulakvelidze comments that the advances Intralytix and other bacteriophage developers, such as Adaptive Phage Therapeutics and Armata Pharmaceuticals, have made have taken longer than he anticipated. “Even with the many years of work and growing number of companies involved in the field, it will still be many years before phage-based therapy becomes a mainstream treatment or at least somewhat commonly used,” he contends.

Surmounting roadblocks step by step
Intralytix was formed in 1998 by Sulakvelidze and his post-doctoral advisor Glenn Morris, an infectious disease specialist who had a patient die after a sophisticated surgical procedure due to a drug-resistant infection of the intestine—and who was not familiar with phage-based therapy. The initial goal of the company, says Sulakvelidze, was to develop phages to treat infections caused by vancomycin-resistant bacteria called enterococci or VRE. It became quickly apparent to the founders that the time was not right for targeting clinical applications given the long list of challenges for human medical applications.

Instead, Intralytix shifted its focus to food safety, which has given the company time to establish greater knowledge, build a manufacturing facility and develop effective production processes, work with regulators, and establish some of the infrastructure needed to support phage-based prod-
ucts. Its first commercial product was ListShield, an all-natural, non-chemical antimicrobial preparation for controlling the foodborne bacterial pathogen Listeria monocytogenes.

Today, Intralytix is using the sales revenues from its portfolio of phage-based food protection products to support the development of nutraceuticals and drug candidates. The company will launch its first dietary supplement/probiotic pill to enhance natural gut resistance against certain pathogenic bacteria in March 2022, with a second to be introduced in 2023.

Some phage-based companies focused on the development of drug candidates are also leveraging advanced genome sequencing and metagenomics technologies to engineer genetically modified phages with improved patentability, according to Resch. He adds that the hope is that these advanced phages will also have enhanced activity without impairing safety, but sufficient evidence of this benefit has yet to be gathered.

Academic centers and government bodies are also getting involved in the field of phage-based therapies, helping startup companies with funding and other means of support. One example highlighted by Resch is IPATH, the Center for Innovative Phage Applications and Therapeutics, which is located at the University of California, San Diego School of Medicine and the first dedicated phage therapy center in North America.

**A few clinical trials**

Over the past one hundred-plus years, phages have been administered to humans orally (tablets and liquids), rectally, topically (skin, eye, ear, etc.) as rinses and creams, intravenously, and via other delivery approaches.

Today, phage-based therapies are in preclinical development for the treatment of a wide variety of diseases, including lung, wound and gut infections, as well as endocarditis and many other diseases that are difficult-to-treat because of the potential for complications due to antibiotic resistance.

When it comes to clinical trials, only a few have been conducted and/or are ongoing in Western medicine, according to Sulakvelidze. Phase I and Phase II studies involving phage-based therapies have been completed in chronic otitis media, respiratory infections, infected burn wounds, gastrointestinal disorders, urinary tract infections, and venous leg ulcers (1). The most common targets, says Sulakvelidze, are gastrointestinal and wound/skin infections.

One of Intralytix’s prototype phage preparations for treating infected wounds was successfully used during a Phase I human clinical trial in Lubbock, Texas—the first Phase I trial in wound healing in the United States. The company’s EcoActive bacteriophage therapy targeting adherent-invasive *Escherichia coli* (AIEC) in Crohn’s disease patients entered a Phase I/IIa clinical trial in 2019 and is currently enrolling participants at the Jcahn School of Medicine at the Mount Sinai Hospital in New York, NY.

In October 2021, Intralytix received clearance from FDA for an investigational new drug (IND) application for ShigActive, a bacteriophage preparation to manage Shigella infections in humans, of which there are approximately 125 million cases and 14,000 deaths worldwide, the majority of the latter in children under the age of five. The company is also in the pre-IND stage with a candidate to treat VRE infections. Altogether, Sulakvelidze says Intralytix will be starting three additional clinical trials in the next 18 to 24 months.

**Hopeful future**

The increasing number of development drug products and clinical trials is a hopeful sign for the future of phage-based therapy and a first step in advancing the field. During the next few years, Sulakvelidze expects to see even more clinical trials and greater numbers of people involved in generating an ever-broadening base of scientific knowledge and establishing the infrastructure needed to enable a phage-based approach to the treatment of disease.

“Eventually,” Sulakvelidze remarks, “there will be more reference centers and clinics—maybe a handful—where people can go to get treated with bacteriophages by properly trained experts with access to the right equipment. When enough centers are established, phage-based therapy will become more commonplace nationwide, but progress toward that goal will be incremental.”

Resch adds that greater capacity to produce phages under GMP conditions will need to be constructed to support the products that advance to late-stage clinical trials and commercialization.

Part of Sulakvelidze’s reason for having high expectations for bacteriophages in medical applications is the experience Intralytix has had with FDA regarding its food safety products. “The first product took four years to get approved, with a lot of back-and-forth between the company and FDA that largely involved educating one another. The agency has required considerably less time (9 to 12 months) to reach decisions on subsequent products,” he observes.

Sulakvelidze expects that experience to translate to the company’s human health products. “FDA’s Center for Biologic Evaluation and Research is very much open and willing to work with companies developing phage-based therapies to establish a regulatory framework for ascertaining their safety and effectiveness,” he comments.

“With the potential for bacteriophages when used in combination with antibiotics as first-line therapies to provide personalized treatment solutions for challenging patient infections, there is the real [opportunity] for this new approach to be democratizing,” insists Resch. That potential in conjunction with the urgent need for solutions to the rapidly growing threat of antibiotic resistance point to a bright future for phage-based therapies.

**References**

Preventive maintenance and periodic inspections do well to offset potential issues and ensure machinery is well maintained, but still require significant downtime, often running to days out of production. Scheduled maintenance also doesn’t take into account individual factors or unique usage of the machinery. Whilst standardized timings or experience might be used to plan for maintenance, it would be impossible to know for sure exactly when issues might arise, and where.

Integrating IoT and AI systems into manufacturing and packaging machines creates a connected ecosystem of machinery, where sensors allow for the possibility of accurate predictive maintenance. Surveys have indicated that the average reduction in maintenance costs (cross-industry) resulting from the implementation of an effective predictive maintenance program could be 25–30%, elimination of breakdowns 70–75%, downtime reduction 35–45%, and production increase 20–25% (1). Data collected from sensors located in key positions on machines can be utilized to acquire specific information that is analyzed by AI systems to predict, with accuracy, when maintenance, repairs, or interventions are needed. Smart connected machinery can communicate and inform management and network operating centers exactly what it needs and before it is needed, which means that machines don’t need to be checked and stopped unnecessarily. This method both prevents machine breakdown and ensures that machinery works optimally.

Preventing machine breakdown. Preventing unplanned breakdowns offers the potential for higher productivity and less waste. In smart manufacturing, embedded feedback mechanisms can provide alerts, via a remotely accessible user interface, to communicate issues with a machine. This communication could take the form of vibration sensors in a rotary machine to identify high friction between bearings or lubrication issues. Health conditions in the machine, such as these, can be treated early, or with minor treatment, rather than major intervention.
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With this early “bad news”, time can be less of a critical factor, and decision-making processes are improved by the data available and can be guided by aftercare experts. Thus, it is possible for throughput to remain high, with the time and type of maintenance needed being planned based on assessment of the data. Maintenance could take place via remote assistance depending on the situation, and in the form of emergency parts changing for critical situations, planned shutdowns, or incremental interventions to spread out the maintenance process.

**Integrating IoT and AI systems into machines creates a connected ecosystem of machinery.**

**Optimization.** Maintenance is not just about preventing breakdown, but also ensuring machinery is operating optimally. Without comprehensive data being collected, it is difficult and time consuming to accurately assess whether or not a machine is operating at suboptimal parameters. With the introduction of sensors to monitor key elements of machinery and operations, the functioning of the machine can be constantly observed, and based on detailed insights, changes can be made to the machine to ensure it is working to its best capabilities.

Considering what is already possible by observing patterns in datasets gleaned from standard sensors reveals an idea of the kind of impact that IoT and AI will have on process optimization and prevention of machine breakdown. To take the example of one of ACG’s fluid bed machines, associates identified the correct interval time for shaking the blower by reviewing data gathered from several sensors on the fluid bed machine. Rather than waiting for an alarm to alert them of failure on the blower, they adjusted the fluid bed shaking interval time from 4 seconds to 6 seconds. As a result, process cycle time was decreased from 23 to 18 hours, and downtime and damages were reduced, as the blower filter needed less regular replacement. To begin with, the shaking time was set to a very low 4 seconds to make sure the filter didn’t get damaged due to excessive particle accumulation. However, this is akin to preventive maintenance where a machine is maintained to a degree beyond what’s required, which results in increased process cycle time.

In this case, if the interval time had been more, then the particles would have accumulated within the filter, resulting in it becoming blocked and torn; if the interval time was less than required, it would negatively impact the process cycle time. Identification of the optimum shaking interval helped achieve a balance. With more IoT sensors, on a wider range of machines, and AI analytics, businesses will be able to identify anomalies and observe patterns earlier on, and make the proper intervention to achieve targeted outcomes.

**Beyond profit**

Predictive maintenance can have significant cost and productivity benefits, with uptime improvements, better overall equipment efficiency, and less product waste. However, organizations need to look beyond profit and assess how these benefits can be best utilized to make further positive changes.

**Safety, health, and risk.** Predicting and managing issues with machinery early will lead to a reduction of safety, health, and quality risks. A reduction in machine failures and a better working knowledge of the machine should also result in a more productive workforce. Plant-level associates can work in a safer environment with fewer concerns relating to issues with machinery arising unexpectedly. They are then able to make better informed decisions to improve productivity and reduce risk.

Additionally, all the data provided by machines and analyzed by AI, may have an impact on machine design. Designs could be focused more around health and safety, with easy access for maintenance, part changes, and cleaning. These changes are yet to be seen as a direct result of predictive maintenance, because the integration of IoT systems into the pharmaceutical manufacturing sector is still in its early stages. However, it is a natural progression from the way machine design is currently performed. Today, manufacturing teams are able to make design improvements based upon feedback, regulations, and individual data provided by associates working in the field. Whilst this feedback has its benefits, it is limited by human bias and capabilities. Associates are only able to assess manually collated statistics from individual cases and will focus on those elements that seem to be important from their work perspective, leaving potentially missed opportunities. Comprehensive, consistent metadata that is objectively analyzed by AI will enable teams to gather an in-depth holistic view of machinery, safety, and operations.

**Maintenance is not just about preventing breakdown, but also ensuring machinery is operating optimally.**

**Sustainability.** Sustainability remains a challenge. From API production, to packaging and disposal, there are many issues pharmaceutical manufacturers are grappling with in this area. However, reducing product rejections, optimizing production, and improving quality will
potentially have an impact on reducing waste, energy usage, and the environmental impact of operations.

Although it’s yet too early to predict the full scope of benefits, it’s likely that this careful, data-empowered method of predictive maintenance will also have an impact on extending the life of machinery, improving the sustainability and cost-efficiency of assets (3). Çınar et al. state that predictive maintenance is “one of the most promising strategies amongst other strategies of maintenance that has the ability of achieving those (minimizing equipment failure rates, improving equipment condition, prolonging the life of the equipment, reducing maintenance costs) characteristics” (4).

The data-empowered method of predictive maintenance may have an impact on extending machinery life.

**Challenges**

There is still some resistance in the pharmaceutical sector to the introduction of smart manufacturing. The industry has been slow to embrace change. However, it is becoming harder to ignore the necessity for technology adoption. Aside from the tangible benefits, companies need to look at how these systems can improve the inner workings of their business and support the wellbeing and safety of employees, as well as the positive impact that can be shared with customers and consumers. Human capital and improving the wellbeing of the global community should be the driver of metrics, although it is important to consider the reasons for reservations regarding the integration of IoT and AI, including data security and the need for culture change.

**Data security.** Ensuring the security of data is crucial. Sensors should only be activated once a customer has agreed to the capability and parameters of the data being collected from their machines. As with all IoT systems, device registration, via passkey or password, is essential and mandatory. Yet, to guarantee security and data integrity, especially as smart manufacturing systems become more widespread, further measures should be introduced. Data diodes that enable unidirectional data flow is one method by which companies can secure customer facilities from interference. Unidirectional data flow ensures data are only transmitted in one direction (outbound traffic from the plant), so IoT sensors cannot be affected by outside tampering (inbound traffic into the plant). Data cannot be transmitted to, but only from, the sensors, guaranteeing machinery cannot be interfered with by outside sources.

**Culture transformation.** Incorporating smart manufacturing solutions and predictive maintenance into operations is not as simple as a cost investment. Changing processes from traditional to digital, or stepping up the use of technology requires complete workforce cooperation. Proper training needs to be provided and preparations must be made to bring all teams on board with any changes and to ensure they are well-equipped to manage the culture change of digitalization. Upskilling of staff and operators at plant level is of particular importance, as they will be the ones implementing and working with these systems closely on a day-to-day basis.

**Embracing the future**

Predictive maintenance is a significant step forward from traditional ways of monitoring and managing machinery. Smart manufacturing gives organizations the ability to gain knowledge of the intimate workings and by-the-minute status of critical elements of the machine, which enables the making of informed decisions in an often less time-critical manner. Faults and issues will always arise, but by utilizing this capability, companies are provided with the benefits of early information and informed problem solving.

**References**

2. ACG, Internal data.
Quality by design (QbD) was an initiative introduced by FDA in 2004 to improve pharmaceutical development and manufacturing. QbD leverages quality tools, such as process performance, that estimate performance during initial setup before a process has been brought to a state of statistical control. By using QbD, pharmaceutical development, and hence manufacturing, becomes a more efficient process. To illustrate the utilization of quality management techniques, process performance will be utilized as an example in the simple process of tablet splitting. Principles and findings can be further extrapolated to more complex processes. For the present study, the process performance metrics of eight different mechanical devices were assessed to evaluate the compliance of these devices with regulatory and compendial criteria. These process performance metrics were used to differentiate the mechanical devices based on their degree of compliance with regulatory and compendial requirements and make recommendations based on values of these metrics, thus increasing process knowledge and understanding.

Tablet splitting: compendial and regulatory requirements
Historically, tablet splitting has been addressed by compendia, such as the European Pharmacopoeia and USP (4), which have specified testing requirements of split tablets. In 2013, FDA further regulated tablet splitting by introducing an industry guidance (5) that defines tablet scoring and requirements of scored tablets. Table I provides a summary of scored tablet testing requirements for both USP and FDA.
Traditionally, quality has played a vital role in all production and manufacturing processes. However, in 2002, the FDA advocated a new approach to quality management, focusing on quality tools such as process performance metrics. In 2013, the FDA further regulated tablet splitting by specifying testing requirements of split tablets.

**Individual weight percent after splitting (IWP).** This test measures the symmetry of the splitting process by comparing the weight of portions produced by splitting to the theoretical weight of that portion. For example, if a 100-mg tablet is split into two halves weighing 45 mg and 55 mg, respectively, then the IWP values are 90% (45/50 × 100%) and 110% (55/50 × 100%), respectively.

**Total weight loss after splitting (TWL).** This test measures the percentage of weight loss owing to splitting in comparison to the unsplit tablet weight. Thus, it measures the combined weight of both halves in reference to the weight of the intact tablet. For example, if a 100-mg tablet is split into two halves weighing 40 mg and 55 mg, respectively, then TWL is 5% ((100 – (40 + 55))/100) × 100%.

### Quality management: the link between QbD and Six Sigma

Traditionally, quality has played a vital role in all products and services. However, focus on quality, especially statistical quality control, evolved after World War II. The 1980s saw an increase in the focus on quality with the development of the Six Sigma program. One of the strategies adopted by Six Sigma is the define, measure, analyze, improve, and control (DMAIC) methodology. In the define phase, key metrics and objectives of the project are defined. The measure phase involves capturing current process performance and capability. The analyze phase involves utilizing collected data and tools to analyze and understand factors contributing to cause-and-effect relationships. The improve phase involves developing changes that improve the process and validating these changes. Finally, the control phase establishes procedures to ensure improvements are sustained.

In the pharmaceutical industry, quality management progressed through several phases. Initially, quality was introduced with the implementation of current good manufacturing practice (CGMP) regulations by FDA in 1978. Early documents focused on quality control, which was mostly achieved by retrospective testing (i.e., quality through testing). However, in 2002, the FDA advocated a new approach outlining its vision for the 21st century; this thinking was later published in a report (7). In addition to quality control, the new vision focused on managing quality through quality assurance and risk management (8). In other words, quality was to be designed into the product from its early development stages rather than solely relying on testing to assure this quality. Thus, the concept of QbD was introduced into the pharmaceutical industry. In similarity to the DMAIC methodology, QbD utilized many elements such as: a quality target product profile (QTPP) through identifying critical quality attributes (CQAs); product understanding through critical material attributes (CMAs); process understanding through critical process parameters (CPPs), linking CMAs and CPPs to CQAs; a control strategy through specifications; and process capability and continuous improvement (9).

### Capability and performance analysis

If a process is normally distributed, then 68% of its outcome will be within one standard deviation of the mean. If specifications are set to be within ±3 standard deviations of the mean, then a higher level of quality is achieved.

### Table 1. Scored tablet testing requirements defined by United States Pharmacopeia (USP) and FDA authorities.

<table>
<thead>
<tr>
<th>Source</th>
<th>Test</th>
<th>Requirement</th>
<th>General formula¹²</th>
</tr>
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| USP    | Individual weight percent after splitting (IWP) | Not less than 28 of 30 tablets have halves within 75%–125% | \[ IWP = \frac{W_{\text{split}}}{0.5 \times W_{\text{whole}}} \times 100\% \]
| FDA    | Total weight loss after splitting (TWL) | Not more than 3% of the whole tablet weight is lost after splitting | \[ TWL = \left(1 - \frac{W_i + W_o}{W_{\text{whole}}}\right) \times 100\% \]

¹ Formula shown is for tablets having a single score only.

² \( W_{\text{whole}} \) is the weight of the intact whole tablet, \( W_{\text{split}} \) is the weight of split tablet portion (\( W_i \) or \( W_o \)).
mean, then 99.7% of the outcome from this process will be within the specification limits. In other words, only 0.3% of the process output will fall outside the specification limits (Figure 1). A 0.3% outside specification limit corresponds to 3000 non-conforming parts per million parts produced by the process (10). Ideally, process specification limits can be adjusted, but in many circumstances, these specifications are set by clients or regulatory authorities. In this case, compliance with specifications could only be achieved by reducing process variability by lowering the standard deviation. To control quality, it is important to utilize statistical measures such as capability and performance metrics that relate process variability (i.e., the voice of the process) to specification limits (i.e., the voice of the customer).

Process capability and process performance. Process capability and process performance are two similar indicators describing how a specific process complies with specifications. Process capability assumes a process is under statistical control while process performance does not. As a result, process capability can be utilized for future inference about a process while process performance describes past process behavior. Mathematically, the only difference between the two indicators is how the standard deviation is calculated. In process performance, the standard deviation is directly calculated from the sample data; while in process capability, several experiments (up to a maximum of 10) are performed, and the data range is averaged and used to estimate the population standard deviation. This case study will utilize process performance as a screening tool to screen the performance of different mechanical tablet splitters and will have no inferences on process capability.

Process performance ratio ($\bar{P}_p$). Process performance is a control measure that describes the inherent variability in a process (i.e., process uniformity) compared to the requirements or specifications. Process performance is determined by calculating the process performance ratio according to Equation 1. In this equation, the numerator represents the specification limits while the denominator represents the variation within a process.

$$\bar{P}_p = \left( \frac{USL - LSL}{6\hat{\sigma}} \right)$$

Eq. 1

where $\hat{\sigma}$ is the estimated sample standard deviation, LSL is the lower specification limit, and USL is the upper specification limit.

A value of unity for the process performance ratio ($\bar{P}_p = 1$) indicates that the numerator and denominator are equal and that the voice of the process equals that of the customer. While this value may be acceptable, it would be considered “tight” and does not allow much room for deviation. The greater the $\bar{P}_p$ value, the more process deviation is allowed compared to specifications, and, thus, the lower number of defects/rejects. In general, values between one and 1.33 are considered to have a marginal performance while processes with $\bar{P}_p > 1.33$ are well performing processes. A Six-Sigma process would have $\bar{P}_p = 2$ (11–13). Values of $\bar{P}_p$ lower than unity indicate a non-performing process as the deviation would be higher than the set specification limits. Figure 2 graphically depicts the process performance at different performance levels.

The process performance ratio ($\bar{P}_p$) in Equation 1 assumes that the specification process is two-sided (i.e., has both upper and lower specification limits). However, some specifications are one-sided. For one-sided specifications, the process performance ratio used is calculated according to Equation 2 (if only an upper limit is defined) or Equation 3 (if only a lower limit is defined):

$$\bar{P}_{pu} = \frac{(USL - \hat{\mu})}{3\hat{\sigma}}$$

[Eq. 2]

$$\bar{P}_{pl} = \frac{\hat{\mu} - LSL}{3\hat{\sigma}}$$

[Eq. 3]

where $\hat{\mu}$ is the estimated process mean and $\sigma$ is the estimated sample standard deviation.

The $\bar{P}_{pu}$ measures process performance with respect to the upper specification limit while $\bar{P}_{pl}$ measures that performance with respect to the lower specification limit.

Process performance index ($\bar{P}_{pi}$). The process performance index is the first generation of performance measures. One of the shortcomings of the process performance ratio is its inability to determine where the process mean is located relative to specification limits. For example, the process performance ratio will be identical for a centered and off-centered process if the two have the same standard deviation as shown in Figure 3. Therefore, another process performance measure is used in this case, the process performance index.
Figure 3. Difference between $\bar{P}_p$ and $\bar{P}_{pk}$ for two processes having the same standard deviation but different averages. LSL is lower specification limit. USL is upper specification limit.

Figure 4. Difference between $\bar{P}_p$ and $\bar{P}_{pm}$ for two processes having different averages and standard deviations but identical performance index values. LSL is lower specification limit. USL is upper specification limit.

($\bar{P}_{pk}$), which is a second-generation performance measurement that measures how the process is performing with respect to either the lower or upper specification limit (i.e., how far outcomes deviate from the limit) and can be calculated using Equation 4.

$$\bar{P}_{pk} = \min(\bar{P}_{PL}, \bar{P}_{PU})$$  \[Eq. 4\]

where $\bar{P}_{PL}$ and $\bar{P}_{PU}$ are the lower and upper limit performance ratios defined in Equations 2–3.

For single-sided processes, the process performance index reduces to the one-sided performance measure.

The Taguchi index ($\bar{P}_{pm}$). The process performance index was introduced as a performance measure for processes where the mean is not centered between specification limits. However, alone, the process performance index remains an insufficient measure of process centering because it highly depends on the value of the standard deviation. As the value of the standard deviation decreases, the value of the process performance index increases even if the deviation from the mean (i.e., the value of the numerator) is relatively high, as illustrated in Figure 4. Therefore, a third-generation performance measure, termed the Taguchi index ($\bar{P}_{pm}$), was introduced (14) to address the shortcoming of the process performance index and can be calculated according to Equation 5:

$$\bar{P}_{pm} = \frac{\bar{P}_p}{\sqrt{1 + x^2}}$$  \[Eq. 5\]

where $x = \frac{\bar{y} - \bar{T}}{\bar{T}}$ and $\bar{T}$ is the midpoint between the upper and lower specification limits, $\frac{1}{2}$ (USL + LSL).

Percent of specification used. The three performance indices mentioned previously ($\bar{P}_p$, $\bar{P}_{pk}$, and $\bar{P}_{pm}$) are useful measures to help understand the process performance, but these metrics have an additional practical interpretation when rearranged, as shown in Equation 6 (15):

$$P = \left( \frac{1}{\bar{P}_x} \right) \times 100\%$$  \[Eq. 6\]

where $P$ is the percentage of the specification band used by the process, and $\bar{P}_x$ is the performance index chosen ($\bar{P}_p$, $\bar{P}_{pk}$, or $\bar{P}_{pm}$).

The percentage of the specification band used indicates how much of the specification limits are being used by the process. Process performance improves as the percent of specification used decreases. For example, a process with a performance ratio of one uses 100% of the specification limit, while a process with a performance of 1.25 uses 80% of the specification limit.
Application in tablet splitting. The limits used in evaluating tablet splitting are those specified by USP and FDA. For USP testing, the IWP test has a LSL of 75% and an USL of 125%. For FDA testing, the TWL test has a one-sided specification limit only (i.e., USL) of 3%. For USP testing, all three performance measures will be calculated (i.e., $P_{pl}$, $P_{pm}$, and $P_{pk}$) while only the process performance index ($P_{pk}$) will be calculated for FDA testing.

The calculated process performance measures will be used as a means for screening the performance of several mechanical tablet splitting devices.

Material and methods
In this work, eight mechanical tablet splitting devices (Table II) were screened for compliance with the compendial and regulatory requirements. A placebo powder (Prosolv EASYtab SP, JRS Pharma; lot number 68090191310) was compressed into 600-mg tablets at a nominal hardness of 20 kPa using a Korsch XP1 single-station press equipped with a cut-through bisect tooling (Figure 5). Tablet splitting was evaluated by taking 30 scored tablets for each mechanical splitter and splitting them. The operation of mechanical splitters was simple and did not require special training or skills and was performed by the same operator for all mechanical devices. The IWP of each half produced and the TWL after splitting each tablet were evaluated by measuring the weights of the produced tablet halves (i.e., 60 halves).

Results and discussion
The results indicate a significant difference in the performance of the mechanical splitters. Figures 6–7 show the results of tablet splitting using the different mechanical devices according to USP (Figure 6) and FDA (Figure 7) specifications (in both figures, red lines indicate specification limits). The IWP after splitting (Figure 6) shows the weight of the split portions (represented as open and closed triangles) that are produced after splitting a whole tablet. Two specification limits exist for this test, 75% (LSL) and 125% (USL). Figure 7 shows the TWL after tablet splitting; this test only has an USL of 3%. Any whole tablet that loses more than 3% of its weight after splitting fails this test and is not acceptable per FDA requirements.

While neither the process of tablet splitting was in a state of statistical control, nor the number of samples was large enough to establish process performance at Six Sigma levels, process performance was utilized as a screening tool to rank-order different mechanical devices.

In examining the results graphically (Figures 6–7), the investigators found it challenging to distinguish the performance of different devices by simply looking at the graphical data. This was especially the case for compliance with USP requirements (Figure 6) where all mechanical devices appear to be equally as good. For FDA compliance require-
Figure 6. The individual weight percentage of produced halves after mechanical tablet splitting. USL is upper specification limit. LSL is lower specification limit.
Figure 7. Total weight loss (TWL) for tablets split using mechanical splitters A1–A8 (Table II).
ments (Figure 7), three mechanical devices fail the tests (A2, A4, and A6), but most of the remaining devices seem to be performing comparably. It is difficult, if not impossible, to rank-order the performance of these devices by looking at the graphical results alone. However, if the calculated process performance indices for the different mechanical splitters are examined (Table III), then those indices provide an easy criterion that can be used to screen and rank-order the performance of different mechanical splitters.

Process performance results in Table III show that all devices passed USP requirements with a minimum process performance index ($\hat{P}_{pk}$) of 1.58 for the A4 device and a maximum performance index of 5.61 for the A7 device. On the other hand, only five devices passed the FDA requirements (about 63% of the devices tested), with A3 showing the best performance of $\hat{P}_{pk} = 8.41$. If the failing devices (A2, A4, and A6) are ignored, the passing mechanical devices can be ranked as A3 > A7 > A5 > A1 > A8 according to FDA specifications. Results clearly show that USP criteria is easier to meet than that of FDA. Results also demonstrate that, although a device such as A6 can have a high process performance in USP specifications ($\hat{P}_{pk} = 2.51$), it can still fail the FDA specification ($\hat{P}_{pk} = 0.52$).

### Conclusion

Process capability and performance metrics are quality management tools that link the observed process variation with the required specifications. These tools are simple to calculate and important to utilize in any given process. This work has utilized process performance metrics for evaluating the process of splitting of scored tablets using different mechanical devices.

These devices were evaluated based on their compliance with USP and FDA specifications. Mechanical splitting devices are not equal in terms of tablet splitting performance. The performance varied based on the specification used to access the splitting process. It is generally easier for mechanical splitters to satisfy USP, compared to FDA specifications.

As a result, developers and manufacturers need to select the best-performing mechanical device that complies with both regulatory and compendial requirements. This cannot be effectively achieved without using quality management tools such as process performance to rank-order the performance of different devices.

### References


8. FDA, "Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations" (CDER, CBER, October 2006).


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**Table III.** Analysis of tablet-splitting results based on United States Pharmacopeia (USP) and FDA requirements.

<table>
<thead>
<tr>
<th>Mechanical device</th>
<th>USP—individual weight percent (IWP)</th>
<th>FDA—total weight loss (TWL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\hat{P}_p$</td>
<td>$\hat{P}_{pk}$</td>
</tr>
<tr>
<td>A1</td>
<td>2.22</td>
<td>2.08</td>
</tr>
<tr>
<td>A2</td>
<td>2.09</td>
<td>1.89</td>
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<tr>
<td>A3</td>
<td>3.77</td>
<td>3.76</td>
</tr>
<tr>
<td>A4</td>
<td>1.67</td>
<td>1.56</td>
</tr>
<tr>
<td>A5</td>
<td>3.58</td>
<td>3.55</td>
</tr>
<tr>
<td>A6</td>
<td>2.52</td>
<td>2.51</td>
</tr>
<tr>
<td>A7</td>
<td>5.61</td>
<td>5.61</td>
</tr>
<tr>
<td>A8</td>
<td>3.47</td>
<td>3.36</td>
</tr>
</tbody>
</table>

¹ The % of specification has been calculated based on the value of the process performance index $\hat{P}_{pk}$ according to *Equation 6*.

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Ammar Khawam, PhD, is a senior managing scientist of product development at Parsolex.
Scientists can work to overcome the challenges associated with protein characterization through empowering technologies.

Protein therapeutics are an important class of medicines that are used to treat a variety of diseases. According to market research, the protein therapeutics market is estimated to grow at a compound annual growth rate of 6.86% between 2020 and 2027 (1). This growth is expected to be driven by the rapid rise in chronic disorders, advancements in technologies, broadening awareness of protein therapeutics, increasing adoption of plasma-derived therapies to manage chronic disorders, and mounting government initiatives to develop healthcare sectors (1).

However, therapeutic proteins are notoriously less stable than conventional pharmaceuticals; and due to their complex molecular structures, they can be challenging to develop successfully (2). “Compared to small molecules and peptides, proteins are much more complex,” explains Khanh Courtney, PhD, senior director, Biologics, Element. “Therefore, the understanding of the biophysical and biochemical characteristics of a protein biomolecule is critical in the identification of critical quality attributes (CQAs) to ensure consistent safety and efficacy.”

As proteins are formed by long chains of amino acids that interact with each other, secondary and tertiary molecular structures are formed, notes Courtney. Beyond the tertiary structure, the protein can bind to itself, which results in even higher order structures, such as dimer, trimer, and oligomer, she states.

“Certain amino acids could be post-translationally modified with phosphate groups, methyl groups, simple sugars or complex sugars, and so on, leading to a highly complex protein therapeutic molecule,” Courtney says. “The folding of the protein, the higher order structure, [and] the composition of its post-translational modifications, particularly of the glycans, are all examples of protein characterizations that could impact the potency and function of the molecule.”

“One of the highest importance is of [the] highest importance throughout all stages of the value chain.”

—Martin Vollmer, Agilent Technologies

The highest importance

“Protein characterization is of [the] highest importance throughout all stages of the value chain from discovery to development, through to quality control,” emphasizes Martin Vollmer, strategic program office lead for Biopharma, Agilent Technologies. “Characterization of a protein provides information about its structure and composition, which is directly linked with its function, leading to a greater understanding of differences and ensuring that quality criteria of developed biopharmaceutical products are met according to regulatory guidelines, ensuring drug efficacy and drug safety.”

For Scott J. Berger, PhD, senior manager, Biopharmaceutical Markets, Waters Corporation, whether making a protein drug via a recombinant or synthetic process, development should start with protein characterization and having as much knowledge as possible about the product. “These processes are imperfect, so they are going to make products with low-level variations that are subject to degrada-
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tion pathways that further raise product variability,” he specifies. “It’s this complexity that creates reliance on sophisticated analytical tools.”

Tools, such as liquid chromatography (LC) and mass spectrometry (MS), have provided process scientists with the ability to monitor important attributes of a molecule in response to changes in the process, Berger adds. “This [capability] gives scientists the flexibility to incrementally refine their process to improve drug quality and yield by establishing analytical comparability,” he says. “Characterization assays often translate to targeted methods for process monitoring and product release where you are verifying that you have control of your process and product quality.”

“ Ideally, protein characterization is done in the early stages of chemistry, manufacturing, and controls program development.”

—Khanh Courtney, Element

A number of challenges

A key challenge related to protein characterization is that methods usually require a lot of test material, Courtney stresses. “Ideally, protein characterization is done in the early stages of chemistry, manufacturing, and controls (CMC) program development so that critical attributes are identified early on. Unfortunately, the early stage of CMC, for instance during process development, consists of small-scale productions done at the lab bench and have low yield,” she states. “This challenge can be, and is being, dealt with by the advancement of analytical methodologies that can assess more than one characteristic at a time in a single sample preparation or method.”

An example of how this challenge is being overcome can be found in the use of high resolution, high sensitivity MS. “This approach can be used to decipher the peptide map of the protein, post-translational modifications, deamidation, disulfide bonds, aggregation, molecular mass verification, glycan structure elucidation, and even tertiary structure determination, all in one approach,” Courtney explains. “By packaging multiple attributes into one method, a small yield of protein produced at the lab bench could produce a wealth of data to assess protein characteristics to better inform manufacturing and quality decisions.”

There are several immediate challenges to protein characterization in Berger’s opinion. “First, is the increasing complexity of the molecules,” he says. “We’re seeing the appearance of bi- and tri-specific molecules, antibody-drug conjugates [ADCs], and complex fusion proteins, all of which have more attribute variation than your typical monoclonal antibody, requiring enhanced analytics to define and monitor them.”

Additionally, in light of the increasing number of accelerated reviews by regulatory agencies, a challenge has arisen in the form of being able to fully characterize molecules in a compressed timescale and at the same time as stability studies and formulation development are taking place, Berger points out. “So, there is an increasing need for efficient analytical platform methods that can utilize prior knowledge to accelerate these studies,” he states.

“Another challenge many organizations face is the lack of actionable knowledge during the clone selection stage of product discovery/development,” Berger continues. “Use of LC–MS at this stage can ensure that a biosimilar, for example, matches up to the target analytical profile of the innovator molecule when it comes to a set of key and critical quality attributes.” When used as a part of a quality-by-design (QbD) approach, LC–MS can help to ensure that the desired product attributes are built into the molecule, he notes. If there is insufficient knowledge about a molecule at this stage of development, it is possible that impurities or instabilities won’t be discovered until after the product is placed into clinical production, Berger warns.

For bench scientists, experimental bias can be a significant challenge, Berger highlights. “A top reason why assay-to-assay test results vary from one scientist to another has to do with complicated and multi-step sample preparation methods,” he says. “For multi-attribute monitoring of biomolecules by LC–MS, it’s important that you have a very high-quality and reproducible sample for meaningful results. To address this need automated sample prep technologies are being investigated by many groups as a tool to improve sample quality and reproducibility by eliminating the human factor from potentially biasing assay results.”

Undesirable secondary interactions can adversely impact analytical data when analyzing organic acids, organophosphates, oligonucleotides, phosphopeptides, acidic glycans, and phospholipids, Berger notes. “One example of a secondary interaction is the non-specific adsorption by certain biomolecules to the metal surfaces—or even to bio-compatible materials like titanium—of liquid chromatographs and chromatographic columns,” he states. “Another type of secondary interaction is caused by the highly active surfaces of proteins which have a propensity to interact with the hydrophobic and electrostatically-active sites on the silica and hybrid silica chromatographic particles in the UHPLC [ultra-high performance LC] or UPLC [Ultra-Performance LC] column.”
These secondary interactions cause difficulties when characterizing and monitoring drug products by size exclusion chromatography (SEC), which is used to determine protein sample size variants claims Bill Warren, Principal Bioseparation product manager, Waters Corporation. If these attributes are not carefully controlled then the safety and efficacy of the product can be adversely affected, Warren specifies. “It’s for this reason that regulatory agencies require drug firms to accurately quantify the protein size variants like mAb aggregates, monomers and fragments in protein drug products,” he says.

“LC and MS have been the empowering technologies for the well-characterized biotherapeutic.” —Bill Warren, Waters Corporation

Vollmer emphasizes that protein characterization is highly complex and is only becoming more complex over time. “In the past, it was mainly monoclonal antibodies (mAbs), hormones, vaccines, modified human proteins, and similar therapeutic proteins. Now with the discovery of antibody [drug conjugates (ADCs)] fusion-proteins, bi-specific Abs, and other modalities, the task of protein characterization now requires a much more flexible approach,” he asserts.

This increasing complexity is then also tied to the skill of the analytical scientist that needs to perform the characterization, Vollmer stresses. “There are a multitude of assays that need to be performed and the instrumentation required is more sophisticated, but costly,” he explains. “Big hurdles are, therefore, the cost of implementation, operation, and skilled personnel.”

“Another important challenge is the large amount of data that needs to be analyzed for meaningful information and further action,” Vollmer continues. “More broadly, regulatory hurdles and inertia in the industry are often roadblocks for fast innovation.”

Empowering technologies

“LC and MS have been the empowering technologies for the well-characterized biotherapeutic,” Warren says. “LC is essential for fully analyzing an intact protein or its sub-units for glycan profiling or peptide mapping or for looking at protein charge or size variants.”

A technique that is useful for characterizing protein size variants is SEC, Warren adds. There have been several new SEC columns that have been brought to the market recently, he states, that address “the problem of secondary interactions (both ionic and hydrophobic) when separating protein aggregates, monomers, and fragments over a molecular weight range of 10,000 to 6,500,000 Daltons.”

Berger also notes that through combining LC and MS, it is possible to establish the primary structure (product sequence), which is a regulatory filing requirement. “With LC–MS, you get to explore the product variation, its stability, and degradation pathways, which ‘hot spots’ to monitor to ensure that the product qualities and your processes are under your control,” he says. “LC–MS is also ideal for looking at a molecule’s higher order structure, which relates to the folding and stability of these biotherapeutics, and how they interact with their protein targets, or themselves when it comes to things like molecular aggregation.”

The structural information obtained by LC–MS can drive product development and can also form the basis of intellectual property, Berger points out. “Understanding higher order structure and stability dynamics may require the use of techniques like hydrogen deuterium exchange or ion mobility mass spectrometry (IMS-MS) and more recent techniques, such as collision-induced unfolding (CIU). CIU is an approach where the mass spectrometer is almost like a calorimeter, adding energy to the protein molecule and seeing how it unfolds within the IMS-MS,” he says. “These techniques allow you to ask questions that go beyond primary structure to understanding the dynamics of its folded structure and interactions with its protein target.”

Courtney highlights three techniques that are important for protein characterization: “High resolution, high sensitivity, orbitrap MS for protein and glycan identification, and structural elucidations; capillary electrophoresis to determine charge heterogeneity; and circular dichroism for secondary structures.”

Although there is no single standard technique to characterize proteins, Vollmer concurs that LC and high-resolution MS are regarded as the gold-standard thanks to the “rich” information such techniques offer on physiochemical properties of the protein. “Other alternative techniques are capillary electrophoresis (CE) and CE–MS because they can provide excellent resolution,” he adds.

“Spectroscopy, such as ultraviolet, Raman, near infrared, or fluorescence, are also widely applied to determine more specific requirements, such as concentration or purity. These techniques are fast and can even be applied inline,” Vollmer concludes. “Cell analysis technologies, such as metabolic analyzers, real-time cell analyzers, cell-imagers, and cell counters are applied to characterize suitable clones and host cells for protein manufacturing.”

References


A New Route to Pharma GDP Compliance and Standardization

Courtney Soulsby and Alan Kennedy

A consensus-based approach to GDP lies at the heart of a new industry-wide program seeking to rationalize, standardize, and harmonize the adherence to pharma transportation norms and regulatory guidelines.

The logistics associated with the safe and efficient physical transportation of pharmaceuticals is increasingly taxing the minds of logisticians as medicines become more complex and labile and their regulatory oversight intensifies. The statutory need to maintain the therapeutic and physical integrity of drugs during transit renders the management of quality and the adherence to good distribution practice (GDP) guidelines an absolutely critical part of the pharmaceutical supply process.

GDP’s European origins

In 2001, the European Union issued Community Code Directive 83 (1) defining a framework for the harmonization of the regulations relating to medicines including the rules governing their distribution. As far as GDP is concerned, this code built on the original EU GDP guidelines of 1994 (2) and has culminated, amongst other things, in the revised EU guidelines of November 2013 for human medicinal products (3) and the guidelines for APIs of March 2015 (4).

However, although the EU guidelines that were introduced in 2013 have formed a template for many subsequent national regulations, even within the EU the exegesis of GDP is open to wide interpretation. To a large extent, this is because GDP is (necessarily) non-prescriptive in nature and the guidance has been enacted in the form of a community directive rather than a regulation. This places responsibility in the hands of ‘National Competent Authorities’ which govern the authorization of wholesale distributors and their compliance with the guidelines.

For now, there is no single global GDP standard despite the harmonization efforts of bodies such as the International Council for Harmonisation (ICH), European Compliance Academy (ECA) and the Pharmaceutical Inspection & Cooperation Scheme (PIC/S). There are literally dozens of national and regional GDP standards in operation around the world. And although most of these are similar and operate under Marketing Authorization Holder (MAH) and Wholesale Dealer Authorization (WDA) type licensing systems, there can be much difference when it comes to detail and enforcement.

Systemic flaws

GDP guidelines are basically an extension to the GMP regulations which are in force around the world to govern the quality of manufacture of pharmaceuticals and their ingredients. These guidelines cover clinical trials as well as commercial drugs, APIs, and veterinary products. However, despite this common starting point, GMP is fundamentally different from GDP in that the GMP process takes place within a relatively controlled environment whereas GDP processes largely take place at arm’s length, outside the direct control of the manufacturer and involving numerous organizations of varying competence, expertise, and scale.

These supply chain dependencies are both critical and unavoidable, creating a high number of dilemmas and vexations that are endemic to the pharma-logistics process. These include:

- Supply chain fragmentation—logistics is one of the world’s most fragmented business sectors rendering it notoriously difficult to control and change.
- Fragility and low resilience—the vulnerability of the global logistics chain to large-scale disruption has been cruelly exposed by the COVID-19 pandemic.
Variable infrastructure—huge handling and storage variabilities in terms of both capability and capacity, especially cold-chain, are apparent across countries and markets.

Duplication of effort—collectively the industry unnecessarily replicates an enormous swathe of work especially in relation to asset utilization and quality compliance.

Security vulnerabilities—these especially relate to counterfeit product, which is driving track-and-trace legislation.

Poor consignment visibility—another product of structural fragmentation which precludes dynamic product monitoring and timely interventions.

Supply chain opacity—the industry’s congenital ‘silo mentality’ and protectionism curtails co-operation and inhibits the development of supply chain trust.

Training shortages—rising standards and regulatory demands

Figure 1. The perceived benefits of a more integrated approach to good distribution practice (GDP).

What do you think will be the biggest benefits that might accrue from greater GDP collaboration and harmonisation?

- Removal of duplicated effort, overlap and repetition
- Proactive reduction of some of the inherent risks
- Simplification of GDP compliance from standardisation
- Collaboration of pharma companies coming together
- Lower cost of pre-qualifying / audit of logistics partners
- Reduction of quality and regulatory non-conformances
- Common reference point for continuous improvement / benchmarking
- Cost reduction through standardisation, resource sharing, data exchange & economies of scale
- Faster responses to unpredictable events

40%

12%

12%

12%

8%

16%

Fig. 1
have highlighted a dearth of good GDP training in many locations.

• Sustainability issues—the carbon footprint of shipping medicines (especially by air) is a growing concern.
• Technical standards—the absence of universal technical standards is an impediment to sustained improvement across the sector.
• Rising costs—the explosion in freight rates, both air and sea, over the past 12 months is forcing pharmaceutical companies to look closely at long-haul distribution costs.

Taken together, these factors create a degree of complexity that makes the consistent and reliable execution of GDP across the pharma supply chain a very elusive goal. Indeed, a survey (5) had no less than 40% of pharmaceutical shippers and logisticians citing the reduction of complexity as one of the biggest perceived benefits of greater GDP collaboration and harmonization (see Figure 1).

All this points to the existence of a huge amount of unnecessary replication, regulatory revisionism, compliance ambiguity, and reinventing of wheels when it comes to good distribution practice.

Questioning the logic of logistics
Any system for improving and streamlining GDP compliance is contingent on a comprehensive review of contemporary quality policies and procedures, for example, by questioning the rationale behind each individual pharmaceutical company:

• finding, assessing, and validating large numbers of different carriers and suppliers
• developing and maintaining discrete operational qualification (OQ) and performance qualification (PQ) test protocols
• designing multiple system and product evaluation and qualification programs
• conducting rigorous training programs for ever-changing products and pack-out permutations
• continuously replicating arguably interchangeable lane validations?

• generating large numbers of proprietary standard operating procedures (SOPs) and key performance indicators (KPIs)
• using/developing digital quality monitoring systems that are not interoperable.

GDP exceptionalism
Whether or not it is possible to pragmatically address all the various issues at play in the world of pharma, GDP is down to questioning embedded beliefs and practices as well as having a good understanding of the context in which they have developed. For instance, the notion that each and every medical product and shipping lane requires a dedicated transportation protocol needs to be challenged in the light of the latest technical and procedural developments. Although there will always be a need for unique and highly specialist transport arrangements for niche, very sensitive, and potentially dangerous pharmaceuticals, the vast majority of bulk prescription medicines and vaccines fit into one or two of just a small handful of generally accepted storage environments and temperature bands.

The argument that each and every transportation case is comprehensively different and therefore requires a unique approach is highly conjectural. When it comes to the transportation of medicines, the reality is that there is huge scope for a more standardized and harmonized approach to medicine distribution if only the various supply chain stakeholders are prepared to work collectively towards a common end.

Nevertheless, if such a recognized and widespread need for a more concerted and inclusive approach to GDP compliance exists in practice, it inevitably begs the question as to why the status quo prevails. Perhaps part of the answer can be gleaned from the survey mentioned previously, in which nearly half the respondents cited either personal or corporate inertia as the single biggest barriers to a more ‘joined-up’ approach to GDP (see Figure 2) (5).

Multi-Modal Compliance and Standards program
It is against this backdrop that the British Standards Institution (BSI) and Poseidon, the independent pharma logistics network, came together in early 2021 to co-develop and execute the Multi-Modal Compliance and Standards (MMCS) program conceived as a consensus-driven foundation for industry-wide GDP standards and providing guidance through the growing maze of GDP regulations; one that is global in scope and covers all modes of carriage for bulk pharmaceuticals.

The MMCS program is aimed at pharmaceutical shippers and the entire distribution chain and is being designed to bring consistency, certainty, and con-
continuous improvement to the complex process of meeting international quality and regulatory standards for the sale, efficient, and sustainable distribution of medicines, vaccines, and APIs.

“The entire pharma-logistics field stands to gain from this collaborative initiative which will improve quality, reduce compliance costs, and promote process and technical harmonization. A more joined-up approach to GDP compliance presents a sustainable way of improving outcomes, reducing costs, and extracting more value from logistics quality in these unprecedented times,” said Angus Metcalfe, BSI Group’s Managing Director, Global Healthcare, when the program was announced (6).

Universal need. With its industry-consensus approach, the MMCS program has been conceived as a universal GDP compliance system that fills the void in the market for a more harmonized and standards-driven approach to quality, qualification, certification, and training in the distribution of vaccines and other medicines.

The MMCS model is being designed to:
- greatly simplify the quality compliance processes especially from a shipper’s perspective
- remove huge amount of duplicated effort, overlap, and repetition amongst pharma companies
- proactively attenuate some of the risk inherent in the pharma logistics process
- introduce greater standardization of player, process, product, and system including universal technical standards for key supply chain elements
- bring pharmaceutical companies together to minimize process divergence, aggregate volumes, share resources, and collectively innovate
- reduce the high number of quality and regulatory non-conformances
- promote continuous GDP improvement as dictated by legal statute, common sense, and moral obligation
- provide shippers and logistics service providers (LSPs) with a common reference point for continuous improvement in quality and compliance
- integrate seamlessly into legacy logistics systems
- support and complement the need for greater sustainability when it comes to pharmaceutical logistics
- provide a comprehensive GDP training support program
- reduce compliance costs as a result of standardization and economies of scale
- create a system of shared supply chain audits to streamline risk management, vendor performance and GDP compliance (83% of survey respondents [5] are receptive to this)
- strengthen physical and digital supply chain security by creating a common platform for GDP interoperability.

Program scope and structure. Ultimately, the pharmaceutical industry has the end-goal of delivering safe and effective therapeutic outcomes for its patients. However, this noble, patient-centric goal involves a complex synthesis of numerous quality-related factors, with adherence to GDP being just one vital part of the overall equation. For this reason, the MMCS program needs to be not only technically valid and robust but, at the same time, flexible, scalable, affordable, and universally accessible to align with myriad supply chain stakeholders and accommodate different tactical approaches to GDP compliance. In turn, this will compel a degree of process standardization and unification in order to curtail unnecessary compliance permutations and vouchsafe GDP.

Figure 3 shows the main building blocks of the MMCS program. As a joined-up and universal risk management system for logistics, the MMCS will comprise multiple operational threads all configured and aligned to optimize their combined effect. Some of the more important strands of the program are as follows:
- Standards/guidelines—In the field of pharmaceutical GDP, there are a lot of regulatory and industry guidelines but precious few independent standards with the upshot that there is a variety of different approaches and interpretations. MMCS is investigating the creation of an overarching generic standard (or standards) covering pharma GDP processes and behaviors from a strategic perspective, and then underpinning this umbrella prescript with a series of technical standards as necessary. The fundamental keys being universality, repeatability, and consistency.
- Shared audit platform—A supply-chain audit scheme is expected to form an important element of the MMCS program with an important role in ensuring GDP–compliance to a recognized indus-
Quality/Regulations

Figure 4. Breakdown of Multi-Mode Compliance & Standards (MMCS) program Consultation Cluster by category.

try standard. The MMCS team is currently assessing the demand and potential for a shared audit platform where the industry can mutually accept independent audit results and absolve the audited parties from having to endure multiple assessments from different principles. Such a common resource means that a successful audit would confer an industry-recognized compliancy status.

• Certification—Certification is a frequent requirement of pharma-logistics customers who need their suppliers to demonstrate that they have the appropriate quality systems in place and can meet pre-defined standards. Such conformity verification has an important role to play, and third-party certification will be another important element of the MMCS program. The design of the MMCS certification scheme will fully reflect the need for true program objectivity and ‘real-life’ legitimacy of the process and results.

• Training—GDP training is a core pillar of the MMCS program which is seeking to work closely with established training organizations and specialists to develop the necessary agenda, content, and formats for differing regions and markets. This training component will be managed by the well-established BSI Training Academy, which has a global reach and trains more than 200,000 people every year with an unrivalled portfolio of courses.

• Supply chain qualification—According to the United Kingdom’s Medicines and Healthcare products Regulatory Agency (MHRA) (7), “this is one of the highest risk areas of Good Distribution Practice.” Yet despite this risk, end-to-end management of supply chain GDP is one of the weakest areas of regulatory compliance. Although it is the responsibility of licensed MAH and WDA organizations to qualify and periodically re-qualify their end-to-end supply chains in accordance with GDP and written technical agreements, it is extremely difficult, costly, and resource-intensive to successfully monitor and manage convoluted and constantly mutating logistical formations.

Industry consultation. Clearly, it is absolutely crucial that the component parts of the MMCS program accurately reflect the needs and priorities of the potential user base and other stakeholders.

For this reason, an official MMCS Consultation Cluster has been established comprising volunteer experts from a broad spectrum of the industry’s stakeholder groups to advise on the program and ensure its neutral, non-partisan status.

Figure 4 shows the current percentage breakdown of the MMCS Consultation Cluster by category. Input is being solicited from both individuals and organizations from right across the industry including responsible persons, established best-practice agencies, quality bodies, and regulatory authorities. The goal is to engage with the industry to improve, consolidate, and standardize the pharma-logistics process without unnecessary duplication, toe-treading, or reinventing of wheels.

Conclusion

The distribution of life-saving and life-enhancing medicines has recently been center stage in the public domain as a result of the continuing COVID-19 crisis. However, the pandemic is not only a tragedy; it is an opportunity and a turning point. With so much at stake and no end in sight, it is time for the industry to come together to find ways of improving and harmonizing how the industry complies with the rules surrounding the safe and efficient distribution of vital medicines.

References

2. EC, 94/C 63/03 Guidelines on Good Distribution Practice of Medicinal Products for Human Use.
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Validation of Compressed Air Systems

Company Summary
Trace Analytics, LLC is an ISO 17025-accredited laboratory specializing in the analysis of surfaces and ambient and compressed air. We test for contaminants such as particles, water, oil, gases, and microorganisms in manufacturing facilities according to ISO 8573, ISPE, FDA, and custom specifications.

Content Piece Summary
Validate compressed air systems for pharmaceutical processes to ensure quality for its designated use. Learn about testing parameters, specifications, and more.

Company URL
https://www.airchecklab.com

Compressed air systems are a critical component of many pharmaceutical manufacturing facilities. With any new system creation, addition, or change, a validation should be performed to ensure the compressed air is of appropriate quality for its intended use. This validation process must collect enough data to draw scientific evidence that the system quality is appropriate (Senra, Levya, Perez, et. al, 2017).

To set up a successful compressed air system validation, it is important to designate specification requirements, timeline, protocols, documents, and training.

Specification Requirements and Testing Parameters
The ISPE Good Practice Guide for process gases asserts that compressed air usage in pharmaceutical manufacturing should be free from contaminants and routinely maintained and tested (2011).

ISO 8573 dictates testing for particles, water, total oil, and microorganisms in compressed air. This standard provides a purity class chart to help users select limits.

Determine the purity limit for each potential contaminant for each process line being validated. There are a variety of quality standards and guidance documents available that can aid in establishing appropriate limits and analytical methods (ISO 8573, USP, ISPE, or CGA).

Particles can be analyzed in a variety of ways. Some specifications require sizing and counting as in ISO 8573-1 Classes 1-5. Alternatively, the weight of the particles via gravimetry is another method to determine contamination levels.

Laser particle counters provide instant particle count results and immediate feedback on the quality of the compressed air.

Oil and hydrocarbon requirements may vary depending on specification. Oil vapors and organic solvents are defined by ISO 8573 as a mixture of hydrocarbons composed of six or more carbon atoms. Total oil for ISO 8573 Class 1 and 2 requires the combination of oil aerosol and oil vapor results. A filter and a charcoal tube can be used to test for total oil. If oil mist results are required in the 5-25ppm range, a source bottle vial using GCMS technology is used.

Microbial requirements are also vague and dependent on a risk assessment unique to the facility. Testing for bacteria, yeast, and mold is an important part of ensuring the safety of compressed air used directly and indirectly on products. Further identification of genus and species can allow users to check for certain types of microorganisms that may pose a risk.

Gas purity should be considered during the validation process. If the system requires oxygen, nitrogen, argon, or nitrous oxide, the purity levels can be tested along with contaminants.

Timelines
Many validations require passing results for several days in a row. In this case, schedule rush results for the first few days of sampling. Laser particle counters can be used for immediate particle results in the field.

Water vapor detector tubes can alert users on-site about water contamination issues too.

To determine the sampling schedule and timeline, consider how long each sample will take and how many samples are required at each point. More stringent limits often require a greater air volume.

Sampling Set Up
Ensure there is an appropriate sampling port set up for every point of use in the validation. Consider the materials, the locations, and the ease of access for successful sampling and delay prevention.

Tubing and fittings should be stainless steel or a conductive polymer. Other softer metals and plastics can lead to shedding. Long permeable hoses can result in water contamination. Seals should be welded or use stainless steel. Putty and PTFE tape are known...
to shed and should be avoided at sampling points. Use particle-free stainless steel valves or have stainless steel shut-offs.

A thorough purging of system piping before sampling is essential in avoiding particle contamination from construction, installation, or modification of the piping.

**Documentation and Training**

Documentation and training certificates must be recorded and stored for each validation. Chain of custody, training documents, calibration certificates, and analysis reports should be organized and completed.

A third-party laboratory can provide you with calibration certificates and training modules. Thorough completion of data sheets will result in quick and succinct reports.

**CONCLUSION**

When performing a validation of a new or modified compressed air system, identify the specification requirements, sampling timeline, and required materials for successful testing. Working with a third-party accredited laboratory that specializes in compressed air and gas testing makes the process straightforward. For more information, please contact Trace Analytics via email: sales@airchecklab.com or phone: 512-263-0000 ext 5.

**Resources:**

Selecting and Optimizing the Right Manufacturing Partner

William Bakewell

Optimizing the use of partners for clinical trials depends on selecting the right contractor. Significant resources are needed to bring new drugs to market. Companies that historically have not used third-party manufacturing may consider outsourcing rather than adding internal capabilities if their new product line requires specialized manufacturing equipment or expertise that are not available in-house. Virtual pharmaceutical companies, for example, which have no internal manufacturing capabilities, may use multiple contract manufacturing organizations (CMOs), contract development and manufacturing organizations (CDMOs), or contract research organizations (CROs).

Selecting the right manufacturing partner(s) and optimizing the use of those partners can include several key benefits, such as accelerated development and production timelines; reduced equipment costs and access to specialized equipment, both for production and analysis; and technical and regulatory expertise that can facilitate and expedite filing.

From a quality perspective, the sponsor and external service provider are responsible for the quality of the product, with the study sponsor ultimately being responsible for “approving or rejecting drug products manufactured by the contract facility” (1). This requirement has prompted some sponsors to choose an independent third-party laboratory to perform release and stability testing, a strategy that is particularly advantageous if a sponsor is using multiple manufacturing sites.

Criteria to consider

Utilizing a single CRO as the analytical testing site for all the sponsor’s manufacturing sites increases the consistency of the data because the same analysts, equipment, and methods are used to analyze samples from multiple manufacturing sites. Most CROs offer method development, method validation, and stability testing, although these same services may be offered by the CMO or CDMO. If an independent laboratory is used for release and stability analysis, then the sponsor or CDMO will often be approved as a backup testing site. CROs may offer services such as mass spectrometry, protein characterization, microbiology, extractible leachable testing, and impurity identification that may not be part of the service offering from a CDMO.

Several criteria should be considered when selecting a CRO, CDMO, or CMO for analytical services. These criteria include, but are not limited to, the following.

Ownership of methods, protocols, and data should be clearly defined.

Ownership and intellectual property. Understanding the legal framework that a CMO, CDMO, or CRO uses is important and especially so if the service provider is outside the United States. Contracts and quality agreements can help define these points but may not wholly mitigate issues with intellectual property. Ownership of methods, protocols, and data should be clearly defined as it can impact regulatory filings and method transfer.

Risk reduction. One of the core principals of quality by design (QbD) is risk reduction. Selecting a service provider should include risk analysis. Effective communication is critical to the success of any outsourced program, and the risk associated with managing the program should be evaluated as part of the contract and selection process. For example, if the service provider is in a different time zone or is in a country whose primary language is not the same, communication may be more difficult. Similarly, vendor location can impact audits and
site visits. Management of the program may require more resources from the sponsor if the service provider has limited project management capabilities, is in a different time zone, or has limited program management resources.

Service provider reputation and capacity. Understanding the service provider’s past performance with projects of a similar scope, from companies with a similar size, and with similar management capabilities is information that should be gathered early in the process. Identifying the production and analytical capacity needed and assessing the ability of the service provider to deliver on time is also an important part of the analysis. One should identify critical manufacturing and analytical components and the levels of redundancy if failure should occur.

Shipping and supply chain. Outsourcing to either a contract manufacturing site or analytical laboratory means shipment of materials. If the service provider is overseas, then shipment of materials to the US may be required and, depending on the product, may require special handling due to temperature or safety restrictions. Early planning to ensure that sufficient material remains to support the clinical and analytical studies in the event of a shipping failure is prudent.

**Effective communication is critical to the success of any program.**

Furthermore, temperature recording devices should be used in controlled-temperature shipments, and the CRO must be able to download the information. If multiple manufacturing sites are used, setting stability testing and performing release testing at a single analytical site can reduce or mitigate shipping risks.

**Building efficiencies**

Efficient utilization of CDMO, CMO, or CRO resources can significantly reduce the amount of capital investment in manufacturing and analytical equipment a sponsor must expend. The time needed to bring new products to market also may be reduced.

As with any internal project, if the sponsor uses a third-party service provider, the sponsor will be involved in day-to-day communications and operational decisions and should ensure that sufficient quality project management resources have been identified to support the program. This is particularly true if multiple CMOs or CDMOs are used to manufacture the product.

It is more efficient if a single CRO serves as the analytical laboratory for all the CMO or CDMO aspects of the program. Minimizing the number of external partners can reduce this program management workload, while using a single analytical lab can reduce risk and costs while resulting in improved quality.

**Reference**

Q. We, a contract manufacturing organization (CMO), have a written rule that describes that we will not show batch records, which have not been completely reviewed and approved by the quality function, during a customer audit. We consider this an absolute necessity to avoid an auditor finding missing or incorrect entries in the batch record. Yet, we received a critical finding for that in a recent audit. We pointed out to the auditor that we are following our quality system, but the auditor would not change the criticality of the observation. Do you think this is fair?

A. Clearly, if this had been a regulatory inspection, refusal to present a batch record, whether reviewed by your quality unit or not, would be considered preventing an inspection, with all its consequences (1). However, this was an audit, so this is a different situation.

We must consider why a CMO may not wish to present a batch record during an audit. The one obvious and valid reason is client confidentiality. But even this can easily be overcome by asking the client to use an impartial auditor.

You cite a very different reason, namely the need to have the batch record first reviewed and approved by the quality unit in order to have a “perfect” batch record. The best way to demonstrate the error in this is by presenting real examples from various CMO audits.

The regulations specify that batch record entries must be made contemporaneously (2). That means as close to the event as is possible. During an audit of a filling line, it was found that the machine had broken down and two engineers were busy repairing the equipment. As this would take a while, the operators had left the line and went to have an unscheduled break. The review of the batch record revealed that there were no entries for the following:

- The equipment having broken down, or when
- The shift operators having left the room, or when they left
- The engineers being present in the room, or when they entered.

The site’s quality system explicitly required all these to be documented, yet it hadn’t happened. Only the possibility to review the batch record allowed the auditor to find and record this deviation. Even a later review by the quality unit could not have found these errors and omissions. Thus, only a review of the batch record at the time of the audit can uncover such non-compliances.

When the shift operators returned to the line, they were confronted with the missing entries. Thereupon, one of the operators started to enter the data from memory, in fact backdating the events. Again, something impossible to detect at a later date.

### Batch record entries must be made contemporaneously.

The regulations also specify that entries cannot be made before the actual activity has taken place (3). A good time to perform audits is during lunch breaks when staff are away from their workplaces. During an audit of a packaging line, a batch record was found that had signed entries for completed actions that would only take place after the lunch break. If the batch record had not been presented in that audit, it would not have been possible to find this serious deviation from the basic principles of good documentation practice.

Batch record reviews by the quality unit typically take 40 or more days at CMOs, by which time the audit report has long been written and issued. In most cases, auditors would thus be unable to even review the “sanitised” version of the batch record. These few actual examples clearly demonstrate the absolute need for auditors to have access to the batch records of the activities they are reviewing. If this is prevented, they cannot verify the truthfulness (i.e., the integrity) of data in the batch record. And to most auditors, this is a critical observation.

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1. FDA, Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection, Guidance for Industry (October 2014).
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