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Frequently Asked Questions About Quality Control vs. Quality Assurance
Like oncoming hurricanes, we respond with trepidation to Greek letters for emerging COVID-19 variants. Apart from fraternities, or perhaps high-tech product names, we mostly ignore the ancient Greek alphabet. But now omicron is on nearly everyone’s lips. While understandable, this is probably a distraction from putting energies into areas that would better serve our long-term interests. Namely, new antiviral pill treatments and rapid tests. Although virus evolution tends to favor weaker but more transmissible variants the further an outbreak persists, we cannot bank on COVID-19 following this course.

Acyclovir is used as part of the cocktail mix treatment for HIV but is most commonly used for herpes and shingles. An infectious agent replication process can potentially be slowed down enough by an antiviral like acyclovir for the patient’s own immune system to take over disease elimination. There are three antivirals entering the armament against COVID-19, with still more to progress through clinical trials. They will likely become a mainspring for beating back and finally overwhelming our currently never-ending surges.

But like all antivirals, they have a small window within which to be effective, about three days from onset of symptoms. So, we return full circle to the dire need for cheap, accurate rapid tests, and encouraging the behaviour to use them. After nearly two years, we have the weapons to fire back at COVID-19. Our next test is, do we have the organizational prowess to make tests readily available, and do we have the resolve to act communally to use them? We struggled to do this for COVID-19 vaccines. Can we pass this test for antiviral pills?

Mike Hennessy, Jr
President and CEO
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EDITOR'S COMMENT

Spinning Success?

U niversity spinouts enable the commercialization of innovative research from academic institutions, providing early-stage project visibility for Big Pharma companies and investors, creation of intellectual property, and technology transfer services. The benefits of university spinouts, such as BioNTech for example, have been irrefutably proven over the course of the COVID-19 pandemic. Intellectual property services and R&D tax credit specialists, GovGrant, performed an analysis of data for companies founded in the past 20 years. Their analysis revealed that, in the United Kingdom, university spinouts in the fields of pharmaceuticals and biotechnology managed to raise the most capital (1). In fact, half of all the capital raised, which is worth £5.9 billion, went to pharmaceutical and biotech spinout companies.

Additionally, based on its analysis, GovGrant found that seven of the top 10 most successful university spinouts from the past decade are housed within the pharmaceutical and biotechnology industries. The top-ranking spinout, Exscientia from the University of Dundee, is valued at £784.5 million (1).

However, despite the publicised success stories, there are still hurdles for European university spinouts to overcome. A potentially success-limiting issue for university spinouts is the continuing lack of sufficient late-stage funding (2). Even with growth in late-stage funds since 2010 and higher returns on investment in Europe, the region still lags behind the United States and China in the biotech sector (3). Then there is the challenge with equity shares and revenue royalties that have been specified as “too high” in Europe, which is not necessarily the case for US academic entrepreneurs (4).

So, how might Europe as a whole begin to take advantage of the innovation borne from academic institutions in the longer term? Domestic funding, particularly during the late stages would be a good start (5).

References

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Digitalization Moves Forward in Pharma Equipment and Processes

Bio/pharmaceutical manufacturing harnesses the benefits of digital transformation.

Jennifer Markarian

The benefits of digital maturity in pharmaceutical manufacturing were made evident by the COVID-19 pandemic during 2020 and 2021, as the sudden need to develop, manufacture, and distribute treatments and vaccines intersected with travel restrictions, social distancing, and supply chain interruptions. Digital technologies that could meet these new challenges and aid manufacturing scale-up and speed to market, such as automated digital data collection and augmented and virtual reality (AR/VR) remote collaboration tools, were already available and had been adopted by some, but the new demand spurred greater adoption. The need to solve manufacturing challenges gave more companies the incentive to initiate or make further progress on their digital transformation journeys.

“These events directly showed the payoff of information technology (IT)/operational technology (OT) integration achieved over the last several years, but also revealed that we have an opportunity to do much more,” says Dan UpDyke, strategic marketing manager at Rockwell Automation. “The ability for the industry to pivot and quickly bring new therapies to market highlighted the need for flexible, saleable, and connected manufacturing systems. We have already seen an increase in integrating data and recipe management through a manufacturing execution system (MES) and flexible distributed control systems (DCS),” says UpDyke. “These are technologies that enable faster time to market by reducing the efforts to shift to new products.”

“As an industry, we’ve seen we need to be more efficient and we need to be able to monitor and manage processes remotely from a centralized location. People are focused on process intensification and how to better digitize and automate their processes,” says Merrilee Whitney, head of the BioContinuum Platform at MilliporeSigma, the United States and Canada life science business of Merck KGaA.

The pandemic created a higher awareness of the need for digitalization, adds Dirk Wollaert, Vertical Market Pharma at Siemens headquarters in Belgium. Digital technologies were key to the success of the rapid development and rollout of the COVID-19 vaccines, facilitating cross-company collaborations even across national borders. “Globalization and industry standardization to facilitate smoother transition from one production plant to another became more important,” he explains.

Another change that accelerated in the past two years was a transition to the cloud for software solutions and data storage, adds Pamela Docherty, Life Sciences Industry manager at Siemens USA. “The ability to push data from the manufacturing floor to the cloud creates a backbone for digitalization,” she says.
In bio/pharmaceutical manufacturing, the application of “Industry 4.0” technologies, such as digitalization, must be aligned with regulatory requirements, including good manufacturing practices (GMPs). The International Society for Pharmaceutical Engineering (ISPE) has trademarked their initiative as Pharma 4.0, also dubbed the “Smart Factory,” and has developed an operating model, which the Pharma 4.0 special interest group notes goes beyond IT to organizational, process, and resource aspects (1).

“There is a cultural aspect to digitalization because it’s a significant investment that results in changes to the operational structure of a facility; it is beneficial when the digitalization comes from the top,” explains Yvonne Duckworth, automation engineer and Industry 4.0 subject matter expert at the CRB Group, a life sciences engineering and construction company. “We are seeing more often that management is driving the adoption of digitalization in new facilities. It is becoming a standard and expected part of facility design.”

In the past five years, pharma manufacturers have been moving toward digital maturity. Assessed using the BioPhorum Group’s Digital Plant Maturity Model (2), some manufacturers are at level 1 (predigital); some are at level 2 (digital silos and islands of automation); many are at level 3 (connected plants) on their way to level 4 (predictive plant with real-time predictive analysis), and others want to adopt some aspects of level 5 (autonomous, adaptive plant), says Duckworth.

Although in past years, digitalization primarily meant moving away from paper-based systems to digital reports that were then printed to electronic or physical paper, a new paradigm enables a jump from Pharma 2.0 paper-based systems to the Pharma 4.0 operator-centric connected plant, said Gilad Langer, industry practice lead at Tulip, which supplies a cloud-based front-line operations platform (3). “This paradigm shift changes the culture and the processes, but doesn’t significantly change the operator’s workflow. Instead, digital apps are built to bring the physical world to the digital world with sensors and cameras, with digital output as the evidence. Data from equipment and human activities are collected via the industrial internet of things (IIoT),” explained Langer.

**From data to digital twins**
Digital tools depend first on good data collection. Having equipment that is set up for data collection and data analytics is becoming increasingly important, says Duckworth. Machine sensors and process analytical technology (PAT) instruments can communicate directly with data collection systems using the IIoT. These large quantities of data are needed for machine learning (ML), including artificial intelligence (AI) systems and digital twins, which are representations of the physical world in the digital world. Visualizing data in ways that scientists and engineers can use to improve understanding and to optimize processes is also important. Technologies can enable an “end-to-end digital thread of information,” says UpDyke. “Multi-site manufacturing in different markets is pushing the industry towards more connectivity, improved visibility across sites and organizations, and increased knowledge and information sharing that will enable expedited recipe development.”

New England Controls, Inc. (NECI), which partners with Emerson, has developed and deployed new digital tools in the past year that enable access to data sources and aggregation into analytical tools to link the “physical plant” to the “digital plant,” says Michael Cody, director of digital and clinical manufacturing at NECI. Access to data with operational context is crucial for pharma manufacturing facilities, says Cody. “The need to aggregate and analyze data from a variety of data sources is pushing equipment and technology providers to be able to interface and communicate with those digital tools in a meaningful way,” he explains.

Digital twins are a tool being increasingly used in a wide range of scenarios, from engineering optimization of individual pieces of equipment to analysis of full manufacturing systems. Examples from the past year, says Docherty, include digital twins for process development with an innovative mixing application, a representation of a new skid to enable faster fabrication, an offline training system for a continuous direct compression line, and an alerting system to ensure that people were keeping proper distance on the manufacturing floor.

Siemens also collaborated with GlaxoSmithKline on a digital twin pilot project that modelled and controlled the adjuvant particle manufacturing process. The project proved the concept that digital twins could be used in vaccine process development and transferred to manufacturing (4). As biopharmaceutical facilities shift to modular, multi-product facilities, digitalization enables efficient automation. A DCS can be used to connect the components, even as the process flow changes depending on how the different production modules are combined, says Docherty.

Siemens and Sartorius, for example, demonstrated a modular production system using the Siemens DCS with Sartorius’ Biostat bioreactor system. The companies set up an agreement to build standard interfaces between the Sartorius unit operations and the Siemens control system for closer integration (5). This system would allow the option of a fully paperless manufacturing facility.

**AR/VR tools**
AR digital tools are finding a wide range of uses in pharma manufacturing. Prior to 2020, AR was being developed for training and as an aid for technicians following standard operating procedures, for example, and it was being used for remote equipment
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maintenance and troubleshooting. When the pandemic suddenly made being on site impossible, AR/VR suppliers, such as Apprentice IO, stepped up with kits that included smart glasses and the technology to connect remotely (6) and pharma manufacturers and their suppliers began using them for tasks such as remote factory acceptance testing (FAT) and installations. The efficiency of these tools is expected to drive continued use. For example, reports Duckworth, using AR for FAT has now become an accepted practice.

Manufacturers also began using AR/VR tools for remote inspections, audits, and facility tours. Suppliers such as Avatour offers cloud-based communication platforms with 360-degree video capabilities so that viewers can control what they are seeing. “By combining [this communication] with sensor data and geo-location stamps, these platforms provide independent third-party validation of what exactly transpired during each site visit,” asserts Devon Copley, cofounder and CEO of Avatour.

Regulatory agencies also used these tools for what the US Food and Drug Administration (FDA) calls Remote Interactive Evaluations of facilities. Although such tools will not replace physical inspections, their use is expected to continue (7).

**Efficient development and tech transfer for mRNA vaccine manufacturing**

The data analysis and clear communication allowed by digital tools has demonstrated its benefits for process development and technical transfer, making time to market faster. Digital manufacturing technologies were successful in helping vaccine manufacturers, such as Moderna and Pfizer, accelerate their technology transfer and manufacturing process.

“The capability to perform technology transfer from Moderna to their contract manufacturing partner, Lonza, was enabled by the digital technologies deployed in their respective facilities,” says Cody. “Both Moderna and Lonza utilize DeltaV as their process automation system and Syncade as their manufacturing execution system. NECI teams partnered with Moderna and Lonza teams to transfer equipment automation strategies and electronic batch records from company to company, accelerating the manufacturing capacity and establishing supply chain capability as the Moderna COVID-19 vaccine was completing clinical trials and FDA emergency use approval.”

The availability of digital tools and the collaboration of implementing them in a refurbished facility was key to the speed of bringing BioNTech’s mRNA vaccine to commercial production in Europe, adds Wollaert. The process was brought online in under six months, while under normal circumstances it would have taken at least one year, he observed.

Siemens, a long-time partner of BioNTech, assisted the company in converting a facility in Marburg, Germany to mRNA vaccine production using end-to-end digitalization of production. Siemens Opcenter Execution Pharma was chosen as the new MES, and the digital system enabled conversion to paperless documentation of production with electronic batch records. Although the process has a number of manual work steps, operators are guided through these with the software’s workflow management component. The Siemens Simatic PCS 7 distributed control system was used to automate processes (8).

**Looking ahead**

FDA recognizes the role of digitalization and is working with industry suppliers to better understand these technologies. "The pandemic created significant opportunities for education and experimentation of digitalization with FDA,” says Jason Spiegler, senior director of Life Sciences Strategic Initiatives, Siemens Digital Industries. Although initial projects looking at digital twins took place within FDA's Center for Devices and Radiological Health (CDRH) (9), the understanding developed in device manufacturing can be applied to other FDA branches, suggests Spiegler. Spiegler also co-leads a joint FDA and industry computer software assurance (CSA) team that is focused on educating and promoting the adoption of risk-based CSA best practices for the life sciences industry. “CSA is foundational for unleashing the potential of digitalization on the shop floor,” says Spiegler.

Although paper-based systems are still prevalent in the industry, the benefits of digital and automated systems were made more clear by the upheaval over the past two years, and the industry can expect more digitalization of manufacturing equipment and processes in the coming year.

"There is more of an acceptance that digital transformation is necessary and worth the investment in a regulated industry. This new awareness will help drive digital transformation and move the industry significantly forward,” predicts UpDyke.

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Stabilization of Amorphous APIs

Polymeric amorphous solid dispersions are the most commonly used technology, but amorphous APIs remain inherently unstable.

A large percentage of small-molecule APIs in development today suffer from poor solubility and bioavailability. Stabilizing these APIs in their amorphous forms can help overcome these issues because a supersaturated state is achieved upon dissolution and delivery. Such a state can result in enhanced absorption across gastrointestinal membranes and improved bioavailability, according to Lindsay Johnson, global technical marketing manager for BASF’s Pharma Solutions business.

“The high thermodynamic energy of an amorphous, supersaturated state is inherently unstable, however, and such systems are driven towards crystallization, liquid-liquid phase separation, or non-descript precipitation,” Johnson says. Tendencies to recrystallize, absorb moisture, and participate in side reactions that generate impurities must also be overcome.

Solid dispersions lead the stabilization way

Depending on the chemical nature of API candidates, there are a variety of mechanisms that can be used to overcome solubility challenges. Amorphization of the API is one mechanism that can be pursued, observes Johnson, and commonly amorphous APIs are stabilized in amorphous solid dispersions (ASDs) formed via solvent evaporation processes such as spray drying (SD) or fluid-bed coating or melt processes such as hot-melt extrusion (HME).

These methods for stabilizing amorphous formulations are polymer-based, notes Daniel Joseph Price, strategic marketing manager, excipients for solid dosage at MilliporeSigma. “Although different processing methods are used and formulations vary, the end result is the same: a polymeric matrix, with hopefully a homogenous distribution of API throughout the polymer,” he adds. The distribution of the API in the polymer essentially immobilizes the API in the amorphous form, preventing re-crystallization.

Currently, there are 17 commercially available spray-dried dispersion amorphous drug products and 13 approved HME products (1,2). “Both of these technologies are established in the industry, easily scaled-up, and continuous,” comments Molly Adam, an R&D engineer at Lonza.

There are a variety of mechanisms that can be used to overcome solubility challenges.

Both methods have advantages and disadvantages, too. Spray drying does not expose the API to high temperatures, but requires the use of large quantities of organic solvents and nitrogen gas and can have low throughputs, all of which make the process costly, Adam says. While extrusion has a lower footprint and a higher throughput, the process involves high temperatures and shear stresses that can degrade some APIs.

Many factors to consider

Generally speaking, the selection of amorphous formulation technologies should be guided by the glass-forming ability of the API, according to Price. “The glass-forming ability essentially describes how likely it is for a molecule to re-crystallize,” he explains. “Poor glass formers are molecules that have very poor stability in the amorphous form, and so have an inherent re-crystallization risk. It is therefore recommended to only use polymeric amorphous solid dispersions when working with good or moderate glass formers,” he continues.

The choice of spray drying or HME depends on several factors, including processing space, scale-up needs, performance drivers, and the properties of the API, says Gereint Sis, an R&D scientist with Lonza. Important physicochemical properties that drive API stabilization are the melt and glass-transition temperatures (Tm and Tg, respectively).

APIs with significantly high melting points are not typically amenable to HME due to degradation, while APIs with poor solvent solubility are challenging for spray drying.

Ultimately, the amorphous system (API-polymer interactions, weight per cent of API, temperature, humidity, and the region of the phase diagram...
the formulation occupies) will drive the extent of stabilization (3).

“The optimum selection strategy involves cooperatively conducting high-throughput, small-scale manufacturing, iterative in silico modelling, bench-top testing, polymer screening, and discriminating in vitro testing,” Sis states. The resulting optimum stabilization method should ensure performance, manufacturability, physical and chemical stability, and enable patient compliance, he adds.

One challenge, Sis observes, is the difficulty of striking a balance between these metrics while alleviating complexity and lowering costs. “Strategic and agile technology selection methodologies can help manage these issues,” he says. In addition, adding robust data sets coupled with machine learning to current selection strategies will likely ensure shorter timelines and alleviate cost burdens to drug-product-development lifecycles (4).

Choosing the right excipients is crucial

Common excipients include polyvinylpyrrolidones (PVPs), their copolymers, and their cross-linked derivatives, polyvinyl acetates (PVAs), and some functionalized cellulosic materials such as hydroxypropyl methylcellulose acetate succinate (HPMCAS). Typically, a binary API-polymer system that affords favourable API-polymer interactions to provide the stabilization is used in an ASD (3). These excipients are usually required to have specific material properties, including a relatively high Tg (usually 70 °C or higher), according to Johnson. Polymers with high Tg values are great at stabilizing amorphous APIs because they increase the Tg of the dispersion and decrease mobility, according to Adam. She says that polymers with a wide processing temperature range are great for HME because they have a lower chance of degradation.

Poloxamers or polyethylene glycol (PEG) are also common in HME to improve processability by plasticizing the system, which decreases its melt temperature and melt viscosity. For SD, polymers with good organic solubility and low solution viscosity when dissolved are crucial to enable sufficient solubility for both the API and polymer.

Even though amorphous APIs are stabilized in ASDs, instability can remain an issue during storage and once the formulation has been administered to the patient.

Depending on the stabilizing mechanism, Johnson also notes that excipients for ASDs may contain functional groups that can participate in specific polymer-drug intermolecular interactions or have a rough solubility parameter that matches the hydrophilic/hydrophobic balance of the API in order to offer non-specific interactions that can be stabilizing.

Furthermore, polymers can aid in stabilizing the drug in gastrointestinal fluids in vivo and in the solid state during storage, according to Adam. Neutral polymers like PVP grades and HPMC can maximize dissolution rates throughout the whole range of pH of the GI tract. Enteric polymers such as HPMCAS and Evonik’s Eudragit L functional delayed release polymer can enable acid-sensitive APIs to be released in the intestine rather than the stomach if they degrade at low pH or have low solubility in the stomach.

For poor glass-forming APIs with inherent mobility, Price points out that mesoporous silica has emerged in recent years as an excellent excipient for stabilization. “The steric confinement of the API in nanosized pores after loading substantially reduces the mobility of the API in the formulation,” he explains.

Opportunities for instability still exist

Even though amorphous APIs are stabilized in ASDs, instability can remain an issue during storage and once the formulation has been administered to the patient. “The one downside to polymeric ASDs is the inherent mobility of both the polymer and the API in the formulations, which can lead to re-crystallization of poor glass-forming APIs,” Price states.

The mechanisms by which amorphous forms destabilize are phase separation and crystallization, according to Sis. “When an amorphous solid dispersion phase separates, distinct polymer-rich and API-rich amorphous phases form, which can make the amorphous API more prone to crystallization. Phase separation may or may not be a precursor to crystallization, with the rate-limiting step for crystallization being either diffusion or crystal nucleation,” he explains. Nucleation occurs when small seed crystals of the API form that then grow until a thermodynamically stable polymorph is obtained, according to Price.

Internal factors affecting the extent of stabilization of ASDs include the API loading, the polymer properties, and the drug-polymer interactions within the ASD, Sis outlines. For instance, hygroscopic excipients that absorb moisture will have negative consequences, as will formulations that contain plasticizers that increase polymer and API mobility, according to Johnson.

Environmental factors such as humidity and temperature can thus also affect the chemical and physical stability of the amorphous API within the formulation by increasing the kinetics of unwanted reaction pathways, such as degradation in the presence of water. Increased API mobility leads to a shift in the phase diagram, phase separation, and API recrystallization (3). “Smart formulation decisions and storage...
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strategies are necessary to mitigate these risks,” Si says conteds.

The behaviour of the amorphous form upon dissolution in the body must also be considered, says Price. “When an amorphous API is dissolved, supersaturation generally occurs, and the API is in solution at concentrations higher than its thermodynamic solubility. Supersaturation is not a stable condition and is thermodynamically unfavourable. The API may precipitate out of solution and undergo nucleation and crystal growth, or API-rich liquid domains may separate out of solution,” he says.

Upon dissolution, observes Johnson, the stability of amorphous APIs is often segmented by their relative molecular and physicochemical properties, which will dictate which formulation approach is likely to be successful at stabilization. “In order to be amorphous and solubilized, any drug molecule needs to dissociate from its crystal lattice, and the dissolve media needs to solvate the drug molecule at the molecular level. Both of these processes require energy to either overcome drug-drug intermolecular forces or solvate the compound, respectively,” she explains.

Depending on which step is more solubility-limiting for a particular API, Johnson continues, the molecule can be referred to as a “brick dust” molecule or a “grease ball”. “Grease ball” and “brick-dust” APIs are associated with low and high melting points, respectively, and thus Tm and lipophilicity (log P) are often predictors of this categorization. In fact, Tm and log P can be used in combination with an API’s amorphous stability to steer the selection of formulation type, according to Johnson.

“The supersaturation concentration achieved relative to that amorphous solubility is what dictates the destabilization process—whether direct crystallization that occurs below the amorphous solubility threshold or liquid-liquid phase separation that occurs above the amorphous solubility threshold,” Johnson concludes.

It is therefore important, stresses Price, to ensure not only the stability of the amorphous form in the solid state, but also stabilization of the supersaturated state upon dissolution.

**Increasing interest in co-amorphous systems**

Recent literature has expanded the interest in the field in co-amorphous systems, specifically ones that are not cocrystal forming. These co-amorphous systems include the API and a low-molecular-weight molecule that may be another pharmacologically relevant API or an excipient, Johnson observes.

She adds that such formulations are commonly produced via mechanical milling, melt quenching, or solvent evaporation.

As an example, Price points to the spray drying of a mixture of an API with an amino acid, with the latter stabilizing the API in the amorphous form. “The two main benefits of this approach are processing and quality. The two main benefits of this approach are processing and quality. For small-molecule coformers, it is easier to identify cosolvents for spray drying, and from a quality perspective, a small-molecule coformer is more well-defined and easier to control than a polymer,” he states.

Co-amorphous forms may also benefit from higher intermolecular interactions that prevent crystallization, higher conformational flexibility to prevent phase separation, and the anti-plasticizing effect of small molecules (5). They have also been shown to have increased solubility, dissolution rates, and physical stability compared to polymer ASDs with weak intermolecular interactions, Adam comments.

There are challenges to the formation of co-amorphous systems, however. Their typically higher molecular mobility, for instance, can lead to a greater tendency to crystallize during processing and storage, according to Johnson. She notes that significant performance variability can result, so co-amorphous formulations must be extensively studied in order to mitigate these impacts.

**Several technology advances of note**

Recent advances in ASD technology are helping to overcome some of the limitations posed by the nature of poorly soluble APIs. High-shear mixing as an alternative to HME has the benefit of fast processing times combined with reduced exposure to high temperatures, according to Adam. “This technology has the potential to greatly impact the use of amorphous APIs by opening up the processing space where both SD and HME fall short, because it can be used for APIs with low organic solubility and high melt temperatures without degrading them,” she comments.

For APIs with poor solubility in common SD solvents, Adam points to temperature-shift spray drying as another important manufacturing advance. In this process, a slurry of the API is rapidly heated using an inline heat exchanger before atomization to increase solubility and throughput around 10-fold (6).

Another development noted by Adam involves increasing the drug loading for ASDs while improving stability and maintaining performance. High loaded dosage form (HLDF) architecture takes advantage of a high Tg, polymethacrylate-based copolymer alone cannot effectively stabilize the amorphous API under these conditions,” she explains. “HLDF not only allows for higher ASD drug loadings, but also decreases tablet size and tablet burden,” she adds.

**A new approach: induced amorphization**

With traditional ASDs, the API is already in the amorphous state before it is processed into tablet
form. Induced amorphization is the process of amorphizing crystalline API within a dosage form, thus converting from crystalline to amorphous phase during tabletting. Deliberately utilizing this technique on a final dosage form can be described as in situ amorphization (ISA) and can be achieved using microwave radiation and other methods (7,8).

Price points to several examples in which APIs have been combined with small-molecule coformers such as amino acids, compressed into a tablet, and irradiated with microwaves to trigger ISA. One of the benefits of this approach is the ability to avoid using large weight fractions of polymer excipients, which dilute the concentration of API in the product, according to Sis. Physical stabilization of ASD formulations typically involves employing large weight fractions of polymers or other excipients in the final dosage form, which in some cases causes increased tablet burden, possibly lowering patient compliance (8).

“Decreasing the need for long-term amorphous API stabilization results in final dosage forms containing only crystalline API and having dramatically reduced excipient fractions,” Sis explains.

In addition, eliminating the need to manufacture SD or HME formulations could avoid flowability issues associated with ASDs and drive down manufacturing costs (7). “Other important advantages to this approach relate to the stability and shelf-life of the product,” Price comments. “If the API is converted to the amorphous form directly at the point of care (pharmacy or hospital), the shelf-life relating to the stability of the amorphous form is less important,” he posits.

There are significant hurdles that must be overcome before such a dosage form is realized, however, particularly with respect to regulatory and quality concerns, Price temporizes. The technology is currently in its infancy, however, Sis notes.

In at least one example, some seed crystals were still present following microwaving of a tablet formulation (8). For some drug products, that may not affect the dissolution rate, but for others it could have a negative impact.

Overall, Sis believes ISA technology appears promising and warrants further development and investigation, with efforts focused on complete crystalline to amorphous conversion. He observes that considerations should also be taken to develop and understand the landscape in which US Food and Drug Administration approval could occur. “ISA process technology must first be proven safe, effective, and scalable,” he concludes.

Drug loading also remains an issue for amorphous API dosage forms because they sometimes require high amounts of polymers to help with stabilization.

Continuous development required

Rapidly evolving characteristics for candidate drug substances are driving the need for continued advances in technologies for the stabilization of amorphous APIs. Already formulators are challenged by the poor solubility of Biopharmaceutics Classification System II and IV APIs in the development pipeline.

“The ideal scenario for each of these drug substances would be to achieve a kinetic (beyond physio-relevant timelines) or thermodynamic increase in solubilization that allows for effective bioavailability,” contends Johnson. To achieve that goal, she believes continued investment in novel excipients that balance the need for increasing solubility while not hindering absorption due to competing thermodynamic or partitioning mechanisms will be necessary.

Adam points to the increasing number of “brick dust” candidates in the pipeline that are poorly soluble in both water and typically used organic solvents. That makes SD ineffective due to poor throughput or high emissions of harsh solvents. Because they often have higher Tm values, HME is also often challenging or not possible.

“Strategies that can overcome the manufacturing complications with brick dust compounds will drive future formulation opportunities for needed therapeutics,” she concludes.

Drug loading also remains an issue for amorphous API dosage forms because they sometimes require high amounts of polymers to help with stabilization. In addition to HLDF architecture, Adam remarks that further improvements in stabilization technologies that enable decreased polymer amounts are needed to address this issue.

For Price, growing numbers of proteolysis targeting chimeras (PROTACs) and beyond rule-of-five (bRo5) compounds with molecular weights greater than 500 Daltons making their way through the clinic will be an important driver of innovation in amorphous technologies. "These larger molecules have the potential to totally transform the treatment of disease, in much the same way that mRNA is currently doing. The big difference is that PROTACs and bRo5 molecules have a high likelihood of being orally bioavailable and thus can be delivered orally. Development efforts must therefore be directed at identifying amorphous technologies for the formulation and stabilization of these novel and exciting modalities to ensure acceptable absorption from the GI tract,” he says.

References

It’s a Matter of Taste-Masking

Increased patient-centricity and alternative dosage forms require careful consideration when selecting the best taste-masking approach.

Felicity Thomas

A s most APIs have an unpleasant or bitter taste, solutions to help mask the flavour are integral in ensuring a dosage form’s palatability and commercial success. To learn more about the potential solutions currently available to formulators for taste-masking, as well as those approaches in the pipeline, best practices, and excipient considerations, Pharmaceutical Technology Europe spoke with Kevin Hughes, manager Regulatory Affairs at Colorcon; David Tisi, technical director at Senopsys; and Bing Xun Tan, PhD, Pharmaceutical Application Laboratory manager at Roquette’s Asia Pacific Innovation Center in Singapore.

Importance of taste

PTE: How important is taste-masking and what formulation approaches are currently available?

Hughes (Colorcon): Many APIs inherently possess a bitter taste. If a medication is not palatable, the patient may opt to discontinue taking their dose. Failure to take medication as prescribed can lead to avoidable healthcare costs, and potentially increased morbidity and mortality. While objectionable taste may be one of several reasons for poor adherence, every measure that minimizes these reasons helps.

The most popular oral dosage forms include liquids, powders, granules, and tablets—especially orally disintegrating tablets (ODT) and chewable tablets. Each one has pros and cons, depending on the target age group. Liquids, powders, and granules provide the greatest flexibility in dosing, provided there is a simple way to meter the powders. The commonly used techniques/methods of taste-masking include organoleptic methods, polymer coating, hot-melt extrusion, microencapsulation, complexation using ion-exchange resins, and spray-drying.

A more recent application is the use of ion-exchange resins, the resin-drug complexes formed will elute only a limited percentage of the drug in the saliva pH. Thus, the taste of the drug is masked without interrupting the drug release profile.

Tisi (Senopsys): Simply put, patients will not routinely take medicines that are unpleasant to them. A patient may take their first dose or even tolerate a bad tasting acute therapy, but for chronic indications, poor palatability has a negative effect on adherence/compliance.

Aside from the ethics of improving patient quality of life and the business case made for improved adherence, there are regulatory obligations and rewards for improving palatability in special populations. Both FDA (the US Food and Drug Administration) and the European Medicines Agency (EMA) require palatability to be considered in a sponsor’s Pediatric Study and Investigation Plans, respectively (1,2), in the submission package for the adult form. Such studies should include an assessment of formulation palatability.

Properly addressing the palatability challenge of a specific formulation will depend on the target form, type of API, chemical properties, and taste-masking challenge (how unpalatable the API is).

Tan (Roquette): Taste-masking solutions can enable the development of innovative orodispersible dosage forms, which are considered more patient-friendly. In the nutraceuticals market, where consumers can choose from a multitude of commercial offerings, product taste can be a deciding factor when it comes to making their purchasing decision.

Taste masking of pharmaceutical drug products is generally achieved through one, or a combination, of the following three approaches. The first approach involves chemical modification of the API to reduce bitterness.

The second approach uses excipients in formulation to facilitate a direct sweetening effect and/or reduction of the perceived API bitterness. Careful selection of excipients can enable formulation strategies using flavours, sweeteners, and bitter blockers. Pleasant-tasting, highly viscous, or lipophilic vehicles can also provide an effective taste-masking effect.

Lastly, advanced processing of the API or drug product can help minimize oral solubility and direct contact with...
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the taste buds. Common approaches include coating of API particles with a physical barrier; tablet film coating or sugar coating; microencapsulation; embedding of API particles in a matrix; microspheres and liposomes; complexation of API with cyclodextrins or ion-exchange resins; and adsorption of the API using insoluble powders.

**Best practices**

**PTE:** Are there best formulation practices to follow for taste-masking?

**Tan (Roquette):** In formulation, the difficulty of taste-masking is increased when the API possesses a strong bitter taste, high solubility in the buccal cavity, or when a high dose of the API is required.

It’s best practice to consider taste masking early in the product development process, as major regulatory agencies now require new drug product developments to include paediatric trials. [As a result of regulatory requirements] pharmaceutical companies are focusing on taste-masking solutions and palatability studies that can aid development and demonstrate patient compliance of the drug product for children. Early consideration of the potential need and solution for taste masking can help minimize potential delays later in the process.

**Hughes (Colorcon):** Several factors go into the decision process for the formulation, including properties of the API, dose level, dosage form, desired release profile, and so on. Both dissolution profile and taste profile contribute to the acceptability criteria for taste-masked formulations. However, each drug product will have different release profile requirements to meet an acceptable level of taste-masking depending on the dose strength and organoleptic response to the API. Ideally, the taste-masked dosage form should prevent the release of an unacceptable tasting medicine until the API has left the mouth, then allow for immediate release once the dosage has been ingested.

There are two main categories of coatings for taste-masking: pH-independent and pH-dependent. For most solid oral dosage forms or tablets, the active (API) is blended with several excipients, and a well-designed film coating, either pH-dependent or pH-independent, to adequately mask objectionable tastes for the brief residence time in the mouth before swallowing. Alternative dosages forms, such as chewables and granules, can increase the contact time in the mouth, giving an unpleasant experience and/or lingering aftertaste. In these cases, it is often necessary to create a barrier, such as a specific taste-mask coating, between the API and the taste buds to improve palatability and aid compliance.

**Tisi (Senopsys):** Formulators need to establish a target product profile (TPP) as soon as possible, as it guides all downstream development. The TPP outlines important questions including identifying the drug form, clinical strength, and dose volume. If these are initially unknown, an understanding of a drug’s sensory properties early on will focus development on those formulations most suitable to the challenges of the molecule.

Many (though not all) drugs have bitter or other aversive sensory characteristics, which may include a negative taste, smell, or irritation. These characteristics represent different perception pathways and importantly, the approach for dealing with each is fundamentally different. For instance, an API with only slight or moderate aversive sensory characteristics has many more formulation options than does a very intense or lingering API, which will require physical encapsulation as part of the formulation.

**Additional challenges**

**PTE:** Is the use of alternative dosage forms creating new challenges for taste-masking?

**Tisi (Senopsys):** Special populations such as paediatrics or geriatrics can have difficulty swallowing adult oral solid forms (dysphagia). Without exception, easier-to-swallow dosage forms increase the opportunity for contact with relevant sensory receptors of the patient. Accordingly, alternative formulations have an increased palatability challenge compared to traditional tablets and capsules. Some API sequestration taste-masking approaches (e.g., particle coating) result in an increase in particle size that often results in a gritty texture. Grittiness may reduce palatability in infants who have not been introduced to particulate foods. In addition, the presence of particulates can encourage chewing as part of normal oral processing. This can rupture coatings, releasing API in the oral cavity where it will be perceived. Additionally, some multiparticulate formulations are intended for dosing in foods, and the physicochemical properties of the foods may affect palatability, particularly if they are coated with a pH sensitive polymer.

**Tan (Roquette):** The pharmaceutical industry is actively looking into more patient-centric and age-appropriate dosage forms. Alternative dosage forms such as ODTs or orally disintegrating films (ODFs) are examples of these developments, to name a few.

Such products are designed to rapidly disintegrate in the mouth, where bitter APIs can have a prolonged direct exposure to taste buds, which results in poor palatability. However, excipients such as hydroxypropyl-β-cyclodextrin and pea-based maltodextrin have been successfully used to mask ODFs containing dimenhydrinate, an antihistamine used to treat motion sickness and nausea, and loratadine, also an antihistamine used to treat allergies (3,4).

**Hughes (Colorcon):** Alternative dosage forms such as sachets, ODTs, and chewable dosage forms pose additional challenges in taste-masking due to increased contact surface area as well as residence time in the mouth, enhancing any unpleasant taste and/or lingering aftertaste. In these cases, it is often necessary to create a barrier, such as a specific taste-mask coating, between the API and the taste buds to improve palatability and aid compliance.
Exciplent opportunities

**PTE:** What impact might the new excipient pilot programme, launched by the FDA’s Center for Drug Evaluation and Research (CDER), have on taste-masking?

**Hughes (Colorcon):** The new CDER pilot programme for novel excipients is a welcome initiative from FDA, it offers a new pathway for drug manufacturers to get an FDA review of novel excipients before the excipients are used in a formulation. Before this, the selection of a novel excipient by a drug manufacturer carried a higher risk, the New Drug Application could get held up by questions being asked about the safety and quality of a new excipient for example. With this initiative, the drug manufacturer can do this up-front, and this will reduce the risk to their timeline and make it much easier to select a novel excipient for dosage forms. Taste masking is one of the areas where different approaches and new materials are being explored all the time, and new materials that have no history of use in pharmaceuticals or foods can be assessed more quickly under this programme.

**Tisi (Senopsys):** Senopsys is a strong supporter of CDERs’ pilot programme to expedite the use of novel excipients. Co-processed flavour and sweetener system technologies similar to those used in the confectionery and chewing gum industry can sustain release of the flavour system over time. Such development has been hindered by the current lengthy excipient approval path.

**Tan (Roquette):** There are limited excipient options today that may be used to taste-mask APIs, and even fewer for formulations meant for paediatric patients. New pharmaceutical processing techniques used in taste-masked formulations, such as 3D-printing, also require suitable excipients better designed to facilitate these modern processes (5). The new pilot programme, launched by CDER, could enable the introduction of novel excipients, which may have a precedence of use in food or research in other industries—such as food—where there is already existing emphasis and expertise in terms of taste.

**In the pipeline?**

**PTE:** Are there any approaches in the pipeline that you believe will hold great promise for taste-masking in the future?

**Tan (Roquette):** A pea maltodextrin product from Roquette (KLEPTOSE Linecaps) has been primarily designed for taste-masking and solubility enhancement applications, with a particular suitability for paediatric formulations.

The pea maltodextrin can decrease exposure of the API to the taste buds through a specific mechanism of action and complements the current range of taste-masking excipients available to formulators. This excipient has been shown to exhibit a taste-masking effect on model APIs, such as loperamide hydrochloride and dextromethorphan hydrobromide (6).

**Hughes (Colorcon):** The traditional way to taste mask a bitter-tasting active material is to put a barrier between the active material and the sensory receptors for taste or to hide the bitterness of the material by including a flavour or sweetener in the formulation. It is common for both methods to be used at the same time.

New ways of placing that physical barrier around the bitter API are being evaluated, such as ion-exchange resins that can be used to create an API-resin complex that blocks the taste of the API but does not impact its bioavailability; hot melt coatings can be applied to the API or tablet to become a barrier that does not dissolve in the mouth and pH-sensitive polymers that are insoluble in the mouth but dissolve in the stomach pH can also perform this function.

Another interesting approach is to block the taste receptors, Danielle Andrews from University College London in the United Kingdom had a poster at the European Paediatrics Formulation Initiative Conference in September 2021 where she showed that sodium salts could be used as a ‘bitter blocker’ to effectively switch off the taste receptor temporarily (7).

There is plenty of activity in this area, especially around paediatric medicine development.

**Tisi (Senopsys):** One of the more interesting technologies that has not yet been fully employed in formulation development is the use of novel flavouring materials that disrupt taste signal perception. In humans, bitter taste is detected by a family of several dozen bitterness receptors (TAS2Rs). APIs are typically promiscuous in their receptor targets, activating multiple TAS2Rs simultaneously. Novel compounds are under development which act as antagonists to these receptors.

While promising, there are a number of hurdles to this approach. By their very nature, molecules that disrupt the taste signal cascade are bioactive compounds, and most drug developers are reluctant to risk their drug on possible interaction with an excipient. Next, signal disrupting excipients are proprietary compounds that have to be matched to the specific set of receptors that act upon their API, so this approach is not a one-size-fits-all compounds magic bullet.

Finally, the published data on this class of materials shows some bitter attenuation, but not complete masking. Accordingly, if used it would be one of a multi-pronged approach to palatability.

**References**

The authors introduce the idea of asymmetrical tolerance intervals as an aid in fully assessing product performance relative to product or process requirements. Tolerance intervals are generated by collecting data through sampling of representative product and processes and using tolerance interval factors (k) to create the tolerance limits. Tolerance interval factors are widely available in tables and available in many statistical computer programs.

Determining if a product will conform to requirements is an activity that most quality practitioners must confront and deal with in their careers. Being faced with a litany of codes, standards, contracts, specifications, and procedures begs the question, what’s a sound and effective method to assure that a yet to be produced product will meet requirements in the future? In this paper, the authors introduce using statistical tolerance intervals that can be routinely used to assess a product and to provide a range within which, one can expect product attributes to be contained.

The assessment process generally begins by collecting representative product samples from the population of interest, assessing the samples with defined procedures, and generating statistics (\( \bar{x} \), the sample average and \( s \), the sample standard deviation) with which one can characterize the product’s conformance to requirements. The key phrase here is “representative product samples”. If the collected samples don’t fully represent the variability in the manufacturing and measurement processes, the product will not be adequately characterized.

With representative samples available, one path forward would be the use of a process capability index to characterize the product’s performance, such as \( \hat{C}_{pk} \):

\[
\hat{C}_{pk} = \min\left[ \frac{USL - \hat{\mu}}{3\hat{s}}, \frac{\hat{\mu} - LSL}{3\hat{s}} \right]
\]

[Eq. 1]

Where:

- \( USL \) and \( LSL \) are upper and lower specification limits
- \( \hat{\mu} \) is estimated process average, usually \( \bar{x} \), the sample average
- \( \hat{s} \) is estimated process variability, usually \( s \), the sample standard deviation
- note: calculating \( \hat{C}_{pk} \) assumes that our sample data has a normal distribution.

Small values of \( \hat{C}_{pk} \) (0.3) indicate that a significant percentage of the product (30%) falls outside the range of product requirements. Large values of \( \hat{C}_{pk} \) (2.0) indicate that a significant proportion (99%) of the product falls within the product requirements. Process capability measures provide a figure of merit for reflecting conformance to requirements. One of the

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shortcomings of process capability indices is that they don’t reflect the uncertainty of \( \mu \) and \( \sigma \) when calculating the index. Using statistical intervals addresses this uncertainty.

Common statistical intervals used to assess product performance include:

- Confidence intervals assess how well sample statistics estimate the parameters associated with a population that was sampled from. A statement such as, “with 95% confidence, the true population average, \( \mu \) will be contained within an interval” can be made.
- Prediction intervals generate an interval that will contain one or more future product samples, based on previously obtained samples, with a specified probability. A statement such as, “with 95% confidence, the next 10 units of product that will be produced will be contained within an interval”, can be made. This type of interval is applied to situations when producing small numbers of product.
- Statistical tolerance intervals are used to generate an interval within which a specified proportion of a sampled population falls, with a stated confidence. A statement such as, “with 95% confidence, 99% of a population will be contained in an interval”, can be made. This type of interval is commonly used in specifying an interval within which future production will be contained.

Most introductory statistics courses fully address the use of confidence intervals. Prediction and tolerance intervals may or may not be addressed even in advanced courses. The authors’ focus will be on the use of tolerance intervals to describe product performance.

**Tolerance interval basics**

Tolerance intervals (TIs) were first discussed in 1941 as a means to develop specifications for use in the release of lots of product using sampling plans (1). The strategy was to develop control procedures and sampling plans for product attributes based on process capability as expressed by tolerance limits. TIs can be directly linked to the use of variables sampling plans for use in systematically determining the acceptability of lots of product (2).

Tolerance intervals fall into the following two basic categories:

- Nonparametric TIs do not assume that the data describing the product has a specific type of statistical distribution. These limits are sometimes called distribution free TIs. These nonparametric intervals are conservative in that they will be larger than their parametric counterparts.
- Parametric TIs assume that the data describing the product follows a specific statistical distribution. The most commonly used parametric TIs assume a normal distribution. Because of the normality assumption, the intervals tend to be smaller than nonparametric TIs. These intervals will be the focus of this paper. A discussion of methods to determine if a data set is normally distributed is contained in reference 3 (3).

TIs can be expressed as one-sided or two-sided types. One-sided TIs (sometimes called tolerance bounds) consist of a single upper or lower limit. Two-sided TIs provide symmetric limits around a central value, usually an average.

Unfortunately, the notation used in describing TIs varies from source to source. For the purposes of this paper, the following notations in describing the intervals are used:

- \( n \)– number of samples collected that represent the population
- \( \bar{X} \)– average of the representative samples
- \( s \)– standard deviation of the representative samples
- \( \mu \)– population mean, usually unknown but estimated by \( \bar{X} \), the sample average
- \( \sigma \)– population standard deviation, usually unknown but estimated by \( s \), the sample standard deviation
- \( p \)– proportion of the population contained by a TI
- \( 1 - \alpha \)– confidence associated with a TI
- \( k \)– tabulated TI factor used in calculating tolerance limits
- USL and LSL– upper and lower specification limits.

The authors provide the following formal definition of a TI:

A tolerance interval is a statistical interval that provides limits within which at least a certain proportion \( (p) \) of the population falls, with a given level of confidence \( (1 - \alpha) \). TIs are calculated based on a sample of observations from the population of which we are characterizing, using a TI factor \( k \), and are calculated for two-sided TIs as **Equation 2**:  

\[ \bar{X} \pm k \times s \]  

**[Eq. 2]**

One-sided TIs are stated as **Equation 3**:  

\[ TI_{\text{lower}} = \bar{X} - k \times s \text{ or } TI_{\text{upper}} = \bar{X} + k \times s \]  

**[Eq. 3]**

**Calculating tolerance intervals**

If one had complete knowledge of the product or process capability, one would know the values of \( \mu \) and \( \sigma \). In this case, statistical methodology in the form of the standard normal distribution (actually the inverse cumulative normal distribution function, \( Z \)) can be used to calculate an interval, within which the population’s values would fall (with 100% confidence). For example, with \( \mu = 98.5, \sigma = 2.1, p = 0.90 \) and \( Z_{1-(l-p)/2} = Z_{0.95} = 1.645 \), we could calculate the following two-sided interval (**Equation 4**):

\[ \mu \pm Z_{0.95} \times \sigma = 98.5 \pm 1.645 \times 2.1 = [95.05, 101.95] \]  

**[Eq. 4]**

Using this calculation, one can state “with 100% confidence, 90% of the population data values fall within the limits shown above”.

Let’s use an example to illustrate the calculation of a two-sided TI. Suppose one has collected the following representative information about a product’s performance with respect to a specific product attribute:

- Sample size \( n = 10 \)
- Sample average \( \bar{X} = 98.5 \)
- Sample standard deviation \( s = 2.1 \)
Because the values of the population parameters \( \mu \) and \( \sigma \) are not known, tolerance interval factors can be used to provide limits. TIs reflect the uncertainty of not knowing the actual population parameters and using sample estimates in their place.

To calculate a TI based on the sample attribute values, calculate a \( p \), \((1 - \alpha) \) tolerance interval using the following:

Proportion of the population to be contained by the TI \( = p = 0.90 \)

Confidence associated with the TI, \((1 - \alpha) = (1 - 0.05) = 0.95 \)

One can obtain the appropriate tolerance interval factor using Equation 5 (4, Table A.10b):

\[
k = g(1 - \alpha, p, n) = g(0.95, 0.90, 10) = 2.856 \quad \text{[Eq. 5]}
\]

Calculating the tolerance limits based on the sample data:

\[
\bar{x} \pm k \times s = 98.5 \pm 2.856 \times 2.1 = [92.50, 104.50]
\]

One can state with 95% \((100 \times (1 - \alpha)\%)\) confidence that at least 90% \((100 \times p\%)\) of population data values fall within the given limits.

As seen from these calculations, knowing the true mean and standard deviation of a population narrows the interval range because complete knowledge of the population is known. However, if we have only sample statistics describing the population, we use a tolerance interval factor \( k \) that reflects this uncertainty of the sample statistics. But what do these tolerance limits actually represent?

**TI factors explained**

TIs can be visualized via the following analogy:

- Select a tolerance interval factor \( k \).
- Generate a large (infinite) number of samples of size \( n \) from a normal distribution, with each sample having a mean \( \bar{x}_{\text{sample}} \) and standard deviation \( s_{\text{sample}} \).
- For each sample in step 2, calculate an interval, \( \bar{x}_{\text{sample}} \pm k \times s_{\text{sample}} \).
- Determine the proportion of future values contained by each interval in step 3.
- Confidence \((1 - \alpha)\) represents the proportion of intervals in step 4 that will contain at least 100 \( \times p\% \) of future values.

**Figure 1** shows an example using \( n = 10, p = 0.90, (1 - \alpha) = 0.95 \), and \( k = 2.856 \). Intervals that contain at least 90% of the population values are indicated in blue. Those that contain less than 90% of the population are indicated in red. The rightmost vertical axis shows population intervals calculated using the Z distribution.

Therefore, confidence represents the proportion of tolerance intervals that contain at least the proportion \( p \) of the population for a given \( k \). Some authors refer to \( p \) as the percentage of future values “covered” by the TI and the confidence level being the proportion of intervals that “cover” the percentage \( p \).

If we increase \((1 - \alpha)\) or \( p \), the value of \( k \) (as well as the tolerance limit range) will increase, and vice versa.

**Comparing TIs to requirements**

In the example above, two-sided tolerance limits of \([92.50, 104.50]\) have been calculated. If the product specification is 90.0 to 110.0, and if the sample data are indicative of the population, there is assurance of meeting the specification (with the caveat of 95% confidence and containing 90% of the population). However, if the specification is 95.0 to 105.0, the entire TI is not contained within the specification range and the product does not meet the requirements. The following section discusses some techniques to further evaluate TIs versus specification limits.

Shown in **Figure 2** are the two specification limits noted in the previous section as well as the TI, 95% \((100 \times (1 - \alpha)\%)\) confidence and proportion of at least 90% \((100 \times p\%)\). Two questions one could ask:

- When comparing the TI to the \([95, 105]\) specification, we note that the TI is not completely contained within the specification. Could we calculate the proportion of product (which we know is less than 90%) that is contained within the specification limits?
- When comparing the TI to the \([90, 110]\) specification, we note that the TI is completely contained within the specification. Could we calculate the proportion of product (which we know is more than 90%) that is contained within the specification limits?

The answers to these questions are not directly available through the use of conventional tolerance calculations, because these limits are symmetrical by definition. There are two options available to address these questions:

- It is possible to approximate two-sided tolerance limits using one-sided limits addressing the problem of asymmetrical TIs.
- A computer simulation evaluating tolerance intervals based on the asymmetrical specification limits of interest could be performed.

First consider the one-sided approximation approach.
One-sided asymmetrical approximation

Reference 4 (4), p. 204, specifies that, “One-sided tolerance bounds can also be used to obtain approximate two-sided intervals.” For example:

- Two-sided calculation: $n = 10$, $(1 - \alpha) = 0.95$, $p = 0.90$ yields $k = 2.856$.
- One-sided approximation: $n = 10$, $(1 - \alpha/2) = (1 - 0.05/2) = 0.975$, $p = (1 - (1 - 0.90)/2) = 0.95$ yields $k = 3.259$ (a 14% TI increase).

The one-sided approximation is conservative in that it provides a wider TI than its two-sided counterpart. The approximation can also be useful if one wished to generate approximate asymmetrical two-sided intervals. This is not necessarily a one-step calculation, but can be calculated through the use of available software.

The authors have developed computer programs, using the R statistical system (5) described as follows, to address these calculations. Some examples of how additional statements about conformance to specifications may be created are provided as follows.

**Example 1**

- Specification limits $[95, 105]$.
- Sample data $n = 10$, $\bar{X} = 98.5$, standard deviation = 2.1
- TI confidence level $(1 - \alpha) = 0.95$

Using the procedure T1.2.sided.p, which uses one-sided TIs to approximate two-sided TIs and estimates the proportion $p$:

$T1.2.sided.p(n=10, x.bar=98.5, std.dev=2.1, lower.limit=95, + upper.limit=105, one.minus.alpha=0.95)$

Yields the result, $p = 0.6879388$. The statement can be made:

“We can state with 95% $(100 \times (1 - \alpha)\%)$ confidence that at least 68.8% $(100 \times p\%)$ of population data values fall within the given limits.”

**Example 2**

- Specification limit $[90, 110]$.
- Sample data $n=10$, $\bar{X} = 98.5$, standard deviation = 2.1
- TI confidence level $(1 - \alpha) = 0.95$

Using the procedure T1.2.sided.p, which uses one-sided TIs to approximate two-sided TIs and estimates the proportion $p$:

$T1.2.sided.p(n=10, x.bar=98.5, std.dev=2.1, lower.limit=95, + upper.limit=105, one.minus.alpha=0.95)$

Yields the result, $p = 0.9804355$. The statement can be made:

“We can state with 95% $(100 \times (1 - \alpha)\%)$ confidence that at least 98.0% $(100 \times p\%)$ of population data values fall within the given limits.”

As previously mentioned, using one-sided TIs to approximate two-sided intervals leads to conservative estimates. Less conservative estimates may be obtained by using computer simulation to calculate TI parameters.

**Simulating tolerance intervals**

More exact (and less conservative) TI estimates can be developed using computer simulation. The downside of such an approach is that it’s a computationally intensive (minutes versus seconds of computer execution time) approach.

The authors have developed a suite of TI simulation programs. Because of the nature of simulation, the estimates produced are subject to error. The programs provide estimates of uncertainty by calculating a standard error of estimate (SEM) statistic as shown in Figure 3.

One-sided approximations versus simulation results for proportion are summarized below:

**Example 1:** One-sided approximation: 68.79388
Simulation result: 76.99859 (SEM = 0.002811)

**Example 2:** One-sided approximation: 98.04355
Simulation result: 98.98825 (SEM = 0.000413)

Simulations are based on 25 runs of 2,000,000 simulations. The approximate total wall clock time for each simulation is two minutes. Note that the simulation results are less conservative than the one-sided estimates as expected.

**TI software**

The R statistical system and the R tolerance package (6) and (7), provide a framework for calculating one-sided TI approximations. R is free software available under a GNU General Public License and will run under UNIX platforms, Windows, and MacOS. The authors have developed a suite of R routines to calculate the one-sided approximations. Included in the suite:

- T1.2.sided.p—calculate approximate $p$ for two-sided TIs given $n$, $(1 - \alpha)$, $\bar{X}$, $s$, LSL, and USL.
- T1.2.sided.alpha—calculate approximate $(1 - \alpha)$ for two-sided TIs given $n$, $p$, $\bar{X}$, $s$, LSL, and USL.
- T1.2.sided.n—calculate approximate $n$ for two-sided TIs given $(1 - \alpha)$, $p$, $\bar{X}$, $s$, LSL, and USL.

Multiple additional routines to provide greater ease of use of the tolerance package are also included. These routines are available in reference 8 (8). Full documentation, multiple examples, and validation results are also provided.

The simulation programs were developed for the Windows operating system. The programs use a multiprocessing approach to reduce the amount of wall clock time required to obtain solutions. The programs run as Windows command line applications. Programs include:

- k_sim—this is a “proof of concept” program illustrating that simulation may be used to accurately generate tolerance interval factors. All other programs are based on the approach used in this program.
• TL_sim—this program allows for assessment of one and two-sided TIs. Given \( n, (1 - \alpha), p, \bar{x}, s, \text{LSL}, \) and USL, the program can solve for one unknown \( n, (1 - \alpha) \) or \( p \).
• TL_eval—generates population proportion coverage estimates based on a specific requirements range. This program is useful when wishing to compare the coverage of TIs in which at least a certain proportion \( (p) \) is contained versus the average proportion contained. These programs are available in reference 8 (8). Full documentation, multiple examples, and evaluation results are also provided.

**Conclusion**

Tolerance intervals are a useful tool for assessing and setting specifications or judging conformance to requirements. They allow consideration of the uncertainty of process or product variability not available in process capability metrics. They may be used to establish variables sampling plans to control product quality.

**References**


**Lynn D. Torbeck** is a statistician with Torbeck and Associates. **Chuck Pheatt** is Professor Emeritus with Emporia State University.
Analytics Advances for Optimizing Downstream Processes

Simple, inexpensive, real-time analytics are urgently needed for high-value products.

Cynthia Challener is contributing editor to Pharmaceutical Technology Europe.

Downstream processing operations have a direct impact on biopharma product quality and cost. Therefore, optimization of downstream biologics purification steps is not surprisingly focused on increasing productivity and reducing cost, while maintaining the highest possible quality. Two specific areas receiving attention, according to Martin Vollmer, biopharma program manager in the Lifescience Analysis Group at Agilent Technologies, are continuous manufacturing with automation/integration of associated analytics and the adoption of single-use technologies, including a shift from traditional column chromatography to membrane-based techniques.

Capture chromatography, adds Darren Verlenden, head of bioprocessing, MilliporeSigma, has been an early target for improvement due to the high cost of goods associated with this operation. Adoption of advanced capture methods, such as multi-column capture, has been slower than expected, however, due to complexity and regulatory concerns, he observes. The focus has therefore shifted to flow-through polishing. “Analytics in this space are needed to move from monitoring critical process parameters to monitoring critical quality attributes, with in-line or at-line aggregate analysis seen as an important need,” Verlenden says.

Indeed, the biopharmaceutical industry continues to express interest in technologies that enable process control while improving process development times and quality. There is particular need for advances downstream due to the dramatically higher productivity achieved in upstream manufacturing today, according to Phil Vanek, chief technology officer at Gamma Biosciences.

“Increasing interest in automation and continuous manufacturing and the advent of manufacturing strategies for advanced therapies (e.g., cell and gene) are compelling more chained or continuous manufacturing methods to allow for more walk-away operations,” Vanek continues. “These approaches not only improve cost efficiency, but when properly implemented can improve product quality and reduce risk through closed operations and increased use of automation,” he asserts.

High-throughput potential

Full integration of analytical technologies helps to provide real-time answers, reduce costs, avoid costly failures, and makes processes much more efficient, notes Vollmer. “Online and inline process analytical technologies will provide continuous insight into the process and into the quality of the drug substance,” he states.

Overall, therefore, the incorporation of rapid, high-throughput analytics enables more informed decision making in process development, resulting in improved processes, Verlenden summarizes. However, for these high-throughput development and analytics to also reduce development timelines, he cautions that novel approaches to data collection and processing are needed to overcome the inefficient, largely manual, paradigm of today.

While advanced control is lagging for a variety of reasons, including the different control architectures within the diversity of equipment being deployed in manufacturing today, Jonathan Hartmann, president and CEO of Nirrin Technologies, believes that with new technologies and the market demand for integrated control in operations, the control aspects (for full automation) will quickly catch up.

In addition, Hartmann observes that for next-generation therapies in particular, process analytics promise to improve not only their therapeutic potential and potency, which is often predicated on the manufacturing process itself, but also the ability to assure their safety through process consistency and control, as well as their cost effectiveness through automation and simplified manufacturing.

Existing tech has limitations

With Chinese hamster ovary (CHO) cell productivity routinely exceeding titers of 10 g/L, Vanek notes that
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many biologics manufacturers are looking to address knock-on effects such as column fouling and protein aggregation. “The ability to continuously monitor downstream unit operations and operate under conditions that avoid product yield losses, especially after affinity and polishing steps when the value of the product is at its highest, are of extreme importance,” he comments.

Particularly for advanced therapies, Vanek says that real-time monitoring and control of critical quality attributes, such as full capsid adeno-associated virus productivity, can have a positive and significant impact on product potency, cost, and safety.

Industry needs technologies that enable process control while improving process development times and quality.

Most analytical technologies employed today, however, are still used in an offline manner, and results are not available in real time, which causes delays. Samples are removed from the stream and submitted for testing with results produced hours or days later.

“With those techniques, immediate reaction on fractionation or in optimizing yield and recovery is not possible; the approach today can be compared to performing a post-mortem analysis,” Vollmer explains. “Such delays preclude decision making to inform the next round of experiments and slows overall development,” adds Verlenden.

Any reduction in this timeline should speed development, according to Verlenden. “As biopharma moves to connected and continuous processing, the ability to monitor critical quality attributes in real (or near-real) time will further enable optimization and streamline key decision points,” he states. Vollmer agrees that the goal must be to get results when there is still time to take action in response. He notes that connecting liquid chromatography (LC) or spectroscopy online or inline will provide this capability.

“Using advanced analytical approaches including machine learning,” adds Vanek, “will deliver data that can identify process pitfalls and opportunities for improvement addressing quality and yield, as well as set the stage for predictive analytics that could allow users to intervene or abort processes that are likely to produce out-of-specification results.” Additionally, real-time data collection and analysis can be coupled to feedback controllers to enable automation and hands-free process management in the future, contends Vanek.

While there are some inline sensor technologies available on the market today, Vanek laments that they can be costly, slow, and/or complex, and often measure surrogate events in the process that are then indirectly correlated to the desired metric. It is important, stresses Hartmann, to consider the physical time needed to not only capture data, but also analyze and integrate the results of that analysis into a real-time control instruction set, to allow for process automation.

Digital innovation

The desire for faster and more flexible analytical solutions for downstream processing is driving innovation. New “Industry 4.0” digital capabilities will be essential before fully automated feedback loops can be leveraged, according to Vollmer.

One of the key challenges of existing downstream-processing analytics, Vanek observes, is the need to sample product and analyze the material offline, as many of the on-line technologies measure only surrogate analytes or cannot process the data in real-time. “As new applications are developed, or existing methodologies are being adapted to on-line measurements, it becomes easier to realize improvements in performance. In doing so, integration of the data into manufacturing execution systems and process chaining for continuous manufacturing, together with increased automation, become enabled,” he explains.

Advances in connected and continuous manufacturing, in particular, are increasing expectations for rapid decision making, agrees Verlenden. “Success in this area cannot be fully realized without an advancement in analytics,” he observes. New robust analytical equipment fully integrated into the process and specifically designed for this purpose helps to facilitate adoption as well, Vollmer agrees.

Regulatory is also a key driver with expanded data package requirements, Verlenden says. Design-of-experiment approaches, for instance, require additional analytical data in downstream-processing applications. “In essence,” Verlenden states, “improving analytics will allow for shorter development cycles to enable manufacturers to accelerate speed to market and reduce costs, while in the future, these analytics will enable the transition to process control based on critical quality attributes.”

Implementation challenges

As with the adoption of any new technology, the conservative nature of the biopharmaceutical industry has led to slower-than-desired action with respect to the implementation of more advanced analytics that can facilitate downstream process optimization. “Our industry tends to conservatively adopt new technologies, and this continues to slow down adoption,” says Verlenden.

There are other challenges as well. “Inertia within the industry to switch, primarily caused by regulatory constraints and the high cost of implementation, is a key hurdle,” Vollmer notes. In addition, as analytical technologies move from established off-line methods to at-line or inline methods, there is likely to be a period of decreased efficiency where, for instance, methods are run both off-line and at-line or inline, according to Verlenden.
"While this duplication will be a necessary step to realize the future potential of at-line and inline analytical testing, it will require investment and acceptance of this intermediate inefficiency," Verlenden comments. Ultimately, however, Vollmer believes that the pay-off will be lower-cost production and better drug quality.

Vollmer is clear that implementing new technologies into regulated manufacturing environments can introduce many challenges, from data compatibility across legacy systems to methods revalidation and even respecifying acceptance criteria for a product—all of which can be regulatory headaches or worse. "To make it worthwhile the investment from a cost- and risk-perspective, adopters of new technology have to have confidence that the method will be reproducible, reliable, and scalable, with the added information providing significant advantages over existing methods," he explains.

Some movement is occurring Advances, while not numerous, are being introduced and demonstrating their benefits. Some downstream process innovations are being spurred by upstream process improvements in conventional biologics manufacturing, such as productivity increases and continuous manufacturing, according to Vanek. The demand is also increasing, he notes, due to the broader array of biologics being manufactured including plasmids, RNA, and viral vectors; the physical nature of these materials makes purification with conventional downstream methods challenging.

"This diversity of products is one key element driving innovation. Real-time analysis using rapid methods and their integration into existing workflows is another innovation driver. Analysis that addresses not only product quantity, but simultaneously product quality, can be a real-time and cost-saver in the steps towards releasing a therapeutic product," Vanek adds.

Vollmer points to online LC, new Raman spectroscopy solutions, and new near-infrared (NIR) instruments and LC/capillary electrophoresis (CE)-based analyzers that target very specific single-attribute applications.

Implementation of Raman spectroscopy for bioreactor feedback control, Verlenden notes, is contributing to increased efficiency, productivity, and quality through inline analysis, chemometric analysis, and feedback control. One specific example is MilliporeSigma’s Procellics Raman Analyzer with Bio4C PAT Raman Software, which currently enables upstream scientists to deliver harvest material with more highly controlled quality attributes that should, in turn, reduce downstream purification challenges.

Technologies in development aim to move analytics from offline to at-line, in-line, and online.

"Eventually this technology should be useful for streamlining future adoption of Raman and other spectroscopic techniques for monitoring critical quality attributes such as concentration, aggregates, and formulation composition," Verlenden believes.

More advances on the way Other technologies are under development with the goal of moving analytics from offline to at-line and online and enabling the monitoring of not just critical process parameters but also critical quality attributes.

"Process control based on critical quality attributes will provide additional degrees of freedom that are not possible today," observes Verlenden. “For example, if aggregate levels could be monitored in real time, an excursion early in the process that today would require rework or a deviation could be corrected downstream within identified parameters to meet process purity goals. This type of approach would represent a fundamental change in how we develop and manufacture biologics," he adds.

Agilent is focused on the development of online-LC solutions because this technology offers significant versatility, according to Vollmer. "Online LC is a very promising technology since it has the power to analyze multiple process and product-related attributes. With LC, it is possible to measure a multitude of parameters and get high-quality data from the analysis. LC is also a technology widely used and well-known in the pharma industry, and it can be connected to a variety of different detectors that provides different angles of insight," he explains.

The key to successful online LC, Vollmer stresses, is to develop analytical instrumentation that seamlessly plugs into the overall process software environment.

Nirrin Technologies, meanwhile, utilizes the strengths of NIR, including rapid reliable results with a very high dynamic range, by combining new sensor deployment designs with novel laser technology, contends Hartmann.

Hoping for even more While many of these developments are still in the early stages, scientist involved in the development of analytical solutions for downstream processing continue to set their sights well beyond what might be possible in the near term.

For instance, Vollmer would like to see the introduction of online LC-mass spectrometry (MS) technologies for downstream processing applications. "Online LC/MS would provide an additional layer of insight into the process," he says. First, however, simplification and user friendliness must be improved for MS so that operators working on downstream processing lines who may not be analytical experts can operate these platforms with ease.
Current techniques

There are numerous techniques that are currently available for particle analysis, which can be categorized around both chemical and physical properties, Lindsay explains. Additionally, it is possible to use single or multiple methods to reveal the expected materials performance so that an acceptable product can be yielded, he adds.

Particle size methods. "Material solubility is a significant contributor to product performance where particle size reduction correlates with increased surface area to influence rate of dissolution. Thus, multiple methods are used to measure particle size," Lindsay says. "A desirable decrease in particle size can facilitate higher dissolution with increased surface area and can also increase the rate of degradation and impact product stability too. Therefore, particle size analysis is one of the most important techniques."

A relatively easy method that requires minimal expertise and no sample preparation is sieving, which includes air jet sieving, specifies Lindsay. However, with this method between 10 g and 100 g of material is consumed, there is a lower particle size limit (>20–50 µm), the range of sieves reduces data points, and it is only possible to be used with dry materials, he states.

Through the use of light microscopy with high resolution-image analysis, it is possible to fully visualize and inspect particles, Lindsay confirms. This method provides such advantages as a 1–1000 µm dynamic range, visualization of solubility (if it occurs), capability of confirming aggregation and particle fragmentation, and the ability of confirming crystallinity, degree of crystallization, crystal quality, and shape. Considerations to take into account when using this approach are solvent evaporation; multiple fields of view; and non-random particle orientation if particle size or shape is also being measured.

Laser diffraction only requires a small amount of sample (>10 mg...
to a few grams), can be used with wet or dry particles, and offers a dynamic size range of 0.01–2500 µm (dependent on instrument, technique, and configuration of instrument), Lindsay continues. For wet analysis, however, the solubility of the material should be considered, he adds. Additionally, expertise for method development is required, and the particle shape needs to be contemplated when the technique assumes a sphere.

A small quantity of sample (≤1 mg or less as a minimum) is also required when using dynamic light scattering (DLS) as a technique for particle size analysis. The dynamic range offered is between 0.3 nm–10 µm and the estimated average molecular weight range catered for is 1 x 10^5 to 1 x 10^10 Daltons (both dependent on instrument, technique, and configuration of instrument), Lindsay states. Similar considerations are required for DLS as with laser diffraction: solubility, expertise, and particle shape.

Dynamic image analysis or Micro-Flow Imaging (ProteinSimple, Calif., USA) is another particle size technique that only requires a small quantity of sample (<1 mL). This approach offers a dynamic range of 1–300 µm (dependent on instrument, technique, and configuration of instrument), provides the ability to see particles, allows visualization and measurement of particle shape and morphology, tests most of the sample, can be used with high viscosity samples (up to 20 centipoise), and can enable visualization of contaminant particles, Lindsay asserts. Solubility and expertise are considerations to take into account with this method, along with the need to view sufficient images for confirmation of particle distribution because particles are visualized in a random orientation.

“A consideration for all methods discussed is that the sample tested must be representative of the bulk; particle size is measured through a variety of techniques, where in development orthogonal approaches may be taken to evaluate which provides the more meaningful data to control quality,” Lindsay stresses.

Particle property evaluation methods. “Other techniques can be employed to visualize particles, isolated or not, to better describe the particle and aid in identification of potential contaminants,” states Lindsay.

When evaluating surface area of particles, it is possible to use the Nitrogen Brunauer-Emmett-Teller (BET) method. “Surface area most influences solubility of a material in solution and can be additionally measured as an orthogonal technique to particle size,” Lindsay says. “As particle size decreases surface area increases per unit mass and reported as m²/g to positively increase potential dissolution rate. Thus, particle size/surface area is used to help control dissolution rate in some products.”

Measuring the surface area of particles becomes particularly important for chemically unstable compounds, Lindsay explains. For these compounds, if there is an increased surface area there will be an increased degradation rate, which influences the formulation protection or coating that has been implemented to prevent degradation.

Surface charge method can be used to evaluate the Zeta potential—the charge on a particle at the shear plane. This property is important for the understanding and prediction of how particles will interact in and successfully stay in suspensions with other particles, Lindsay confirms.

Flowability of particles, which is critical for powder blends, can be measured with a variety of methods, such as funnel, angle of repose, powder viscometry/rheology, and so on. “The ability to flow evenly is a requisite for gravity assisted processes, where flow is uneven or there are vibrations differences in flow, density, particle size can lead to size or material separation to de-mix a once uniform blend,” Lindsay says.

Pycnometry/a densitometer can be used to measure the material density at a material level and to measure that property at a bulk scale, it is possible to use tap and bulk density testing. The latter method can also provide details that will allow for an understanding of how particles will settle together, Lindsay notes.

Particle identification methods. All products to be administered via injection need to undergo a visual inspection to check for particulates as per regulatory guidance, such as the United States Pharmacopeia Chapter <790> and European Pharmacopoeia Chapter 2.9.20 (1,2). The visual checks involve an inspection of the sample against a black and against a white background, with the naked eye and without magnification, under standardized light conditions, Lindsay states.

Light microscopy can be used to visualize the particles and their surface properties to a size of 1 µm. Additionally, this technique allows for particle geometry to be evaluated and measured, and can provide confirmation of crystal properties, Lindsay reveals. A simple count of particles in liquid samples, at set sizes between 10 µm and 25 µm, can be done using light obscuration, he adds.

Microscopy coupled with Fourier-transform infrared or Raman spectroscopy may be used to identify particles greater than 10–20 µm, although particles must be cleaned of other materials to improve spectral quality, Lindsay stresses. Scanning electron microscopy and energy dispersive X-ray analysis are useful for the visualization of the material and for elemental identification, particularly for metal/alloy contaminants.

Great advances

“Particle analysis techniques have advanced greatly from the simple sieve to the use of laser and high-speed image and spectroscopic systems to gather more meaningful

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Looking Past the Pandemic: The Future of GMPs in Aseptic Processing

While supply chain disruptions have resulted in many alterations to workplace practices, they have also presented an opportunity to get ahead of changes to the EU’s upcoming revision of Annex 1.

The supply chain disruptions brought on by the COVID-19 pandemic resulted in significant changes to workplace operations. In the context of aseptic production, the impact on ongoing operations is certainly present, but it can be more clearly felt in the trends beginning to take shape in advance of the European Union’s upcoming changes to Annex 1 regulatory guidelines. These changes, which are largely concerned with overhauls to contamination control strategy and procedures, are poised to enforce changes in the European aseptic manufacturing landscape.

Navigating supply chain disruptions

Patrick Nieuwenhuizen, director senior consultant at PharmaLex, notes that in aseptic production, existing contamination control procedures were already in line with the types of measures that were being enacted on a global scale following the onset of the pandemic. Instead, changes in aseptic production workflow were more along the lines of finding ways to get staff that needed to be in the building (e.g., manufacturing personnel, quality control lab technicians, cleaners) present and performing their tasks in a safe and socially distanced manner.

According to Philip Vanek, chief technology officer at Gamma Biosciences, a life sciences tools company backed by private equity firm KKR, the biopharmaceutical manufacturing industry continued to face significant added pressure to consistently meet quality measures. Adhering to good manufacturing practices (GMPs) already significantly limits the ways a company can operate; throwing a pandemic in on top of that necessitates creative thinking as a means of navigating these supply chain disruptions.

“Necessity is the mother of invention,” says Vanek. “Most established equipment manufacturers scrambled to meet demand in the already stressed supply chain. One change that we did observe early on was an increasing expression of interest and demand of equipment and single-use consumables from smaller, lesser known brands that could substitute in the manufacturing workflow [as a replacement for those that were in short supply].”

The short supply of some consumable single-use parts led some to consider stainless-steel alternatives that allow them to rely on in-house procedures rather than continual shipments from an outside supplier. Properly maintained stainless-steel systems can last upwards of 20 or even 30 years without needing a full replacement, adds Nieuwenhuizen.

It is because of this increased scrutiny on holistic process development that companies have begun fine-tuning their contamination control strategies.

With single-use-systems, however, the need to clean systems between cycles is eliminated, saving time and money on validation and revalidation procedures. Richard Denk, senior consultant, Aseptic Processing and Containment at SKAN, believes that validation concerns are absolutely front of mind for manufacturers.

“The word ‘validation’ will have a big impact on equipment design and cleaning procedures in the future, as current designs are often not easy to clean and for that reason need to demonstrate a robust validation,” says Denk. “If we look at the pipeline in the future, many new products in development are considered highly potent. [At the same time,] inappropriate cleaning procedures are the most common findings during GMP inspections in shared facilities.”

Understanding the changes to Annex 1

Single-use systems are just one way companies are attempting to ease the load of maintaining GMP requirements with a compromised workforce. The industry was always

Grant Playter
going to need to engage in some level of introspection into common methods and practices in advance of upcoming changes to Annex 1.

Following several drafts and comments from various pharmaceutical companies and organizations, the EU’s changes to Annex 1 are set to have a pronounced emphasis on contamination control strategies. Notably, the revised guidelines contain detailed instructions on isolators and restricted access barrier system (RABS) technologies and new sections on form-fill-and-seal systems and single-use systems. “For the company to demonstrate they have a good understanding about their processes and what risks and controls they have in place was often sufficient to have a validated process,” says Nieuwenhuizen. “Now it becomes more important to provide justification and evidence why the process you have designed as a company and the controls you have implemented are adequate to assure that you have an aseptic or sterile product.”

It is because of this increased scrutiny on holistic process

development that companies have begun fine tuning their contamination control strategies. There are various ways to factor optimal contamination control into one’s aseptic production process, says Denk, who was the GMP lead for the development of the SKAN-Groninger robotic filling line. Denk’s line was fully automated, including measures that help in contamination control such as viable monitoring and automatic delivery of indirect product contact parts.

According to Vanek, companies have invested in technologies that de-risk manufacturing, including process analytical technologies and continuous closed manufacturing. “Technologies that improve production efficiency in terms of classified space utilization, such as automation enabled by non-destructive measurement abilities for all aspects of particle analysis to the limits of what physics will allow is expected, Denk states. In time industry should expect to see more analytical instrument techniques be part of the PAT solution to reduce some laboratory testing outside of the particle analysis areas too,” Lindsay adds. “The regulations already support alternate techniques to better manage risk and assure quality. Data analytics with smarter artificial intelligence will help identify and correct processes, within defined and approved design and quality-by-design spaces, seamlessly to enable more effective production.”

new process analytics and high-efficiency closed continuous production systems, have been in the spotlight. The momentum towards single-use manufacturing in aseptic processing, both upstream and downstream, is likely to continue and perhaps accelerate with the adoption of new process analytical technologies and the data sciences that support them.”

The upcoming revision to Annex 1 has incentivized manufacturers to do everything in their power to minimize direct contact of product by operators. With this context in mind, the trend toward single-use-systems, automation, and other strategies to close systems and minimize contamination is not likely to go away even after the pandemic has fully passed. PTE

References

Analytics
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sample data on the particle to better describe the particle shape, size, density, and identity faster,” says Lindsay. “Also, providing the sample is representative, results are obtained with much less material thus enabling accurate measurements on very expensive materials at lower cost.”

Thanks to advancements in optical and spectroscopic techniques, it is now possible to capture images of the particle flow in real-time, allowing for particle identification, Lindsay reveals. Additionally, smaller particles (>0.3 nm) can be optically detected and measured using light scattering techniques, he adds. “Data processors, detectors, and processing speed have contributed significantly to the advancement of new instrumentation that are both smaller and faster than previous instruments,” Lindsay says. “Bench instrument components are now being built into flowing or blending processes to also enable real-time in-situ non-destructive analysis and include final in vial measurements so that no additional material is consumed. Spectroscopic techniques, with complex libraries and processing for spectral analysis, enable real-time monitoring of blends to confirm material concentration and uniformity.”

In the future, continued advancement in analytical measurement abilities for all aspects of particle analysis to the limits of what physics will allow is expected, Lindsay emphasizes. Further miniaturization of instruments to enable measurements of lower volumes and greater speed in flowing systems and an increased use of process analytical technology (PAT) solutions that separate offline analysis will transpire, he states. “In time industry should expect to see more analytical instrument techniques be part of the PAT solution to reduce some laboratory testing outside of the particle analysis areas too,” Lindsay adds. “The regulations already support alternate techniques to better manage risk and assure quality. Data analytics with smarter artificial intelligence will help identify and correct processes, within defined and approved design and quality-by-design spaces, seamlessly to enable more effective production.”

For more on aseptic processing, go to PharmTech.com to read the following:
- Automating Aseptic Manufacturing
- Moving Out of the Lab to Optimize Microbial Control

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Accelerating Project Delivery with a Lean Alternative to DBB

Lean delivery offers a promising solution to supply and manufacturing bottlenecks by integrating project teams early on and widening the team’s field of view.

In 2020, as the pandemic forced many industries to slow down, pandemic-focused project delivery teams were moving faster than ever. Their goal was to expand the world’s COVID-19 vaccine manufacturing capacity in record time, even while the vaccine candidates themselves were still in development.

With so many unknowns and such immense pressure to move at warp speed, how did those project teams ready themselves to succeed? For many, the solution lay outside of traditional design-bid-build (DBB) delivery. Like a relay race, DBB moves forward in phases, with one group completing their section while the next awaits a handoff. With no time for such a linear approach, teams working on pandemic-related expansions embraced a model that looks less like a relay and more like a synchronized swim. They brought all project stakeholders to the table early, from executive-level decision-makers to construction subcontractors to equipment vendors. Instead of boxing themselves into individual phases, these cross-functional teams worked to integrate their project delivery steps, relying on collaboration and parallel delivery to reduce rework and address known supply and manufacturing bottlenecks.

As a result of this historic effort, COVID-19 vaccine manufacturers around the world are now collectively producing 1.5 billion doses per month (1), with capacity growing all the time. It’s a scale-up success story like no other, and it demonstrates what can happen when companies look for alternative delivery methods that lie beyond the long shadow of DBB.

Forward-thinking drug manufacturers would be wise to take notice, particularly as the pandemic’s ‘warp speed’ mentality takes over the industry—a phenomenon that CRB confirmed in a recent survey of North American companies from across the life sciences (2). More than 500 respondents ranked speed-to-market among their lowest business drivers before the pandemic; today, it’s their top priority by a wide margin.

In the European Union (EU), where biotech investment—and, correspondingly, investors’ pressure to move fast—rose by 39% between January 2020 and January 2021 (3), project leaders are equally hungry for speed, if not more so. To satisfy that appetite, delivery teams need to go lean. That’s the key to completing projects up to 50% faster.

Lean principles
But what exactly does it mean to ‘go lean’? In an apparent contrast to its name, lean means integrating more people into the project team early on and widening that team’s field of view. Client executives, design and construction experts, trade partners, vendors, and commissioning and qualification specialists join forces from day one, eyeing the finish line from the starting blocks. Working together, this cross-functional team can achieve cost and timing certainty within the first 15% of the project’s total schedule. This clears the way for teams to initiate parallel, highly efficient workstreams. Even before construction begins, for example, they can ship drawings for long-lead equipment to manufacturers, exploiting the benefits of offsite fabrication and finding stability despite a drop in Europe’s manufacturing output and ongoing supply chain disruption (4).

For all of this to work, project teams need not only the will of owners to release their grip on DBB, but also a set of flexible, tested-and-true principles designed for lean delivery. These principles help to redistribute the risks and rewards of a capital project so that individual interests are subordinated to the overall project outcome. They facilitate complex relationships across the EU and around the world, making it possible to bring the right experts to the project at the right time, regardless of where those experts are located. Most of all, these lean principles will help teams deliberately establish and maintain a culture of trust and accountability throughout the design and construction lifecycle, incentivizing collaborative decisions and goal alignment—a necessary condition for moving fast. The following is a sample of those lean principles in action.

1. Model the culture from the top down. The culture of trust and transparency that we’re prescribing cannot flourish without support...
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from project leaders and owners. They are responsible for creating an environment in which lean can thrive—an environment in which redundant effort is eliminated and team members are selected early and respected for their qualifying expertise. For that to happen at all, it must first happen in the executive suite.

2. Bring the project team together early in the delivery process. For lean delivery to work, project teams must be not only willing to integrate and overlap project phases that were traditionally sequential, they must also integrate team functions that, in the past, may have had little overlap. That means engineers working shoulder-to-shoulder with trade representatives, each expert contributing their perspective to help build certainty into early designs and to reduce the frequency and volume of time-consuming information handoffs throughout the project.

3. Define the project’s conditions of satisfaction in a project charter. A project charter is part navigational instrument, part code of behaviour, and part onboarding tool. It’s co-authored early in a project’s lifecycle by the integrated delivery team, and while the charter itself is important (it defines vital elements such as schedule, target costs, conditions of satisfaction, etc.), the process of creating that charter is equally valuable. This process creates an opportunity for team members to practice the behaviours that make lean delivery successful, like communicating openly and finding alignment across disciplines. Getting the chartering process right can make a big difference to a lean project’s outcome, which is why many lean teams rely on experienced chartering facilitators to start them off in exactly the right way.

4. Enable the culture with lean tools. All the bureaucracy in the world can’t achieve what a culture of trust and transparency can, and with the right tools to uphold it, that culture can pull even the most ambitious projects through the complexities of an accelerated timeline, a turbulent global supply chain, and a heavily regulated environment. These tools may include:

- **A big room**: A central location, often virtual, where client representatives, project designers, construction managers, trade partners, and other stakeholders work next to one another. This ‘shoulder-to-shoulder’ concept of co-location greatly reduces the ‘churn’ often involved in seeking answers from a more traditional, decentralized project team. As a result, decision-making is faster, smarter, and more balanced against the needs of the project as a whole.

- **Last planner system/pull planning**: This approach, which applies to all project phases from design through delivery, ensures that the team members who schedule tasks and make promises are the same people responsible for doing the work. This contributes to the ethos of accountability and trusted partnership that defines lean delivery.

- **Building information modelling (BIM)**: Cloud-based BIM software is as much a communication platform as it is a tool for optimizing facility design, which makes it an important enabler of lean delivery. By allowing project owners, equipment vendors, trade partners, and other stakeholders from across the EU to co-author a single, harmonized digital model, today’s advanced BIM applications facilitate real-time feedback and help remote teams run scenarios, identify potential design clashes, and coordinate equipment far in advance of installation. Today’s emerging experiential technologies, like augmented reality, are extending the role of BIM software in facilitating lean delivery by instantly ‘transporting’ a team member to Basel (Switzerland), for example, right to a job site in Ditzingen (Germany), where that team member can collaborate seamlessly with on-the-ground trade partners.

- **Target value delivery (TVD)**: Under the premise of TVD, cost drives design, not the other way around. As a result, every team member shares ownership of the budget (and the business case driving that budget). This philosophy may sound simple, but it effectively addresses the complex issues of cost overruns that plague so many construction projects.

**Leaning into a new way forward**

Those who know lean delivery know this: to move faster without losing quality or cost control, you must lose your unnecessary or redundant processes. Lose your barriers to collaboration. Lose the belief that there is only one right way to manage risk and deliver a complex capital project.

In exchange, you will gain momentum and flexibility, and the level of deep team integration that’s necessary to make a project work across multiple countries and on an accelerated schedule. The project teams working to expand our global COVID-19 vaccine manufacturing capacity know this, and soon more teams across our industry will experience the benefits of lean delivery on their own projects, too.

Of course, it’s not as though traditional project delivery is about to disappear altogether. Certain projects (and certain project leaders, accustomed to their well-established ways of working) will suit its sequential systems, which offer their own rewards. But the rewards of lean delivery are too plentiful and too assured to ignore. Speed comes much more easily to teams that are moving in the same direction, without the freight of unnecessary checks and balances. That direction, for lean delivery teams in this age of scientific breakthrough, is up, up, and away.

**References**

The release of the SARS-CoV-2 virus genetic sequence in January 2020 marked the beginning of an intense period of R&D activity in a race to find effective vaccines to halt the devastating consequences of the global pandemic. The benefits of that unrivalled focus have been made clear. The time from the genetic sequence’s release to the submission of the first vaccine Phase III clinical trial data for regulatory review (from Pfizer–BionTech) was just 314 days—an unparalleled acceleration of typical timelines that could be more than 10 years for the development of a vaccine in normal circumstances (1).

However, the sheer volume of developers working in the space across a range of modalities (including recombinant viral vectors, live attenuated vaccines, recombinant proteins, and nucleic acids), using different methods of data collection and evaluation, made comparison of immune responses to find the most effective candidates extremely challenging. The unique circumstances called for a shift in vaccine R&D, to an approach focused on collaboration and harmonization. One group at the heart of this shift has been the Coalition for Epidemic Preparedness Innovations (CEPI) centralized laboratory network. The network’s reference labs have effectively transferred a number of assays to laboratories across the globe for a coordinated assessment of SARS-CoV-2 vaccine candidates, allowing for the most efficient global response to the pandemic.

The CEPI centralized laboratory network
As the SARS-CoV-2 virus began to spread, the Bill and Melinda Gates Foundation (BMGF) and CEPI, a global coalition of public, private, philanthropic, and civil society organizations aimed at accelerating the development of vaccines against emerging infectious diseases, set out to bring much needed alignment and efficiency to the global response, and to ensure the most effective vaccines would reach the most people in the shortest amount of time.

The CEPI centralized laboratory network was established in October 2020 to allow for centralized analysis of samples from vaccine candidate trials to mitigate the risk of variations from independent analyses and to enable head-to-head comparisons of immune responses induced by multiple vaccine candidates (2). The CEPI network is made up of nine laboratories worldwide: Nexelis in Canada; UK Health Security Agency (UKHSA, formerly Public Health England) and National Institute for Biological Standards and Control (NIBSC) in the United Kingdom; VisMederi Srl in Italy; Viroclinics-DDL in The Netherlands, icddr,b (formerly International Centre for Diarrhoeal Disease Research) in Bangladesh; Translational Health Sciences and Technological Institute (THSTI) in India; Q2 Solutions in the United States; and the Universidad Nacional Autónoma de México (UNAM) in Mexico City. The laboratories were selected based on their capacity to perform the necessary studies, but also for their ability to work internationally to harmonize protocols and data.

Developing assays for effective analysis at scale
In February 2020, before the official declaration of the global COVID-19 pandemic, teams at Nexelis and UKHSA began proactive work to develop the immunological tools and reagents that would be required to produce the necessary assays for evaluating the efficacy of the SARS-CoV-2 vaccine candidates on the horizon. Six of these assays across humoral and cellular response, developed and characterized in-house at Nexelis and UKHSA, were selected by the CEPI network to support global SARS-CoV-2 vaccine development programmes. Furthermore, these...
assays have also been used to evaluate the impact of SARS-CoV-2 variants on different vaccines.

To assess the humoral response, experts at Nexelis developed, with complete characterization, the critical reagents to protein targets (pre-fusion full length spike, receptor-binding domain, and nucleocapsid) of SARS-CoV-2 virus for three enzyme-linked immunosorbent assay (ELISA) assays as well as the pseudoparticle neutralization assay (PNA). Meanwhile, the team at UKHSA developed the viral neutralization assay. For assessment of the cellular response for T helper type 1 (Th1) and Th2, Nexelis developed the ELISpot Interferon (IFN)-gamma/Interleukin (IL)-5 assay.

**Shipments is always a challenge for successful assay transfers, and the pandemic has added layers of complexity.**

To date, more than 30 assay transfers have been completed between Nexelis and UKHSA to the other recipient labs within the network. As well as ensuring procedures and protocols were in place for the successful transfer within the network, all the assays were also calibrated against the World Health Organization (WHO) international reference standards to ensure harmonization with other labs performing these assays globally.

Within the CEPI centralized network, UKHSA and Nexelis have been identified as the two main reference labs in the overall transfer strategy. Within the first 12 months of the SARS-CoV-2 pandemic, UKHSA and Nexelis managed to develop a toolkit of qualified and validated assays, which played a crucial role in SARS-CoV-2 vaccines and antivirals worldwide to support global public health as well as vaccine companies in their clinical development and regulatory submission process.

**High quality reagents**

The Nexelis protein science team constructed the SARS-CoV-2 pseudo-virus to allow for the viral particles to be handled in a biosafety level (BSL)-2 laboratory. This allowed the Nexelis and UKHSA teams flexibility to develop, qualify, and validate the wild-type plaque reduction neutralization tests (PRNT), micro-neutralization (MNA), and PNA for SARS-CoV-2.

Before reaching the stage at which an assay is prepared for transfer, the production of high-quality reagents (including pseudoparticle against SARS-CoV-2 and its variants) was the first vital step toward ensuring quality control and consistency of assay performance across the network.

Critical agents such as the SARS-CoV-2 pseudovirus are available to labs within the wider CEPI network further demonstrating the value of the public-private partnerships leveraged to establish a new gold standard for vaccine and antiviral development.

**Preserving assay effectiveness throughout transfer**

Safeguarding the successful transfer of these assays has been critical to the vision of the CEPI network to improve the harmonization of immune response assessment across SARS-CoV-2 programmes.

Shipment is always a challenge for successful assay transfers, and the pandemic has added layers of complexity. The network had to address several potential challenges surrounding everything from import permits and documentation for the different viruses and key components, to the implementation of cold chain logistics and dry shippers to maintain the stability of the key reagents throughout the full transportation process.

**A comprehensive transfer protocol**

A thorough protocol, made up of four elements, has been the driving force behind the transfer process between the reference labs and the recipients. Firstly, this includes an assay overview to ensure that everyone involved in the analyses is aligned with how each assay is being performed in the reference labs and understands the limitations of the assays. A gap analysis was completed to highlight any differences between the reference labs and the recipients across key components, including everything from experimental conditions to equipment to the software used for analysis, so that Nexelis and UKHSA could put plans in place during the transfer process to mitigate the potential impact of any differences between testing environments.

A critical component of this gap analysis was comparison of the software used by scientists to aid with calculations for titers and concentrations. The compatibility of this software between the reference and recipient labs continues to pose a challenge. To mitigate the risk of impact to the assay due to differences in calculations, Nexelis provided the validated SoftMax Pro protocol used in their own lab to the recipients. This meant all labs would be using a fully validated GxP protocol to aid in further safeguarding alignment across the network.

Finally, a laboratory comparison assessment and an assay performance evaluation at the recipient labs were completed to ensure that the quality of the assays was not impacted by the transfer.

Contin. on page 40
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to the manufacturing procedures. Because QA and QC aren’t optional and it’s impossible to say which is more valuable to an organization, it is important to make sure these two distinct and important departments work together.

**QA focuses primarily on the process and QC focuses primarily on the product.**

Q. Should the QA department be responsible for all training?

A. No. QA should be responsible for making sure training is conducted and documented and all employees are current in the expectations defined by the training programme, but it is not realistic to assume QA can conduct all the training needed in an organization. QA might conduct some training, such as annual training on good manufacturing practices, data integrity, etc., but they would not have the expertise to train QC personnel on how to conduct laboratory tests.

Again, this is a great opportunity for the two departments to complement each other by working together to find the most suitable training programmes for employees to attend when in-house training is not feasible.

It is important for QA and QC to work together to ensure a holistic and comprehensive approach to the overall health of the company’s quality culture. **PTE**

Outsourcing — Contin. from page 38

**Future proofing current successes**

As the vaccine landscape continues to develop, it is imperative that both the quality and the persistence of the assay transfers can be maintained in the long term. To ensure this, the network is performing aligned assay trending using the Levey-Jennings control chart to assess assay performance overtime and deploying a proficiency panel, which will be tested every six months to ensure the assays are not drifting or trending.

**As the vaccine landscape continues to develop, it is imperative that the quality and persistence of assay transfers are maintained.**

Since the arrival of the wild-type SARS-CoV-2 virus in 2019, the COVID-19 global landscape has continued to evolve with the emergence of new variants of concern. The ongoing analysis of the assays is a vital component of the network’s efforts to ensure it can productively support the development of effective therapeutic candidates against emerging variants of concern, variants of interest, and potential future variants.

**The key ingredient for a streamlined approach**

The final critical component for the assay transfers was ensuring that the scientists at the recipient labs had access to the necessary expertise to perform the assays themselves. Under normal circumstances, analysts from Nexelis would have travelled to recipient labs to help with transfers but due to the pandemic the reference labs have had to be creative in how they provide essential training and troubleshooting in a virtual format. They created videos and ran full walk-through method standard operating procedure sessions to make sure all scientists were clear on the reality of the assays at Nexelis or UKHSA. They also joined ad hoc teleconferences with recipient lab scientists to regularly align or to discuss any issues such as unexpected results.

Open collaboration and flexibility to work across continents has been critical to the success of the network’s transfer programme.

This open collaboration and flexibility to work across continents has been critical to the success of the network’s transfer programme at every stage during the past 18 months. The ability of eight independent laboratories, competitors in the ‘normal’ world, to work together seamlessly in the pursuit of a shared goal has marked the beginning of a new era of global R&D—one which must continue long after the world emerges from the COVID-19 pandemic, for the benefit of patients everywhere.

**References**

From Lab to Commercial: Fully Integrated Solutions for Dry Powder Inhalation

ON-DEMAND WEBCAST
Aired: Thursday, December 2, 2021

Presenters
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Event Overview
The webinar will provide participants the opportunity to learn about the integration of technologies and capabilities to take a Dry Powder Inhalation product development from early-stage development to commercial stage products. The webinar will present a range of options and discuss considerations for selection of various types of Particle Engineering, Formulation and Device platforms for Dry Powder Inhalation, supported in Advanced Analytical characterization methodologies of the drug product. Case-studies will be provided to support participants diving into specific examples of selected topics.

Key Learning Objectives
- How to select a Particle Engineering platform for DPI development
- How to select a Formulation platform for DPI development
- How to select a Device platform for DPI development
- What to look for in performing Advanced Analytical characterization of DPI drug products

Who Should Watch
Type of Companies: Large to Small Pharma developing Inhaled Medicines
Job Functions: R&D, Supply Chain, Business Development, Product Manager

For questions or concerns, email psingh@mjhlifesciences.com
Frequently Asked Questions About Quality Control vs. Quality Assurance

Susan J. Schniepp, distinguished fellow at Regulatory Compliance Associates, answers some commonly asked questions about the difference between the roles of quality assurance and quality control.

Q. Theoretically, what’s the primary focus of quality assurance (QA) vs. the primary focus of quality control (QC)?

A. The short, simple answer to this question is that QA focuses primarily on the process and QC focuses primarily on the product. However, I don’t think the short, simple answer is adequate, because while the focus of these disciplines may be different, their goal is the same: to ensure that the product produced is safe and effective. QA concentrates on monitoring and perfecting the manufacturing process. This function is considered proactive because the activities and actions associated with QA try to deal with issues before product quality is compromised. In contrast, QC concentrates on testing the product after manufacturing to ensure it meets the acceptable quality product criteria and specifications, making QC more reactive in nature.

I think it is important to recognize and explore that, at times, QC is proactive, and QA is reactive. QA can adopt a reactive role when dealing with a deviation that occurred during manufacturing, especially if the deviation segues into an investigation. Deviations and investigations are reactions to mistakes made during manufacturing, thus putting QA in a reactive position. QC can adopt a proactive role, especially if the QA department is involved in in-process testing or incoming raw material testing because of the potential for out-of-specification (OOS) investigations.

OOS investigations are initiated by the QC test laboratory when the active ingredient, excipients, or the product fails to meet specification. When the OOS is initiated because of an aberrant result from an in-process product test, the laboratory is in a proactive position because their goal is to determine whether the OOS is due to a laboratory error in testing. If the OOS is determined not to be the result of a laboratory error, then the information needs to be communicated quickly to QA so they can investigate the potential that the OOS was due to a processing error, ideally before the manufacturing run is completed.

The bottom line is that QA and QC perform complementary tasks with the same goal of ensuring patient safety/product quality regardless of their point of reference (product vs. process).

Q. Does the QC department report into the QA department?

A. The current thinking is that the QC and QA departments should report independently to the head of Quality. This makes sense and maintains a check and balance approach to ensuring product quality and patient safety. It also makes sense when we consider the responsibilities of each discipline. As indicated, QC focuses on the product so their responsibilities can include, but are not limited to, batch inspection, product sampling, validation testing, and laboratory testing. QA focuses on the processes so their responsibilities can include, but are not limited to, documentation system management, audits, supplier management, personnel training, change control, and investigation procedures. Another way to look at the difference is the QA department manages the quality management system of the organization by ensuring the standard operating procedures (SOPs) are appropriately initiated, changed, or made obsolete using the change-control procedure, and QC provides the information that is included in the SOPs that are used to generate the product test results. QA and QC should work together from their different perspectives to ensure that products not meeting their safety and efficacy standards are not released to patients. The issues uncovered by QC through testing should prompt a QA review. An example of this synergistic relationship would be repeat non-conforming test results on a raw material leads to a corrective and preventive action (CAPA) investigation that determines the root cause of quality issues is due to a material change made but not reported by the supplier. QA would then use the information generated by QC to update processes and supplier oversight to prevent the problem from recurring in the future. This independent but complementary relationship between QA and QC is critical to be sure the product reaching patients is safe and effective. The best relationship between QA and QC is one in which QC informs QA of issues and QA uses the information to initiate continuous process improvements.
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