Formulating to Control Release Times

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CHAIRMAN’S LETTER

To produce more effective, patient-friendly medicines, drug formulators continue to search for optimal formulations. If a patient can take one versus multiple pills per day or go to a medical facility only once per month instead of weekly for an injection, adherence to prescribed treatments will improve, as will the patient’s health outcome.

Regulators continue to press the industry to do a better job at identifying impurities in drug substances and raw materials, in response to the discovery of nitrosamine contamination in commonly prescribed drugs, and concerns about other potential impurities threatening patient health of drug quality. The Analytics article, “Stepping Up the Search for Unknown Impurities,” reviews mass spectrometry techniques that can identify known and unknown impurities throughout drug development and manufacturing processes.

These insights, and other features in this issue, are once again shared to help drug development and manufacturing professionals achieve the ultimate goal: delivering patients the most effective, high-quality medicines they need and deserve.
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When I first entered the business-to-business publishing world more than 30 years ago, I never expected to spend a significant portion of my career writing about bio/pharmaceutical development and manufacturing. The subjects I have covered are somewhat obscure to someone not involved in that industry, prompting the comment: “There’s a magazine for that?”

As a writer/journalist, I sometimes would question my choice to write about pharmaceutical regulations or bioprocessing equipment versus penning the great American novel. During the past 18 months, however, reporting on the pandemic-related news and bio/pharmaceutical development and manufacturing efforts to combat COVID-19 served as a reminder of the important role media outlets such as Pharmaceutical Technology Europe, Pharmaceutical Technology, and BioPharm International play in their markets, and beyond.

The achievements by the bio/pharmaceutical industry to produce billions of doses of new vaccines has been remarkable; however, it is obvious that more work is to be done. For me, it is time to transition to my next chapter; I will be retiring from my position of editorial director of these publications at the end of September 2021.

I leave with the confidence that the magazines, websites, webcasts, newsletters, videos, podcasts, conference sessions, and other multimedia programmes are in the great hands of the editorial team of Felicity Thomas, Susan Haigney, Jennifer Markarian, Feliza Mirasol, Meg Rivers, Grant Playter, and new editorial director, Christopher Spivey.

I also know readers and advertisers will be supported by the sales team led by Publisher Mike Tracey and the webcast, design, content marketing, audience development, and other experts who have supported the brands over the years. I am grateful for their expertise, dedication, and friendship during my time with the publications.

Parting thoughts

Currently, we are witnessing the impact rumors or misinformation about COVID-19 and vaccines can have on society. As essential healthcare providers, bio/pharma companies cannot contribute to such misinformation or prioritize the bottom line over the quality and safety of the products they produce. Likewise, the companies supporting these efforts are obligated to share information supported by science and data, not marketing or sales objectives.

Keeping a “science first” mantra at the forefront will help ensure the bio/pharma industry can meet its primary obligation of serving patients.

Thank you for the opportunity to represent this industry. PTE

Rita Peters
Editorial Director
Recipharm has the competence, flexibility and facilities to take on even the most challenging projects.

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Pipette Software Update Tool

The Eppendorf Pipette Software Update Tool is a free program that allows liquid handling customers to update the software of their electronic pipettes or multi-dispensers. The update can be performed with a Windows PC with an internet connection, a micro-USB cable, and the product in question.

Recent updates accessible through the program include an improved battery capacity measurement, improvements in the read and write function of user settings, and new features for the Eppendorf Xplorer pipette line-up. Compatible devices include the Eppendorf Xplorer, Xplorer plus, Xplorer plus Move It pipettes, and/or Multipette E3 and E3x multi-dispensers.

Eppendorf
www.eppendorf.com
Achieving these goals can be challenging given the evolving properties of APIs and the increasing desire to develop more targeted medicines. Fortunately, there is a wide range of controlled-release mechanisms available today.

Consistency is key

Successful controlled-release formulations provide for drug release over a defined period of time at a specific rate and at targeted locations, such as the gastrointestinal (GI) tract, skin, muscle, etc., according to Simon Chen, vice president of Bora Pharmaceuticals.

Ideal controlled-release products enable administration once-per-day for oral therapies and no less than once-per-week up to every six weeks for parenteral (subcutaneous, intramuscular) treatments, adds Sudhakar Garad, global head of pharmaceutical profiling at the Novartis Institutes for BioMedical Research. Controlled-release doses are also easy to swallow or administer, cost-effective, stable at room temperature for at least two years, and easy to pack and ship.

Other important properties of successful oral controlled-release formulations, observes Mueller-Albers, include an excellent retardation effect at low polymer doses, very good tabletting behaviour, no ethanolic effect on the swelling properties of APIs to avoid dose dumping if a patient consumes alcohol, and thin polymer layers to ensure short processing and coating times.

Consistency is key

Successful controlled-release formulations provide for drug release over a defined period of time at a specific rate and at targeted locations, such as the gastrointestinal (GI) tract, skin, muscle, etc., according to Simon Chen, vice president of Bora Pharmaceuticals.

The most important property when designing a controlled-release formulation, asserts Brad Beissner, development scientist II with Metrics Contract Services, is to ensure its robustness of API release, particularly for APIs with a narrow therapeutic range.

Robustness with respect to consistency of manufacturing is also critically important for controlled-release formulations, according to Ron Vladyka, director of scientific services, oral and specialty delivery at Catalent. "The defining factor that progresses the dosage unit from a prototype to a commercially viable product is its ability to be repeatedly manufactured in a commercial setting," he says.
Drug release must also be consistent, predictable, and reproducible across population profiles, according to Firouz Asgarzadeh, vice president of pharmaceuticals at BioDuro. Predictable release profiles, he notes, make it easier to determine the number of doses required to maintain therapeutic levels of an API in the plasma of a patient and stay below toxic levels. Robust reproducibility across a large spectrum of patients regardless of intra-patient variability is necessary to avoid the need to personalize each drug for every patient, Asgarzadeh adds.

The release rate of the API in the appropriate location along the digestive tract must also be controlled in a precise and reproducible way to achieve optimal bioavailability of the drug after oral administration and ensure a reproducible clinical response, according to Torkel Gren, senior director, technology officer, and strategic investments leader with Recipharm. “To do so usually means that process parameters and excipient qualities must be very carefully and stringently controlled in terms of loading to ensure the desired release rate consistently across the batch and avoid variation during trials and beyond,” he observes.

In general, summarizes Tejas Gunjikar, application development and innovation leader for IFF’s Pharma Solutions business in South Asia, controlled-release formulations should provide the desired and consistent controlled drug release; should be scalable, stable, easy to administer; and should help reduce dosing frequency and side effects, factors that lead to improved therapeutic outcomes for patients. “Such formulations are generally most acceptable and achieve commercial success,” he asserts.

Building robustness with preferred excipients

Building robustness into the drug product begins early in formulation development with the selection of robust excipients, according to Vladyka. “In general, the selection of excipients for controlled-release dosage forms is performed in conjunction with the quality target product profile and physical and chemical properties for the drug substance, but is governed by the technology being employed to manufacture the controlled-release units,” he says.

Additional refinement or selection of critical excipient properties may be needed to modulate the controlled or localized drug-substance release, such as further sizing of core beads for a layering process or the selection of specific lots of polymer based on functional group substitution values. In some cases, a combination of different polymers with different molecular-weight distributions, degrees of substitution, and other characteristics—all of which must be carefully controlled—are necessary to achieve the desired API release rate, notes Philippe Gorria, senior director of formulation development for Recipharm.

Regardless, the impact of the excipients sets a firm foundation for the optimization and development of the drug product’s formulation and process, enabling the development of a robust product that can be reliably manufactured in a commercial environment,” Vladyka states.

The most preferred excipients for a successful controlled-release formulation deliver a high degree of reproducible performance and are safe for use for oral controlled release, states True Rogers, senior scientist in IFF’s Pharma Solutions business. Examples of such materials are cellulose derivatives including hydroxypropyl methylcellulose (HPMC), ethyl cellulose, cellulose acetate phthalate, etc., and synthetic excipients such as polyethylene oxides and polymethacrylates. Certain naturally derived excipients based on seaweeds and natural gums are also used, but to a lesser extent, according to Rogers.

Because 100% synthetic excipients demonstrate less batch-to-batch variation with greater degree of modulation and control, they are used more often to achieve robust controlled-release formulations, Asgarzadeh notes.

“Ultimately,” asserts Gorria, “controlled-release excipients must be suitable for the manufacturing process, suitable for controlling drug release, and available in a defined, reproducible quality.”

Control with excipients

Although excipients are traditionally thought of as inactive ingredients, they do play functional roles in controlled-release formulations. It is therefore critical, stresses Asgarzadeh, to have an excellent understanding of the material science and structural properties of selected excipients to overcome the various challenges faced by formulators. “Wisely and judiciously selected excipients will facilitate achieving the desired release profile of a controlled-release drug product, which ultimately affects the targeted therapeutic effects of the drug to a patient,” he says.

Functional excipients that have a direct impact on the performance of the dosage unit and its robustness include polymers, pH-modifying agents, and surfactants, which are used to control and mitigate negative factors when combining multiple enabling and controlled-release technologies, according to Vladyka. He adds that suitable binary or ternary polymer mixtures can inhibit or delay recrystallization of an amorphous drug substance. In addition, the availability of various excipient types and grades enables optimization of the performance of the API in the controlled-release formulation and delivery system being developed.

Furthermore, according to Chen, different excipients can be used not only to help modify the release rates of APIs using the same release mechanism, but to modify the release rates of APIs produced using different manufacturing processes, such as coating, mixing, hot-melt extrusion (HME), spray drying, and more.

“A disadvantage of using versatile excipients or polymers from an experienced provider is that these can...
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be applied to a broad range of drugs and used for different formulation approaches such as diffusion-based or matrix systems, as well as in different process technologies like granulation, coating, tableting, and HME,” Mueller-Albers agrees. She also notes that excipients with long track records that have been investigated in numerous in-vitro trials and used in marketed products provide a strong basis for successful in-vivo correlation (IVIVC).

For high-dose controlled-release formulations, Garad notes that there are a few special excipients that play an important role in enabling higher API loadings. It is important, though, that excipient suppliers thoroughly understand their manufacturing processes and provide quality-by-design (QbD) samples that represent the ranges observed for critical material attributes, such as polymer molecular weight, relative substitution levels, particle size, etc., Beissner asserts.

Formulators can be proactive, as well, Beissner says. For instance, for hydrophilic matrix tablets, having at least 25% by weight of the formulation, the rate-controlling polymer helps limit the effects of any naturally occurring raw material variations and ensures tablet-to-tablet release uniformity in the batch. Designing sustained-release coatings to a specific mg/cm² coating thickness based on surface area of the substrate, meanwhile, makes scaling up the film-coating process easier and provides greater assurance of repeatable results.

**Release technology drives excipient selection**

Excipients used on controlled-release formulations are constituted of two main classes: matrix and reservoir systems. The mechanism that controls the release differs for both systems and by matrix solubility (hydrophilic or hydrophobic), explains Joao Marcos Cabral de Assis, global technical marketing manager for pharma solutions within BASF’s orals platform.

Excipients that can form thin films and tablet matrices are particularly applicable, according to Gorría, because they can control drug release by limiting drug dissolution and/or drug diffusion, or even through osmotic pumping effects. Sensitivity to pH will also impact excipient selection for drug formulations intended to target a specific location within the intestinal tract. Controlled-release formulations are typically achieved by utilizing high-molecular-weight, water-soluble polymers to form hydrophilic matrix tablets or by film coating using predominately water-insoluble polymers, according to Beissner.

The majority of controlled-release drugs are formulated in hydrophilic matrices that release APIs by drug diffusion and matrix erosion. Cellulosic polymers such as HPMC, hydroxypropyl cellulose, hydroxyethyl cellulose, and methylcellulose are the most common polymers used in extended-release formulations. Alginates, carbopol, and gelatin are less common examples of these materials.

Hydrophobic matrices release APIs through drug diffusion because the matrix is water-insoluble and does not erode. API solubility is consequently a critical factor for the success of these formulations, according to Assis. He points to carnauba wax, cetyl alcohol, hydrogenated castor oil, microcrystalline waxes, ethyl cellulose (EC), stearic acid, and polyvinyl acetate (PVAc) as examples of lipophilic matrices.

The selection of a hydrophilic or hydrophobic matrix such as pH-dependent or pH-independent polymethacrylate is mainly

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**Finding the right starting formulation**

Formulation scientists face several challenges when formulating a controlled-release drug product, says Tejas Gunjikar, application development and innovation leader for IFF’s Pharma Solutions business in South Asia, due to the properties of the drug, such as its solubility, dose, handling, processability, interactions with other components of the formulation, and the need for delivery to a site/region in the body at a predetermined rate; incomplete API release; and most importantly the ability to provide reproducible performance for consistently attaining the desired therapeutic outcome.

Jessica Mueller-Albers, strategic marketing director for oral drug-delivery solutions at Evonik Health Care, agrees; the properties of the API influence the release kinetics; therefore, it is not so easy to find the right starting formulation.

“Formulator experience is crucial to address the challenges in controlled-release small-molecule drug products. For formulators who have limited experience with controlled-release dosage forms, partnering with a supplier that can provide the right excipient, technology, and process on a short timeline is essential. When formulators work under extreme time pressure, it is also important to have a platform solution that can be applied to several candidates,” Mueller-Albers says.

Collaboration between formulators and ingredient providers during product development and scale-up could identify ingredients and properties that are critical not only to quality, but also to performance, agrees Gunjikar. Industry-leading excipient vendors are an underutilized resource during the development of dosage forms, and their knowledge and experience with the application of excipients can be used to solve issues as they arise, Ron Vladyka, director of scientific services, oral and specialty delivery at Catalent, adds.

Most important is starting the initial formulation development with knowledgeable partners, such as excipient suppliers, Mueller-Albers says. “Establishing such partnerships very early on can accelerate development because the right formulation and process parameters can be found more quickly. We have found that early exchange between an excipient manufacturer and formulator helps overcome challenges such as curing of aqueous controlled-release coatings by in-process curing solutions and avoiding alcohol dose-dumping by modulating formulations,” she explains.
determined by the solubility of the drug because a potential self-retardation effect of the drug at higher pH will have an influence on the release kinetics, according to Mueller-Albers. The same is true for highly soluble drugs that may require strong retardation during stomach passage.

Soluble components are often added to lipophilic matrices and insoluble film coatings to act as pore formers to better adjust drug release. Typical pore formers are povidones (polyvinyl pyrrolidones [PVPs]), polyethylene glycol-polyvinyl acetate (PEG-PVAc) grafted copolymers, sugars, and PEGs.

Reservoir systems consist of a nucleus containing the drug, which can be multi-particulates or a single tablet coated with an insoluble film. Drug release in these systems, says Assis, is carried out exclusively by diffusion and is modulated through film layer thickness, permeability modifiers, and added core components that alter the water-attractiveness. The application is mainly served by insoluble film-forming excipients such as methacrylates, EC, and PVAc.

To choose the right excipient, Mueller-Albers recommends that formulators consider the nature of the API, such as its solubility, charge, etc.; the type and design of the dosage; the strength and duration of the retardation effect; the preferred manufacturing process (i.e., direct compression, granulation, coating, HME, spray drying, etc.); and whether there is a need for easy swallowability, such as for paediatric and geriatric patients.

For instance, Chen comments that for delayed-release formulations, pH-dependent excipients such as methacrylate polymers will provide gastro-resistant functionality; EC would be the choice for pH-independent controlled release such as with multi-particulate drug-delivery systems (e.g., pellets within a capsule); HPMC would be the main choice for monolithic controlled-release delivery systems; and poly(DL-co-glycolide) (PLGA)-based polymers would be preferred for microspheric depot injection formulations.

As with most formulations, Beissner adds that drug solubility plays a major factor in excipient choice. “Lower-molecular-weight polymers are generally used to generate a more erosion-based drug-release profile for low-solubility drugs, while higher-molecular-weight polymers that swell more and afford a diffusion-based drug-release profile are paired with high-solubility drugs,” he explains. The rate of API release from a sustained-release coating is, meanwhile, modified by changing the ratio of the water-insoluble and water-soluble polymers in the formulation and the film coating thickness.

In addition, Gorria adds that for a hydrophilic matrix tablet, powder flow and compatibility will be important while for a product comprising coated pellets, the polymer must be sprayable and generate a strong thin film on each pellet. It also depends on whether API release will be restricted by slow dissolution, by forming a semipermeable membrane, or through a gel.

Other guiding factors can include anticipating the patient characteristics of the target population, such as in the case of paediatric formulations for which excipient options can be limited somewhat because of safety concerns and the availability of process equipment, according to Vladyka. “Available process equipment can dictate the type of excipients that will be used in the manufacturing process,” he explains.

For instance, Assis notes that for poorly compressible APIs, PVAc can provide the plastic deformation needed to increase the compressibility and allow for simple direct compression, saving process time and costs.

Similarly, EC coatings require large amounts of plasticizer to achieve the necessary film elasticity, which leads to formulation and process complexities, according to Assis. In addition, while some aqueous EC dispersions are available, they have long curing times and require high temperatures, thus most EC coating solutions require the use of organic solvents. PVAc-based coatings, he observes, as aqueous dispersion films, are attractive alternatives with high flexibility, pH-independent drug release, lower curing temperatures, and lower dose-dumping risk.

Achieving IVIVC, zero-order release, and robustness

One of the biggest challenges for controlled-release formulations is to achieve IVIVC. “The relationship between an in-vitro property of a dosage form and its in-vivo response is especially important for controlled release oral formulations,” asserts Mueller-Albers. Through the successful development and application of an IVIVC, in-vitro drug performance can be predicted from its in-vitro behaviour. “The establishment of a meaningful IVIVC can provide a surrogate for bioequivalence studies, improve product quality, and reduce regulatory burden,” she adds.

Establishing this correlation can be difficult, however, due to absorption variations in the fed and fasted states for each patient and differences in intestinal tract transit, gut metabolism, etc., patient-to-patient, adds Assis.

Obtaining a zero-order release can also be considered a challenge for formulators. “Push-pull systems are an alternative for achieving this type of release, but the technologies required for their manufacture are so complex that most companies steer away from these systems,” notes Assis. Recently, though, he remarks that the use of a combination of functional hydrophobic matrix polymers (e.g., PVAc) blended in the appropriate proportion with a gastro-resistant polymer such as methacrylic acid and ethyl acrylate copolymer that acts as a pH-dependent pore former makes it possible to ensure linear release.

One challenge that continues to create issues for formulators is the difficulty in achieving targeted release of API in the lower intestine, according to Gorria.

Stability in various forms can also pose difficulties. For instance, changes in dissolution characteristics...
are often observed when the drug product is stored, notes Thorsten Cech, pharmaceutical technology application expert and manager of BASF’s European Pharma Application Lab. While curing can minimize these risks, this property remains a potential critical material attribute that requires thorough investigation during product development.

Ensuring the robustness of API release can be challenging as well due to the inherent variability of the polymers used in controlled-release applications, according to Beissner. “It is important that controlled-release formulations can withstand this lot-to-lot raw-material variability,” he says.

To ensure robust and reproducible release with minimal inter- and intra-patient variability over the intended extended period for controlled release, Asgarzadeh observes that the polymer excipients used in these formulations need to remain intact throughout the GI tract, efficiently facilitate API diffusion from the core of the drug product through the excipient membrane over time, release the drug predictably independent of patient diet, and provide release of the therapeutic level of the API without undergoing any physical transformation.

Formulating high-dose controlled-release drugs

Dose is the biggest challenge from Garad’s perspective. “In controlled-release formulations, the dose should be lower than that for conventional drug products so that it is possible to generate a formulation of a palatable size whether given orally or administered parenterally,” he observes. The final dosage form—a tablet or capsule, for instance—may be very large once you have combined several doses and added release controlling excipients, explains Gorria. Large tablets and capsules can be difficult to swallow for children and elderly patients with dysphagia, leading to reduced patient compliance and thus the effectiveness of the treatment.

For this reason, Garad notes that molecules with a narrow therapeutic window are typically not ideal candidates for controlled release. Very low-clearance molecules are not generally good candidates either, as they keep accumulating, which can lead to side effects.

**Systematic approaches are beneficial**

While it is possible to design a molecule to fit a controlled-release formulation, that is not usually feasible. The current practice, according to Garad, is to take an existing molecule and fit it into a controlled-release dosage form platform technology. “The key is to combine the right physicochemical properties with the right pharmacokinetic properties of the molecule and the right controlled-release technology and the ideal polymer,” he states.

Proactive identification of critical material attributes and their impact on drug release is essential, Cech adds. “Depending on the API’s solubility and other physiochemical properties of the drug, different approaches can be used by formulators to ensure the likelihood of success and to achieve the expected drug-substance release. Considerations such as hydrophilic or hydrophobic matrices, film- and pore-formers, feasibility of the manufacturing process, and product stability can be part of QbD programmes for systematic drug product development,” Cech observes.

A successful strategy takes a combination of deep formulation knowledge and empirical testing, adds Asgarzadeh. “In addition to experienced formulation experts, to ensure the highest likelihood of success it is essential to test controlled-release products in animal models as efficiently and as early as possible before the formulation goes into clinical trials in humans,” he says.

In addition, Cech notes that using alternative methods to investigate processing such as determining the porosity flowability, compactability, and tabletability and subjecting non-optimized formulations to stability testing early on to select the most robust ones might be a good tactic to assure the quality and safety of final controlled-release drug products.

Information can be collected using pharmacokinetic modelling and solubility studies in various media including in simulated gastric fluids (to determine logP, dose, and solution stability). Formulation and process development can range from a broad multi-dosage form approach (evaluation of tablets, minitablets, and multiparticulates) to a single technology, highly focused development plan.

Gren is in favour of investigating several formulation principles and excipient combinations to identify the most appropriate approach for the needs of a given project, and also says it is essential to determine the compatibility between all components of the future formulation to avoid degradation phenomena (polymer/polymer and/or polymer/drug substance).

Equally important, says Vladýka, is using high-quality excipients from industry-leading suppliers that have well-characterized quality attributes throughout the development lifecycle. Because excipients play a direct role in the controlled-release profile itself, Asgarzadeh adds that they should be selected based on prior experience and demonstrated properties that satisfy the needs of the API itself.

“As all drug substances are different, there is no one-size-fits-all solution,” Gren concludes. “Once a suitable prototype is identified, therefore, a design-of-experiment approach is useful in establishing a formulation and process parameter space that gives robust drug-release characteristics. Formulators can then be confident that they understand how the formulation will perform in a variety of real-world situations (several physiologic media), which allows them to refine the finished product to ensure consistent performance, regardless of real-world conditions,” he says. This information is valuable in scale-up to pilot and industrial scales and tech transfer to commercial manufacture. PTE
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Getting a Nose for Vaccines

The intranasal route of administration is showing clinical promise, particularly for COVID-19, but there are multiple hurdles to overcome to ensure successful formulation.

The SARS-CoV-2 outbreak, which started late in 2019, has demonstrated how devastating novel infections can be for the global population. In response to the infectious threat posed by the novel coronavirus, the pharmaceutical industry rallied and managed to develop effective parenteral vaccines in record breaking speeds. However, the COVID-19 pandemic has also brought to the fore the development and distribution challenges associated with mass vaccination programmes as well as difficulties ensuring equitable access to vaccines—a particular challenge for low-income countries.

Rationale behind a mucosal route

Mucosal pathogens, such as SARS-CoV-2, are a major cause of infectious diseases across the world, and the mucosal route of vaccination has been of interest for some time, primarily due to the induction of immune response that is achievable with this form of delivery (1).

Although there are numerous avenues available for mucosal vaccination, the most commonly employed routes are via the mouth and nose. However, the number of licensed mucosal vaccine formulations is limited, and the available formulations tend to use attenuated strains of pathogenic bacteria or viruses, which carry specific risks such as reactogenicity and post-vaccination reversion of the pathogen to a virulent form (1).

Nevertheless, mucosal vaccines provide a strong immune response in patients, both in mucosal sites and systemic circulation (2). Additionally, these types of vaccines also offer cost and administration benefits over the traditional injectable forms (2).

Formulations for intranasal vaccines

Nasally administered vaccines are widely accepted and easily accessible, and have reportedly achieved a better systemic bioavailability and protection from gastric enzymes when compared with orally or parenterally administered vaccines (3). Yet, there are multiple hurdles that can hamper development of nasal vaccines.

Challenges to the formulation of nasal vaccines include, but are not limited to, the size of the dose required, limited efficacy of the vaccine due to mucociliary clearance, the necessity for adjuvants to enhance immunogenicity, restricted delivery volume in the nasal cavity, and normal human defense mechanisms (3). According to expert opinion, the incorporation of effective adjuvants that can trigger both mucosal and systemic immune responses are necessary for noninvasive vaccine delivery, and a more extensive understanding of mucosal immunity is required (4).

Currently, the commercially available intranasal vaccines are FluMist/Fluenz Tetra (AstraZeneca) and Nasovac (Serum Institute of India), which are both liquid, live-attenuated vaccines for influenza administered via a nasal spray (5). Other formulations for nasal vaccines include solutions administered via drops, powders, gels, and solid inserts, although there are no other nasally administered vaccines approved for marketing authorization globally.

Spraying a solution into the nasal cavity is simple for administration purposes; however, some of the formulation may leak from the nasal cavity or into the oral cavity, which would reduce potential therapeutic effect and dose. To overcome these potential issues, it has been suggested by some experts that gelling agents, such as polymers, included in the formulation could increase the residence time of the vaccine in the nasal passage (5).

Solid formats for nasal vaccines can offer the advantage of being more stable than liquid formulations but may have disadvantages in terms of cost and ease of administration due to the potential requirement of specialist applicators. Additionally, there has been interest in the
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development of particulate carrier systems, such as liposomes, for vaccine products (5). To achieve success, however, vaccine formulations that are designed for intranasal administration must maintain the antigen stability, provide sufficient residence time in the nasal mucosa, and should be compatible with other components, such as adjuvants (6).

Clinical prospects for COVID-19

For COVID-19, it has been specified that the intranasal route of administration for a vaccine is promising due to the fact that the normal route of infection for the SARS-CoV-2 virus is also via the nose (6). Furthermore, it is widely reported that vaccines administered intramuscularly are less likely to provide immunity protection in the upper respiratory tract—the area of primary attack from SARS-CoV-2.

At the time of writing, the World Health Organization (WHO) has reported that there are 112 vaccines in clinical development and 184 in pre-clinical development for COVID-19 (7). Of those candidates in clinical phase, only eight vaccines are formulated for intranasal administration (7).

The furthest along the clinical lifecycle, according to WHO, are a viral vector (replicating) vaccine and a protein subunit vaccine being developed by the University of Helsinki—has secured a preclinical candidate, which it reports promise to block COVID-19 where it enters the body (15).

Regarding the other potential intranasal COVID-19 vaccines in clinical development: two are live attenuated virus vaccines—COVI-VAC from Codagenix and Serum Institute of India, and MV-014-212 from Meissa Vaccines; two are non-replicating viral vector vaccines—BBV154 from Bharat Biotech International and PIVS-vectorized vaccine from CyAnVac; and one is an inactivated virus for intramuscular or intranasal administration from Laboratorio Avi-Mex. There is an additional protein subunit vaccine listed in WHO’s COVID-19 vaccine candidate tracker, which is administered intramuscularly for the first two doses and then intranasally for a third dose, from Razi Vaccine and Serum Research Institute (7).

Another potential intranasal candidate that is currently in the pre-clinical stage is a vaccine that uses a common poultry virus, the Newcastle Disease Virus, to produce spike proteins of SARS-CoV-2 (11). The collaborative effort from the University of Lancaster (United Kingdom) and the Texas Biomedical Research Institute has garnered positive results with reductions in both disease impact and transmission in animals (12).

Rokote Laboratories Finland—an academic spin-out company from Altimmune is no longer in development as a result of inadequate immune response in healthy volunteers (8).

Of the vaccines that currently have authorization from regulatory bodies to treat COVID-19, only one is in clinical development as an intranasal formulation (7). The University of Oxford announced the launch of a study investigating the efficacy of nasal administration of the ChAdOx1 nCoV-19 vaccine, which was originally co-developed for intramuscular administration with AstraZeneca, earlier in 2021 (9). The trial will assess the efficacy and immune response of either one dose or two doses of the intranasal vaccine in healthy participants and is expected to take four months (10).

References

Okra gum has desirable properties that make it a suitable polymer candidate that can substitute more expensive synthetic polymers in gastroretentive drug formulation. In this study, the buoyancy properties of promethazine tablets containing okra gum and gas-generating agents sodium carbonate and bicarbonate were evaluated to determine if a new floating drug delivery system for promethazine hydrochloride is feasible. The physico-mechanical properties as well as the swelling indices of the tablets were assessed using standard methods. The in-vitro buoyancy and fluid uptake kinetics of the gum in promethazine hydrochloride tablets were also evaluated. The results showed that the tablets were generally elegant, non-friable, possessed acceptable hardness, and were able to float, while the swelling index showed that the gum was able to imbibe fluid and swell appreciably. The swelling kinetics of the formulations based on the Vergnaud model showed a non-concentration dependent diffusion-controlled mechanism with no burst effect.
for the optimization and application of okra gum, and other naturally occurring biopolymers, at industrial scale. This study is therefore aimed at formulating and evaluating the floating property of a carbonated okra gum containing promethazine hydrochloride as the model drug.

Materials and method

Materials. The following materials were used as procured from standard manufacturers without further purification: promethazine hydrochloride, acetone, citric acid, sodium carbonate and sodium bicarbonate, talc, magnesium stearate, and microcrystalline cellulose (MCC). All solvents and chemicals used were of analytical or reagent grade.

Extraction of okra gum. The extraction of okra gum was carried out according to a procedure earlier reported from the authors’ laboratory (25).

Preparation of floating tablet. The tablets were prepared using the direct compression technique. All the ingredients, except the lubricant magnesium stearate and talc, were accurately weighed in ascending order of their weight and blended uniformly in a mortar for 15 minutes. Flow property of the powder mix was determined, and lubricant was subsequently added while mixing for a further three minutes. Tablets (400 mg) were compressed using a single punch tableting machine (model number 94352, THP Shanghai, Tianxiang ad Chentai Pharmaceutical Machinery, China).

Evaluation of granule properties. To determine flow parameters, the bulk density, tapped density, Hausner index, Carr’s compressibility index, flow rate, and angle of repose were measured using standard methods (25).

Evaluation of tablet properties. The weight variation, thickness, diameter, hardness, and friability test were also determined using standard methods (25).

Polymer swelling studies. One tablet from each batch was weighed before placing it in a petri dish containing 0.1N hydrochloric acid (HCl). At 30 minutes in one-, two-, three-, four-, five-, and six-hour intervals, the swollen tablets were taken out and weighed after mopping off the fluid with blotting paper. Triplicate determinations were recorded. The swelling index, or degree of swelling of the tablet, was then calculated using Equation 1:

\[
\text{Swelling Index} = \frac{W_t - W_0}{W_0} \times 100
\]

where \(W_t\) is the weight of tablet at time \(t\) and \(W_0\) is the initial weight of tablet.

In-vitro buoyancy study. One tablet from each batch was placed in a 100-mL beaker containing 0.1N HCl. The time taken for the tablet to move from the bottom of the beaker to the top and float was noted and recorded as the floating lag time (FLT). The time for which the tablet remained floating on the surface was noted and recorded as the total floating time (TFT). The determination was carried out in triplicates, and the average time calculated.

Statistical analysis. Statistical analysis was carried out using Microsoft Excel and SPSS software, which included mean, standard deviations, variances, and analysis of variance (ANOVA, F-test). At 95% confidence interval, P-values less than or equal to 0.05 were considered significant.

Results and discussion

Percentage yield of gum. The percentage yield of the gum was 20.46% w/w; similar extraction in the authors’ laboratory yielded 20.01% w/w (25). By this comparison, the authors demonstrate that the extraction process used in their laboratory gives consistent yields.

Flow property of the powder mix. The angle of repose, bulk and tapped densities, Hausner ratio, and Carr’s index for batches F1, F2, F4, and F6 (Table 1) show good flow properties, as these values are within the range specified for passable flow characteristics (26). On the other hand, F3 and F5 possess poor flow properties as indicated by their angles of repose, Hausner ratio of 1.44 and 1.40, respectively, and Carr’s index greater than 25%. To improve flow, some measures could be employed, such as inclusion of excipients (e.g., glidants and low-cohesive/hydrophobic lubricants), adjustment of process controls, and use of vibration-assisted hoppers or feeders (27, 28).

Physical and mechanical properties of floating tablet formulation. Table II summarizes the physical quality control tests performed, including weight variation, friability, hardness, thickness, and diameter. The British Pharmacopoeia specifies an acceptable limit for weight variation for tablets weighing ≥ 250 mg as a percentage deviation of not greater than ± 5 % from the mean (29). From the results, batches F1, F2, F3, and F6 passed the weight uniformity test, while batches F4 and F5 did not. This variation in weight could be attributed to factors such as speed of compression and irregularity in pressure exerted by the punches of the tableting machine (28).

Table thickness and diameter was in the range of 3.10 mm to 3.26 mm and 11.94 mm to 12.10 mm, respectively.

Table I. Composition of floating tablets.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1 (mg)</th>
<th>F2 (mg)</th>
<th>F3 (mg)</th>
<th>F4 (mg)</th>
<th>F5 (mg)</th>
<th>F6 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promethazine</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Okra gum</td>
<td>60</td>
<td>80</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>20</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Citric acid</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>MCG</td>
<td>222</td>
<td>202</td>
<td>162</td>
<td>162</td>
<td>162</td>
<td>162</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>
From analysis of results, there was no wide variation in the thickness and diameter of the tablets of each batch (data not shown). The tablet hardness ranged from 3.03 to 6.40 kg/F for the six batches. Although there is no official/pharmacopoeial specification for tablet hardness, it is expected that a good pharmaceutical tablet should not be too strong or too soft; in this respect, the British Pharmaceutical Codex (30) recommends a hardness value between 4–8 kg/F. Generally, literature survey shows that a good hardness value for uncoated tablets should range from 3–8 kg/cm² (28). Tablet hardness affects parameters such as disintegration, dissolution/drug release, and release kinetics as well as the buoyancy properties of the tablet (28). Earlier reports (28) on the evaluation of Captopril floating/bio adhesive tablets concluded that tablets with a hardness of 8 kg/F and greater showed no floating capability. Very hard or dense tablets indicate high compaction and low porosity of the tablet matrix, often resulting in retardation of solvent penetration into the tablet core. Batches F1, F2, F4, F5, and F6 with friability values ranging from 0.32% to 0.54% passed the friability test as these values were within the compendia limit for friability (i.e., less than or equal to 1 % [29]). Low no friability implies good binding property on the part of the polymer/binder used; in this case, okra gum, which has been previously reported to be a good binder and release modifier (23, 25, 27).

**In-vitro buoyancy study.** Data generated from the floating tablet experiment are presented in **Table II** and demonstrate that batch F1 with 15% concentration of okra gum showed no floating property. The tablet lost its integrity and disintegrated a few minutes after coming in contact with the liquid medium. This result may be due to the low-binding effect of the okra gum at this concentration, possibly suggesting that fast-dissolving tablets could be prepared at concentrations below 15%. As the gum concentration was increased from 15% to 20% and 30%, tablets with more intact integrity did not break down or show imbibition or swelling upon coming into contact with the liquid medium. Increasing the concentration of okra gum from 20% to 30% in batches F1 and F2 had no significant effect (P > 0.05) on the FLT (i.e., the time for the tablet to move from the bottom of the beaker to top of the fluid medium in the beaker) or on the TFT of the tablets. Noteworthy, however, is the fact that, on addition of sodium carbonate to the formulation (batches F4 to F6), there was a significant increase (P < 0.05) in the FLT; in fact, an increased proportion of sodium carbonate with respect to sodium bicarbonate in the formulation resulted in a significant increase (P < 0.05) in the FLT. This effect possibly stems from the fact that sodium bicarbonate reacts spontaneously with acid (0.1N HCl) to release carbon dioxide compared to sodium carbonate, whose reaction with acid is a two-stage process: the formation of sodium bicarbonate that then reacts with acid to release the gas. Sodium bicarbonate, therefore, generates gas faster, imparting buoyancy to the tablet within a shorter time compared to sodium carbonate. A shorter FLT (as seen in F2 and F3) is more desirable for floating drug delivery because the tablet does not attach to the distal part of the stomach in this scenario. Doing so could impede buoyancy, rendering the tablet vulnerable to the physiological consequence of gastric emptying (28, 30). The addition of sodium carbonate to the formulation had no significant effect (P > 0.05) on the TFT of the tablets.

**Swelling index study.** It has been reported that the rate and extent of polymer swelling is dependent on the rate of solvent penetration, which is, in turn, determined by the rate and extent of matrix relaxation (25–27). The swellability of a polymer allows for sustained or controlled release of the drug. Measurement of fluid uptake is therefore used mainly as the basis to evaluate the outcome of fluid-polymer interaction(s) (28).

The inherently high swelling index of okra gum and its consequent application has been established in the authors’ laboratory in a separate study (25). The swelling index of batch F1 could not be determined because it disintegrated within a few minutes. There was an observed increase in swelling index up to the fourth hour for batches F2, F3, F4, and F6 (**Figure 1**). This was followed by the erosion of the swollen tablet matrix starting anytime between the fourth and fifth hour. And increased concentration of okro gum from 20–30% in batch F2 and F3, respectively, resulted in a significant (P > 0.05) increase in the swelling index of the tablet at the third and fourth hour, but both tablet batches began to disintegrate afterwards. Batch F4 showed a lower rate and extent of swelling, while batch F5 exhibited the highest extent of swelling and only began eroding slowly after the fifth hour (**Figure 1**). These observations suggest

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Floating lag time (s)</th>
<th>Hardness (Kg/F)</th>
<th>Friability (%)</th>
<th>Total floating time (h)</th>
<th>Swelling exponent (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>-</td>
<td>6.40 ± 0.75</td>
<td>0.32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F2</td>
<td>3 ± 2.12</td>
<td>3.96 ± 0.91</td>
<td>0.54</td>
<td>5.5 ± 0.03</td>
<td>0.0454</td>
</tr>
<tr>
<td>F3</td>
<td>5 ± 1.05</td>
<td>3.03 ± 1.29</td>
<td>2.17</td>
<td>5.0 ± 0.09</td>
<td>0.0612</td>
</tr>
<tr>
<td>F4</td>
<td>240 ± 2.65</td>
<td>3.83 ± 0.72</td>
<td>0.43</td>
<td>6.0 ± 0.24</td>
<td>0.0525</td>
</tr>
<tr>
<td>F5</td>
<td>420 ± 2.19</td>
<td>3.90 ± 1.21</td>
<td>0.44</td>
<td>5.5 ± 0.91</td>
<td>0.0641</td>
</tr>
<tr>
<td>F6</td>
<td>700 ± 4.21</td>
<td>3.88 ± 0.93</td>
<td>0.53</td>
<td>6.0 ± 0.12</td>
<td>0.0575</td>
</tr>
</tbody>
</table>
Swelling index profile of promethazine floating tablets. 

that F5 has a promising potential for use in controlled- or sustained-release drug formulations; high swelling has been established to correspond with slower and prolonged drug release (28). Generally, the swelling behavior of each batch investigated in this study is attributable to their respective formulation compositions.

Swelling/water uptake kinetics. Data obtained from the water uptake and swelling study were subjected to the Vergnaud model to determine the water uptake kinetics. The generalized equation of the Vergnaud model (31) is shown below (Equation 2):

\[ M_t = k t^n \]  

[Eq. 2]

where \( M_t \) is the amount of liquid transferred at time \( t \), \( k \) is the swelling constant, and \( n \) is the swelling exponent.

The swelling constant \( k \) is dependent on the amount of liquid transferred after infinite time as well as the diffusivity and the porosity of the matrix (31). The swelling exponent \( n \) denotes the water uptake mechanism, and the value of \( n \) (Table II) is less than 0.5 for all the formulations in this study, except F1, which disintegrated soon after suspension in the fluid medium. These data indicate a diffusion-controlled mechanism in which the rate of diffusion of the solvent (0.1N HCl) is significantly lower than the rate of stress relaxation of the okra gum matrix. This observation differs from the authors’ earlier work on the fluid uptake kinetics of gellan gum tablets containing metronidazole (31). In that study, the authors established that the water uptake mechanism of gellan gum was a polymer relaxation-controlled mechanism (the stress relaxation process was slower than the solvent diffusion rate). Although both gellan and okra gums are of natural origin, the latter is a plant gum, and the botanical and/or biological source of polymers affects their properties; therefore, the difference in the mechanism of fluid uptake is not unexpected. The low values of the swelling constant suggest absence of a burst swelling or water uptake effect in the polymer (31). The plot in Figure 2 corroborates this result.

Figure 1. Swelling index profile of promethazine floating tablets.

Figure 2. Plot of log percent water uptake by okra gum as a function of log time according to the Vergnaud model.

Conclusion

This study reveals that formulations made with okra gum containing sodium bicarbonate, rather than sodium carbonate, as the gas-generating additive have a better prospect in the preparation of gastroretentive/floating dosage forms of promethazine HCl.

References


Moving Out of the Lab to Optimize Microbial Control

Microbial experts should employ proactive practices on the manufacturing floor, rather than relying on testing.

James Agalloco is president of Agalloco & Associates.

The presence of microorganisms in pharmaceutical products is a potential hazard to patient safety and product quality. Consequently, there are regulatory expectations that microbial populations be appropriately controlled. A publication cited numerous recalls triggered by the actual or suspected presence of microorganisms (1). Clearly, industry faces a continuing problem in preparing products assuring microbial quality on a consistent basis. In sterile products, this expectation is an absolute; for non-sterile products, however, there is some flexibility, although depending upon the route of administration, absence of a particular microbial species is sometimes required. An inherent complication exists with these prohibitions: how is microbial absence in a pharmaceutical product, whether partial or total, to be established? Since the inception of microbial limits, the pharmaceutical industry has relied on sampling of products followed by microbiological analysis as described in the pharmacopoeia. It should be obvious that sampling and analysis has not achieved the desired results; emphasizing testing is not an effective microbial control mechanism to ensure the desired level of microbial control (2–5). This publication outlines practices for control of microbial populations that shift the modality from reactive to proactive.

Regulations and standards

The most basic expectations for microorganisms in pharmaceutical products relate to “…appropriate standards of identity, strength, quality, and purity…” (6). The last of these (purity) addresses concerns for the presence of contaminants that might be harmful to the patient. Microorganisms undoubtedly fall into that category where their presence would cause infection or illness. United States Food and Drug Administration (FDA) current good manufacturing practice (CGMP) regulations include specific, albeit general expectations for microbial control in 21 Code of Federal Regulations (CFR) 211.113 (7):

(7) These subparagraphs mandate the use of procedural measures to provide microbial control of manufacturing processes to maintain the desired microbial state. The regulations are supported by pharmacopeial references for sterile and non-sterile products. United States Pharmacopeia (USP) chapter <71> Sterility Tests includes the following acceptance criteria: "Incubate portions of the media for 14 days. No growth of microorganisms occurs" (2). An informational USP Chapter <1111> Bioburden Control of Nonsterile Drug Substances and Products includes multiple statements of the phrase "absence of …" linked to individual microbial species that vary with the route of administration (5). The results of these tests are presumed definitive proof that a particular lot meets the specified criteria. The test results are used to accept some batches while rejecting others. Environmental monitoring (air, surface, and personnel) along with aseptic process simulations are utilized with sterile products to further assess the effectiveness of operational controls. Raw materials API sampling along with limited environmental assessments are employed with non-sterile processes to assess their microbial content. Utilities, primarily purified water and water for injection, are monitored on a continuing basis. It might seem to some that this compilation of test results assures patient protection from microbial contamination.

“211.113 Control of microbiological contamination.

“(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

“(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.” (7).

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Curiosity is the spark for medical breakthrough. The right CDMO partner can nurture that spark with scientific excellence and expert, reliable delivery. For decades, Curia—formerly AMRI—has accelerated our partners’ work, from research and development through commercial manufacturing. Together, we’ll work to turn your idea into a life-changing cure.
contamination is afforded. The Jimenez study suggests otherwise (1). No amount of sampling and testing can do that because testing is not control. More importantly, it is evident that adequate microbial controls are not sufficiently effective because contamination is recovered all too frequently.

**Microbial control realities**
The largest shift in microbial control strategy may have occurred in the mid-1970s when validation was introduced as the means for resolution of sterility failures undetected by end-product sterility tests (8). The independent assessment of process robustness provided by sterilization validation vastly increased the confidence in the sterility of materials. Validation has evolved to the point where most of the world’s large-volume parenteral (LVP) products are parametrically released without sterility testing. Validation forces a rigor in process/product development and execution that has increased the reliability of processes used for sterile and non-sterile products.

A Parenteral Drug Association survey on environmental monitoring for non-sterile products revealed that industry practices varied widely (9). The United States Pharmacopeial Convention began the development of an informational chapter in its 2005–2010 cycle, and it declared that monitoring was not an effective means to establish microbial control for these products (10). The *USP <1115>* chapter included the following statement:

“A critical consideration in ensuring product quality is to prevent conditions within the manufacturing facility or manufacturing process that favor the proliferation or ingress of microorganisms. Microbial growth in excipients, components, and drug substances is a concern because it creates the possibility that viable microbial content could reach unacceptable levels.” (10).

The emphasis placed on prevention points the way forward, but perhaps lacks clarity on the direction to be followed. A more recent *USP* chapter on sterility assurance outlines the recommended actions more explicitly:

“Sterility cannot be demonstrated without the destructive testing of every sterile unit. In a real sense, microbiological safety is achieved through the implementation of interrelated controls that in combination provide confidence that the items are suitable for use as labeled. It is the controls that provide the desired assurance from microbiological risk rather than the results of any in-process or finished goods testing.” (11).

### Necessary actions
Viewed in this manner, the means to establish microbial control must be derived from the facility, equipment, and utility system design and the operational practices for materials, components, personnel, etc. The appropriate elements are embodied in global CGMP regulations (12). The suggested means to assure control is to place increased emphasis on the design and practice elements that potentially impact microbial contamination, which requires expanded participation of microbiological experts in all aspects of production. Effective microbial control can never be realized solely by sampling and analysis. Increased sampling of products, environments, or personnel will not improve product quality. Enlisting the firm’s microbiological expertise in proactive measures such as vendor audits, facility and equipment design reviews, and facility walk-throughs can provide meaningful improvements in performance. Microbial assessment in this fashion must be recognized as an ongoing process entailing continual diligence by qualified personnel. Best practices go well beyond those listed below and would include:

- Facility and product flow assessments from receiving through shipping
- Cleaning/disinfection/protection of all materials within the facility
- Evaluation of non-production areas of the facility such as utility areas, mechanical spaces, janitor closets, and heating, ventilation, and air conditioning (HVAC) systems
- Housekeeping, cleaning, and disinfection practices for non-product contact surfaces and the facility overall
- Personnel gowning and personnel access practices/flows from building entry to/from all environments
- Practices for material transfer within the facility and especially between environments with differing material exposure
- Equipment flow/protection to/from cleaning and storage areas
- Protection of materials during sampling, storage, and dispensing activities
- Physical examination of the facility looking for evidence of water leakage, spills, excess soil, etc.
- Appropriate storage locations/conditions for engineering materials and equipment

These practices should be extended to API, raw material, and component suppliers to better assure the microbial quality of all items which become a part of the finished product.

### The role of monitoring
Although it is the process elements that provide the true means for microbial control, there needs to be continued assessment of their effectiveness through sampling and testing of environments, utilities (water and air), equipment (post-cleaning), materials (excipients, active pharmaceutical chemicals, in-process and finished goods), and personnel (primarily for sterile products). Reliance on these without fully addressing the other relevant activities is not adequate to secure microbial control. Absence in end-product testing does not mean absence; it means not detected. Although current compendial requirements suggest otherwise, expecting absence of any microbial strain in a non-sterile product is nonsensical (5). Absent a sterilization process, there are no means to assure
absence (13). Absence of microorganisms in sterile products is the goal, and operational practices can come close to realizing that, but nevertheless cannot deliver the absolute state of “sterility”. Regardless of the type of product/process used, testing is not control. That lesson was learned in the mid-1970s in the United States and United Kingdom when contaminated units of terminally sterilized products were administered to patients; sterility testing in this example was inadequate to assure patient safety (8). The means to patient safety is the implementation and maintenance of process controls. Microbial monitoring of all kinds is little more than an inadequate alarm system. It will continue to be used, because even an ineffective alarm is better than no alarm at all. Its lack of utility as the primary means of assuring microbial control, however, must be accepted.

Conclusion

Improvements in microbial control for microbial products aren’t realized by increased sampling and analysis, but rather through the implementation of effective process controls across the manufacturing operations. Sampling and testing play a role in assessing whether implemented controls are effective, but do not provide any means of control. To assure effective microbial control, a comprehensive programme of effective control actions is essential. Individuals with a background in microbiology bring direct understanding of the potential contamination risks and can be especially effective in assessing and improving the performance of the control measures. Their education and insight should be applied where it can be most impactful. As the means to assure that products are devoid of potential microbial contaminants are never absolute, regardless of the product type, control provided is best asserted on the factory floor rather than in the laboratory. Trained microbiologists should make daily reviews of operations, including behind-the-scenes areas such as warehouses, equipment storage, utility, and other environments where microbial presence and proliferation can result in the undesirable ingress of microorganisms into pharmaceutical products. They have the expertise to identify the contamination risks and offer constructive solutions to improve microbial control. It is time for them to leave the laboratory and get out on the factory floor to identify situations that lead to microbial contamination and offer appropriate corrective measures.

References

7. FDA, 21 CFR 211.113 (2008).
In pharmaceutical formulations, phospholipids obtained from plant or animal sources as well as synthetic phospholipids are used. Synthetic phospholipids possessing natural stereochi- mical configuration are preferably synthesized from \textit{sn}\textsubscript{3}-glycerol-3-phosphocholine (GPC), using acylation and enzyme catalyzed reactions. The precursor GPC can be obtained from naturally occurring phospholipids.

In addition to natural phospholipids, synthetic phospholipids are becoming increasingly important in drug delivery, as can be seen from the number of drug products containing synthetic phospholipids. They mainly play a role in parenteral administration and inhalation dosage forms. Parenteral and inhalation products with synthetic phospholipids comprise liposomal formulations, lipid nanoparticles, diagnostic products, and dry powders for inhalation, respectively. Examples of intravenous products are provided in Table 1.

Table I. Intravenous liposome products containing synthetic phospholipids.

<table>
<thead>
<tr>
<th>Active(s)</th>
<th>Drug Product(s)</th>
<th>Main lipid excipients</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>AmBisome®</td>
<td>HSPC, DSPG, Chol</td>
<td>Aspergillus, Candida-, and/or Cryptococcus species infections, visceral leishmaniasis</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Abelcet®</td>
<td>DMPC, DMPG</td>
<td>Invasive fungal infections</td>
</tr>
<tr>
<td>Daunorubicin citrate</td>
<td>Liposan®</td>
<td>HSPC, DPPG, MPEG-2000-DSPPE</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Daunorubicin/ Cytarabine</td>
<td>Vyxeos®</td>
<td>DSPC, Chol</td>
<td>Advanced HIV-associated Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Doxorubicin HCl</td>
<td>Doxil® Caelyx®</td>
<td>HSPC, MPEG-2000-DSPE, Chol</td>
<td>Newly diagnosed, therapy-related acute myeloid leukemia or acute myeloid leukemia with myelodysplasia-related changes</td>
</tr>
<tr>
<td>Irinotecan HCl</td>
<td>Onivyde®</td>
<td>DSPC, MPEG-2000-DSPE, Chol</td>
<td>AIDS-related Kaposi’s sarcoma, Metastatic ovarian cancer, multiple myeloma</td>
</tr>
<tr>
<td>Mifamurtide</td>
<td>Mepact®</td>
<td>POPC, DOPS</td>
<td>Metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy</td>
</tr>
<tr>
<td>Verteporfin/ Benzoporphyrin</td>
<td>Visudyne®</td>
<td>DMPC, EPG</td>
<td>Exudative (wet) age-related macular degeneration with predominantly classic subfoveal choroidal neovascularisation, subfoveal choroidal neovascularisation secondary to pathological myopia</td>
</tr>
</tbody>
</table>

Chol, cholesterol; DMPC, 1,2-dimyristoylphosphatidylcholine; DMPG, 1,2-dimyristorylphosphatidylglycerol, monosodium salt; DOPS, 1,2-dioleoylphosphatidylserine, monosodium salt; DPPG, 1,2-dipalmitoylphosphatidylglycerol, monosodium salt; DSPC, 1,2-distearoylphosphatidylcholine; DSPG, 1,2-distearoylphosphatidylcholine, monosodium salt; HSPC, hydrogenated soybean phosphatidylcholine; MPEG-2000-DSPE, \(N\)-(carboxyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanol amine, monosodium salt; POPC, 1-palmitoyl-2-oleoylphosphatidylcholine.

Table II. Depot injectable products containing synthetic phospholipids.

<table>
<thead>
<tr>
<th>Active</th>
<th>Drug Product</th>
<th>Main lipid excipients</th>
<th>Administration route and Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>ExparelTM</td>
<td>DEPC, DPPG, Tricaprylin</td>
<td>Post-operative at surgical site, e.g., bunionectomy or hemorrhoidectomy; postsurgical analgesia</td>
</tr>
<tr>
<td>Morphine sulphate</td>
<td>DepoDurTM</td>
<td>DOPC, DPPG, Chol, Tricaprylin Triolein</td>
<td>Epidural at lumbar level, pain treatment prior to surgery or after clamping the umbilical cord during caesarean section</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>DepoCyTM</td>
<td>DOPC, DPPG, Chol, Triolein</td>
<td>Intrathecal, lymphomatous meningitis</td>
</tr>
</tbody>
</table>

Chol, cholesterol; DEPC, 1,2-dierucylphosphatidylcholine; DPPC, 1,2-dipalmitoylphosphatidylglycerol; DOPC, 1,2-dioleoylphosphatidylcholine.
### Table III. Parenteral products containing synthetic phospholipids used for vaccines and RNA delivery.

<table>
<thead>
<tr>
<th>Active(s)</th>
<th>Drug Product (Formulation)</th>
<th>Main lipid excipients</th>
<th>Administration route</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patisiran, siRNA</td>
<td>Onpattro® (LNP)</td>
<td>DLin-MC3-DMA, PEG2000C-DMG, DSPC, Chol</td>
<td>Intravenous</td>
<td>Polynuropathy of hereditary transthyretin-mediated amyloidosis</td>
</tr>
<tr>
<td>Single-stranded, 5'-capped mRNA, encoding the viral spike protein of SARS-CoV-2 (mRNA)</td>
<td>Comirnaty® (BNT162b2/20bzinameran) (LNP)</td>
<td>ALC-0315, ALC-0159, ALC-002, DSPC, Chol</td>
<td>Intramuscular</td>
<td>Active immunization to prevent COVID-19 caused by SARS-CoV-2</td>
</tr>
<tr>
<td>Synthetic single-stranded, 5'-capped mRNA, encoding the pre-fusion stabilized spike glycoprotein of SARS-CoV-2 (mRNA)</td>
<td>mRNA-1273 (LNP)</td>
<td>SM-102, PEG2000C-DMG, DSPC, Chol</td>
<td>Intramuscular</td>
<td>Active immunization to prevent COVID-19 caused by SARS-CoV-2</td>
</tr>
<tr>
<td>Varicella Zoster Virus glycoprotein E antigen</td>
<td>Shingrix® (Liposome suspension)</td>
<td>QS-21, MPL, DSPC, Chol</td>
<td>Intramuscular</td>
<td>Prevention of herpes zoster and post-herpetic neuralgia, in adults 50 years of age or older</td>
</tr>
</tbody>
</table>

ALC-0159, 2-[(polyethylene glycol)-2000]-N,N,N-ditetradecylacetamide; ALC-0315, (4-hydroxybutyl)azanediylibis(hexane-6,1-diyl)bis(2-hexyldecanoate); Chol, cholesterol; DLin-MC3-DMA, (6Z,9Z,12Z,15Z,18Z)-heptatriaconta-6,9,12,15,18-pentadeca-4-yl-(4-dimethylaminobutanoate; DOPC, 1,2-dioleoylphosphatidylcholine; DSPC, 1,2-distearoylphosphatidylcholine; MPL, 3-O-desacyl-4'-monophosphoryl lipid A; PEG2000C-DMG, 3'-(1,2-di[myristoyloxy]propyl)amino[10-undecyl]oxy[hexadecyl]amino)octanoate.

### Table IV. Inhalation products containing synthetic phospholipids.

<table>
<thead>
<tr>
<th>Active(s)</th>
<th>Drug Product Formulation (see Table 3)</th>
<th>Main lipid excipients</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Arikayce® (Liposomal suspension)</td>
<td>DPPC, Chol</td>
<td>Treatment of Mycobacterium avium complex lung disease as part of a combination antibacterial drug regimen</td>
</tr>
<tr>
<td>Budesonide, glycopyrrolate, formoterol fumarate</td>
<td>Breztri Aerosphere® (Aerosol for inhalation)</td>
<td>DSPC-CaCl₂</td>
<td>Maintenance treatment of patients with chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Tobi Podhaler® (Powder for inhalation)</td>
<td>DSPC-CaCl₂</td>
<td>Management of cystic fibrosis patients with Pseudomonas aeruginosa infection</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Inbrija® (Powder for inhalation)</td>
<td>DPPC</td>
<td>Intermittent treatment of off episodes in patients with Parkinson’s disease treated with carbidopa/levodopa</td>
</tr>
</tbody>
</table>

Chol, Cholesterol; DPPC, 1,2-dipalmitoylphosphatidylcholine; DSPC, 1,2-diestearoylphosphatidylcholine.

Synthetic phospholipids can also be found in vaccines, in the form of lipid nanoparticles (LNPs) or liposomes in recently developed vaccine formulations for intramuscular administration for the delivery of messenger ribonucleic acid (mRNA) and a disease-related antigen, respectively. LNPs are also used for Maintenance treatment of patients with chronic obstructive pulmonary disease intravenous administration of small interfering RNA (siRNA) in the treatment of rare diseases (Table 3).

Synthetic phospholipids in relevant inhalation products are listed in Table 4. Interestingly, the phospholipids are used in several types of formulations suitable for commonly used inhalation devices.

In the future, synthetic phospholipids and designer lipids may play a more important role in sophisticated drug delivery systems.

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1. van Hoogevest P, Luciani P. Recent Advances in the Use of Phospholipid Excipients in Local or Injectable Depot Formulations. Pharm. Ind. 2018, 8:1104.
Moving Forward with Serialization

Stakeholders work to meet deadlines, maximize benefits, and close gaps.

Hallie Forcinio is packaging editor for Pharmaceutical Technology Europe, editorhal@sbcglobal.net.

Serialization plays an essential role in maintaining supply chain integrity, discouraging counterfeiting, and meeting regulatory requirements. In the United States (US), manufacturers are preparing for the 27 Nov. 2023 aggregation deadline to meet requirements of the Drug Supply Chain Security Act (DSCSA). “Aggregation is the process of ensuring that each unique serialized item is associated to its packaging and that packaging also includes a unique serial number,” explains Marta Schaefer, pharma account specialist at Videojet Technologies.

Europe, Asia, and Latin America have similar objectives for serialization. “It’s a global initiative,” says John Wirthlin, industry principal for Manufacturing, Transportation, and Logistics at Zebra Technologies. He adds, “The whole supply chain is affected. But the US deadlines are a little more aggressive. We are working with a couple of major pharmaceutical companies, who are looking at 10–12 months to implement a process so they will be ready 10–12 months ahead of the deadline. Global companies are looking to identify solutions and test in the US so they can finalize their process and harmonize it across the globe. The feeling is if they start here and meet US requirements, they will be able to address most requirements globally. They want a solution to be as standardized as possible so it can be rolled out to their facilities and third-party providers.”

One third-party provider that is ready to meet aggregation requirements, Reed-Lane, started up its second track-and-trace-ready cartoning line late in 2020 (see Figure 1). The line can serialize individual cartons and aggregate at multiple levels: cartons to cases, cartons to bundles, bundles to cases, and cases to pallets. It also can rework previously serialized items (1).

Data exchange

The November 2023 deadline also involves requirements for the interoperable exchange of data between entities transferring ownership of product. This system includes a secure, interoperable, electronic system between authorized trading partners through which Transaction Information (TI), such as name of the product, strength, and dosage form; National Drug Code; and Transaction Statement (TS), such as paper or electronic attestation by the business transferring ownership of the product. “In this system, for each pharmaceutical product transaction, an authorized trading partner provides TI and a TS to another authorized trading partner ‘in a secure, interoperable, electronic manner’ in accordance with standards established by guidance,” explains Steve Wood, president and CEO of Covectra.

The US Food and Drug Administration (FDA) is running pilot programmes involving industry standards groups such as GS1, wholesalers, and distributors. In addition, pilot programmes are evaluating the use of blockchain and other communal databases. In July 2020, the Partnership for DSCSA Governance released the first version of its blueprint for the 2023 system. It focuses on interoperability standards and implementation.

Wood says, “A lot of progress has been made on the setup of the verification router service network. The focus is now on a secure way of verifying the authorized use of these systems to only allow authorized trading partners to request and respond to verification requests.”

Trends in serialization

With the US deadline for aggregation approaching, many stakeholders are creating processes and tools to improve post-serialization packaging line efficiency.

Julien Faury, solutions lead for Antares Vision Group, reports, “Everywhere we see large companies, early adopters of serialization, and contract packaging organizations upgrading their systems to meet looming aggregation mandates. Not only will this make packaging operations easier to control, but also will help supply chain partners.” However, Faury believes outside help
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However, Videojet offers an ultraviolet (UV) laser system, which produces a high-quality permanent code on high-density polyethylene. UV laser marking creates a photochemical reaction at the surface of the material that resembles ink printing but offers higher resolution and therefore fewer false rejects and better overall equipment effectiveness. Another trend, says Schaefer, is the automation of case and pallet labelling with systems like the Videojet 9550 print-and-apply labeller.

Figure 1. A cartoning line (Reed-Lane) meets track-and-trace requirements for unit-level serialization and multi-level aggregation.
time and reduces costs by minimizing the number of labelling processes and systems on the packaging line. Manufacturers may choose either the T63 Integrated 360 Serialization system or the T65 Integrated 360 Aggregation system. The T63 unit serializes directly on the applied label instead of the traditional “label-on-web.” The T65 model obtains a full 360-degree view of products on the conveyor before insertion into secondary boxes and cases, which eliminates the need for top-down printing of helper codes and the extra processing associated with it (3).

NJM, a ProMach product brand, has introduced the Bottle Tracker and the Cumulus semiautomatic case packer. The Bottle Tracker accommodates a large range of bottle sizes and shapes in a compact machine footprint. “It provides secure code association of the actual serialized code on the label with the helper code to facilitate downstream automated aggregation of bottles in bundles and/or shipper cases,” says Omar Azam, inside sales manager at NJM.

Less expensive and smaller than fully automatic case packers, the Cumulus semiautomatic case packer supports automatic aggregation of bottles in shipper cases. Its smaller footprint allows it to fit on packaging lines currently relying on manual aggregation, where space often isn’t available for a fully automatic case-packing system.

New products from WLS include the capability to print serialized codes on labels off-line on its Autonomy digital label printer, the integration of RFID tag application on some of its labellers, and the ability to match the bottle helper code to the label serialized code (i.e., commissioning) on its RL-420 rotary labeler. The offline printing “can replace the need for serialized code printing on the labeller itself, thus simplifying line integration,” says Sarvey. Integration of RFID tag application (either prewritten or written at the labelling station) eliminates the need for a standalone commissioning station. The company also offers RFID-ready labellers for online configurations. Label printer/applicators from Zebra have been capable of encoding RFID tags for some time but now offer expanded functionalities to accommodate mixed pallet loads. Zebra also is testing tags with a more sensitive proprietary antenna. The tests, in partnership with two major pharmaceutical companies, examined tag performance on hard-to-read products involving liquid or metal. Four products (540 cases each) were tested for readability. Wirthlin reports, “We were able to successfully read case-level RFID labels for the majority of the products and achieved a 99% accuracy rate for hard-to-read products that included dry tablets, liquid vials, prefilled injectables, and foil blister packs. The cases were tagged with Zebra’s ZBR4000 inlay and loaded onto pallets. The pallets were loaded onto a truck via forklift at normal speeds and read by our Zebra Transition RFID Portal at the dock door.”

Covectra recently introduced a modular Serialization Packaging Platform, which can be located anywhere in the supply chain—manufacturer’s warehouse, contract manufacturing organization, third-party logistics provider, wholesaler, or distributor. The Serialization Packaging Platform is designed on GS1 general specifications and is extensible and modular. “The same platform can be configured for manual, semi-manual, and completely automated environments,” says Abhijeet Bhandari, Director of Software Engineering at Covectra. It also supports scenarios where existing aggregation hierarchies are reworked while maintaining data integrity.

For repackagars, Covectra has added the Atlas Repackaging System component to its Atlas Serialization Platform. It enables cost-effective relabelling of previously serialized products and rework products, and it accounts for products removed after packaging for quality-control processes. Targeted toward small and mid-size pharma companies and designed according to good manufacturing practices, the Atlas Repackaging System complies with US Code of Federal Regulations (CFR) 21 Part 11, GS1, and Healthcare Distribution Alliance specifications as well as DSCSA barcoding guidelines for serialized products at manufacturing or packaging operations. The agnostic system connects to commonly used printers, vision systems, and barcode scanners and provides complete reporting features on reworked or relabelled orders (4).

**Future outlook**

Noting that reconciliation remains a manual process in many organizations due to the absence of a standardized process, Bhandari believes, “exception handling and reconciliation of serialized product with the data still needs work on the packaging lines and within systems exchanging serialized data information.” The lack of these checks inevitably leads to exceptions where the physical serialized product and the data with the identifiers for those products do not match, generating “Product/No Data” or “Data/No Product” exceptions. Bhandari says, “We believe more validation checks need to take place by communicating standardized volume information along with the standard [Electronic Product Code Information Services] data formats for this purpose.”

The key to addressing the latest DSCSA requirements is digitizing and sharing information. “We need to connect partners and eliminate silos,” concludes Wirthlin.

**References**

Impurities in pharmaceuticals

Regulatory agencies, such as the European Medicines Agency (EMA), set guidance on the content and qualification of impurities in pharmaceutical agents (3). Three major classes of impurities must be profiled in drug products and drug ingredients: organic impurities, inorganic impurities, and residual solvents.

Organic impurities can include starting materials, by-products, intermediates, degradation products, reagents, ligands, and catalysts. One example can be found in the manufacturing of paracetamol, also known as acetaminophen, which is synthesized with p-aminophenol as a starting material or intermediate. Drug regulatory agencies set strict limit tests for leftover p-aminophenol in the final bulk paracetamol product to assure purity and quality of the preparation (4). Organic impurities may also arise from the breakdown of final products including oxidative degradation, decarboxylation, and hydrolysis.

Inorganic impurities can derive from all points of the manufacturing process and include reagents, catalysts, residual metal traces, and inorganic salts. For example, the presence of inorganic salts may alter drug solubility, or the presence of rapidly oxidized materials can change the colour of the drug, which could deter many patients from taking it.

Residual solvents include materials used in the production process, such as growth-selection agents, viral inactivation agents, and surfactants. These residual solvents can be present in the final dosage form. Trace amounts of compounds from shipping containers may also contaminate drug product. These residual solvents can be toxic or environmentally hazardous.

To protect patient safety and ensure the integrity of the production line, it is common for manufacturers to identify and eliminate types of impurities in drug ingredients before they get into the manufacturing process and the downstream product. Typically, the earlier impurities are detected and removed, the less time and resources are wasted on using a contaminated ingredient.

It is challenging, if not impossible, to completely remove all impurities in the manufacturing process; however, manufacturers should ensure impurities are absent, or present in safe levels, and don’t affect the function of the final product. It is, therefore, imperative to have reliable, accurate, and efficient methods of detecting impurities.

Impurity profiling is a complex procedure owing to the large number and diversity of impurity compounds that can find their way into drugs during manufacturing. Advances in mass spectrometry methods offer solutions for comprehensive impurity detection.

Aaron M. Robitaille is senior product marketing manager, and Brandon J. Bills is product manager, both with Thermo Fisher Scientific.

Stepping Up the Search for Unknown Impurities

Intelligent analytical tools help ensure the quality of small-molecule drug ingredients.
to contain impurities. In these situations, manufacturers must prove a lower quantification threshold for compliance.

### Analyzing unknown small molecules

The large number and variety of potential impurities presents a significant analytical challenge for their detection, quantification, and characterization. It requires the ability to distinguish trace amounts of unrelated chemicals in the background from uncharacterized and unwanted small molecules. One pertinent challenge is that some potential impurities will be unknown beforehand, meaning manufacturers often find themselves searching for them in the dark without a torch. Therefore, there is a need to measure a range of potentially unknown impurities, from very polar to non-polar molecules, in quick and efficient workflows.

Of course, manufacturers need to identify the presence of small molecules with high confidence and quantify them with high accuracy and sensitivity. As a wide range of potential unknown compounds may be present only at very low quantities, a variety of robust analytical techniques with high sensitivity and specificity are necessary to ensure the identification of as many as possible.

Current methods to characterize impurities in drug ingredients involve a set of orthogonal methods to cross check results and offer the most accurate measurement. Historically, chromatography coupled to ultraviolet detection has been the gold standard for profiling small-molecule impurities, but these methods only measure known lists of compounds verified by reference standards and cannot give detailed information on unknowns.

More comprehensive methods, such as mass spectrometry (MS) techniques, can be used to characterize small molecules within samples. MS systems can measure the mass-to-charge of compounds in a sample, which can be used to calculate the molecular weight and chemical formula of detected compounds in a sample and compare these against databases of known contaminants. These methods allow highly accurate and sensitive measurements with high discrimination power, as well as providing options to scan for unknown compounds.

However, older technologies, like single-quadrupole MS systems, often face sensitivity and specificity challenges due to unit resolution detection. Intense, co-eluting isobaric chemical background noise can hide a measured signal from the targeted compound, meaning many analytical laboratories struggle with data reduction and false positives with low resolution systems.

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Identifying unknown impurities

The next generation of MS instruments are designed to unravel complex chemical structures. These instruments are designed to detect, identify, and quantify impurities in drug samples when used in combination with other technologies such as chromatography, allowing scientists to decipher complex structures. Advances in gas chromatography-MS (GC-MS) and high-resolution MS (HRMS) technologies provide user-friendly, all-in-one analysis systems, with ultra-high resolution, high sensitivity, and rapid acquisition rates to obtain the data needed for impurity analysis of drug ingredients.

Some MS-based workflows can evaluate both qualitative and quantitative aspects of impurities at high resolution. Systems providing up to 1,000,000 resolution improve confidence for unknown small-molecule analysis and fine isotope detection for the determination of impurity molecule composition (see Figure 1). Rapid scan speeds allow for clear peak detection against a background of chemical noise, reducing the potential of false positives.

Analytical software packages use intelligent methods to discover compounds with unique fragmentation patterns, allowing automatic peak detection, spectral deconvolution, and putative impurity identification based on library match scores. Such systems enable the identification of unknown metabolites, degradants, and transformation products that could be potentially found inside drug ingredients.

Data-dependent MS3 and higher-order fragmentation methods allow in-depth characterization of precursors to aid unknown small-molecule structure elucidation. Traditionally, small molecules are subjected to collision induced dissociation and higher-energy collisional dissociation fragmentation for structure elucidation. In addition, orthogonal fragmentation techniques like ultraviolet photodissociation (UVPD) enable the differentiation of structurally similar compounds that would otherwise appear to be identical. Here, UVPD can perform complementary fragmentation to provide more accurate annotations of analyte structures, enabling unambiguous characterization of potential impurities.

Advancing impurity analysis

Impurities can leak into drug products during all stages of the manufacturing process. Due to their propensity to alter the efficacy and safety of drugs, it is crucial for manufacturers to identify and quantify impurities during production and in the final product. Profiling drug ingredients allows manufacturers to pinpoint when and how impurities entered the drug and reduces the risk of impurities being passed to the final drug product.

Currently, scientists must employ a range of techniques to identify, quantify, and characterize as many impurities as possible. However, comprehensively analyzing drugs for known and unknown impurities can be challenging for analytical laboratories due to the complexity of samples.

The latest generation of mass spectrometers go beyond the capabilities of previous generations for small-molecule analysis, addressing the need for accurate, efficient, and high-powered impurity detection in drug production. Using the latest technologies, more unknown compounds in pharmaceutical ingredients can be identified, protecting society from the risks of impurities entering drug products.

References

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Mitigating Third-Party Risks: The Benefits of Extending Quality to the Supply Chain

Supply management is a critical component for bio/pharma companies to ensure the quality and safety of finished goods. With the increased prices and regulatory challenges, industries are outsourcing, expanding the supply chain’s risk and complexity.

Research from a 2020 Deloitte survey shows that 84% of respondents said their organization had experienced a third-party incident in the last three years (1). A third-party supplier is a company or entity with whom you have a written agreement to provide a product or service on behalf of your organization.

Companies failing to establish a robust supplier management process expose themselves to financial consequences, compliance concerns, and damaged reputation. By synchronizing and integrating data with suppliers, it will allow collaboration, improve speed-to-market times, and enable implementation of best practices and standardized processes.

Without this insight, it would be nearly impossible to see which suppliers are most responsive, resilient, and aligned with a company’s values. Ensuring that suppliers are meeting regulatory requirements also becomes a difficult feat.

The following describes how organizations can gain visibility into critical supplier activity, gain insight into selecting the best suppliers for their business, and nurture collaboration with critical third parties.

Common challenges faced in supplier management
Organizations that lack effective external quality management capabilities, and instead use manual processes, may find themselves with gaps in communication, process delays, and potential product issues in the market. When this happens, it’s the stakeholder that faces the consequences, not the supplier. Managing an ecosystem of suppliers in this manner presents various risks to an organization.

Some of the more prevalent challenges to consider include the following.

The Nth party. Stakeholders may have thousands of third-party relationships. Lack of oversight into this supplier ecosystem can leave an organization vulnerable to many risks. Organizations must also consider risks posed by the Nth party—the third parties’ suppliers. These connections pose risks, particularly given the fact that the stakeholder rarely has visibility into who they are or that they exist at all.

Supply chain disruptions. The COVID-19 pandemic is a key example of how disruptions can wreak havoc on the supply chain. The industry has seen sourcing issues, transportation issues, and lack of supply chain traceability (2).

Siloed processes. When organizations operate in silos, each department essentially is working in their own bubble and missing key data and insights from other operational areas that may be relevant to their process.

Hindered visibility. A siloed supplier management process results in lack of visibility into the supply chain. Stakeholders may find themselves reacting to supplier quality events, rather than being proactive in preventing them from occurring in the first place.

Onboarding risk. Good supplier management does not start after suppliers have been onboarded. It’s essential to know which suppliers are high-risk before the onboarding process. Supplier management needs to start at supplier evaluation and continue through selection and onboarding.

Inefficient collaboration. Manual processes such as paper, email, or phone make it difficult to share data and track items like change notifications from suppliers. The result is a time-consuming process that relies on manual updates and leaves room for human error.

Supplier collaboration makes a major difference when done well. A McKinsey survey shows that companies that collaborate regularly with suppliers see higher growth, lower operating costs, and more profitability (3).

The functionality of a digital quality management system (QMS) provides visibility into critical supplier activity and helps ensure a high-quality product.

Zillery A. Fortner is product marketing manager, Sparta Systems, A Honeywell Company.
How to transform the supplier management process

An effective supplier quality management process is a critical component for ensuring a high level of brand equity, customer satisfaction, and patient safety. Organizations must align supplier performance with corporate targets to ensure they’re using the best suppliers for their needs.

Manually managing suppliers results in process gaps due to siloed systems, incomplete risk assessments, inefficient means of reporting, and an increase in product deviations and recall inability to provide reliable data on supplier performance.

Organizations can start taking steps toward transforming the supplier management process by taking the following measures.

Automating supplier quality management. Using an automated supplier management system provides visibility into the supply chain, so external issues can be found before they escalate. With all supplier data hosted in a central system where it can be accessed by authorized parties, quality events can be managed consistently and efficiently. All third parties are managed from a single point, making for easy comparison, with automated scorecards that reflect both current data and historical track records. This capability enables organizations to respond efficiently to quality events, and better equips them to deal with audits. Reducing the time to respond to quality events translates to cost savings for the manufacturer.

Managing quality across the supply chain poses a lot of complexity. An automated solution alleviates this by enabling traceability and making each third party accountable for its role in the supply chain.

Integrated functionality of an automated system can provide continuous and clear risk assessments on low-, medium-, and high-risk suppliers. It will also enable documentation of collaboration with suppliers directly within the system.

Breaking down silos. Silos hinder communication. Integrated supplier risk management eliminates silos, which could otherwise disrupt supply chains, cause surprises and business delays, result in duplicate effort across various departments, and slow down the time it takes to respond to quality events.

An integrated approach to supplier management tightly connects an organization with its supplier ecosystem. In doing so, it provides the insight needed to help organizations avoid surprises, meet compliance, and respond faster to risk events.

Be proactive about supplier management. The ability to act proactively is critical for preventing incidents due to poor supplier quality. Organizations can start taking steps to proactively manage suppliers by following these best practices:

• Provide suppliers with key performance indicators (KPIs). Often, organizations focus on the efficiency and effectiveness of internal operations, but do not apply the same approach to third parties. Organizations can ensure that suppliers are meeting performance expectations by providing clear KPIs that measure supplier quality performance.
• Communicate effectively: Communication is key for driving collaboration with third parties. Organizations should engage suppliers and provide routine feedback on the quality of goods and services and have a clear understanding of supplier capabilities.
• Maintain an approved supplier list. Know upfront which suppliers are approved to do business with by keeping and maintaining an approved supplier list. This will limit risks by ensuring you’re only engaged with the best suppliers for your business.

• Leverage cross-functional data. An organization’s quality management efforts must be interconnected among cross-functional teams to truly understand the impact of risks across the enterprise.

**Build a culture of quality with suppliers**

Cloud-based quality management systems (QMS) can help ensure an integrated quality network across suppliers. Internal quality management processes connect with third parties, streamlining communication and delivering comprehensive visibility into issues from raw material through manufacturing to the customer experience. Organizations can use QMS solutions to successfully identify vulnerabilities, gain visibility over supplier tiers and into quality processes. It helps increase supplier accountability, ensuring that suppliers are aligned with resolution requirements and gives insight into which suppliers are top performers. The result is a collaborative supplier management process that allows visibility into the process so you can identify potential issues before they escalate. Organizations that implement an integrated supplier quality management solution will have the tools to start tackling supplier risk proactively and ensure only safe, quality products reach the market.

**References**


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**The Impact of Insufficient Oversight**

*Pharmaceutical Technology Europe* asked Vincent Colicchio, vice president, supply chain and external manufacturing at Dr. Reddy’s Laboratories, about how a lack of proper supplier oversight can impact the pharmaceutical industry and the drug supply chain.

**PTE:** What types of quality issues can be created by insufficient oversight of material suppliers? Of contract manufacturers?

**Colicchio (Dr. Reddy’s):** There are several important materials in the pharmaceutical supply chain such as APIs, key starting materials for API production; excipients; purified water; and packaging materials including bottles, closures, vials, and printed components. The types of quality issues that can be created by insufficient oversight of material suppliers that could impact the supply chain include the following examples:

• Material suppliers that manufacture APIs who fail to comply with [good manufacturing practices] GMPs could produce APIs that contain possible contaminants. This can be through dirty equipment and facilities due to poor upkeep, [poor] cleaning, or processing equipment in disrepair. This risk also pertains to the production of excipients.

• Printed component suppliers that fail to track and control the latest approved document version of the files for labels, patient information leaflets, and cartons risk printing and shipping an older version of packaging materials to their customers. Failure to print the latest approved version could compromise the on-time packaging and supply of finished goods to customers due to possible mislabeling.

The types of quality issues that can be created by insufficient oversight of contract manufacturers include failure to ensure that the contract manufacturer thoroughly addressed all open observations found in an [US Food and Drug Administration] FDA inspection or other regulatory agency inspection in a timely manner. While there are a wide variety of potential issues in this category, it is particularly important that the contract manufacturers properly operate and sanitize the purified water system that is used for production operations and cleaning purposes. Prevention of any microbial contamination is a must in any purified water system. It is also critical that the HVAC systems properly function to maintain production room conditions for temperature and humidity control along with differential pressures at all times.

**PTE:** How is the supply chain impacted by poor oversight of suppliers?

**Colicchio (Dr. Reddy’s):** The supply chain can be impacted by poor oversight of contract manufacturers. For example, in the event that a contract manufacturer fails to properly clean the production equipment or execute its cleaning validation programme, it runs the risk of allowing residues or contaminants to enter into the production process and product. If this occurs, analytical testing would reveal the presence of contaminants. The product would be placed in quarantine until such time that the investigation is carried out and completed with the appropriate [corrective and preventive actions] CAPA. The equipment would need to be re-cleaned. Presuming the original batch fails product release, the product would need to be manufactured again and then shipped to the customer. The delayed shipment of the product to the customer would likely impact on-time and in-full product shipment to the customers and subsequently access to the patients.

—Susan Haigney
A typical gene or cell therapy workflow—from upstream plasmid production and cell culture to downstream purification and final production—requires a massive amount of molecular biology work. Because molecular biology processes can be extremely sensitive to impurities—particularly ubiquitous enzymes, such as DNases, RNases, and proteases that degrade DNA, RNA, and proteins, respectively—molecular biology grade reagents are often required (see Table I). For example, polymerase chain reaction (PCR) is routinely used for plasmid and viral vector production and requires the utilization of multiple buffers, enzymes, and water. To avoid non-specific amplification and prevent degradation of enzymes and target DNA, reagents must be free from DNase, RNase, and protease activity.

Similarly, high-performance liquid chromatography (HPLC) is commonly used in gene and cell therapy workflows for analytics, such as monitoring empty/full capsid assemblies and total capsid protein. Impurities in HPLC reagents can result in extraneous peaks, which interfere with the main peaks in the chromatogram and lead to results that are difficult, or even impossible, to interpret.

How to choose reagent grades
Which grade? Choosing a suitable reagent grade depends on the application and end goal. For research and educational purposes, research use only (RUO) reagents (Table I) are broadly applicable and available at low cost. Although RUO reagents may seem appropriate for developmental stages of cell and gene therapies, their use must be carefully considered. Impurities and contaminants in reagents can affect results, especially when conducting highly sensitive processes (e.g., HPLC, PCR). Additionally, for clinical use, the US Food and

Understanding purity grades
Ensuring quality of raw materials for cell and gene therapies presents unique challenges because the final therapeutics are of biological origin, which means they are inherently complex and often bespoke in nature. The specialized biologics—such as cells and vectors used in cell and gene therapy development and manufacture—have been of recent focus. However, reagents—including growth media, process buffers, antibiotics, and general chemical solutions—that are used to produce cells and vectors are equally critical to reliable, optimal results and final product quality.

To determine the suitability of materials for cell and gene therapy applications, a monograph that includes the general description, specifications, requirements, and tests necessary for a manufacturer to designate a substance as meeting a specific purity grade can be used. Several international agencies supply purity grade regulations in food, drug, and medicinal product manufacture (see Table I).
Table I. Overview of common reagent grades.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Application</th>
<th>Example applications in cell and gene therapy</th>
<th>Example reagents commonly used in cell and gene therapy workflows</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Grades</strong></td>
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</tr>
<tr>
<td>ACS</td>
<td>Often regarded as a gold standard for meeting or exceeding the standards set by the American Chemical Society (ACS). Purity of equal to or greater than 95% are required.</td>
<td>Reagents are suitable for food, drug, and medical applications as well as general protocols requiring strict quality specifications.</td>
<td>Bacterial and viral culture</td>
<td>Media, buffers, and solutions</td>
</tr>
<tr>
<td>Reagent</td>
<td>Often considered equivalent to ACS grade, although no standard specifications exist.</td>
<td>Reagents are suitable for food, drug, and medical applications as well as general protocols requiring strict quality specifications. Frequently, these are solutions or dilutions of ACS grade reagents.</td>
<td>Bacterial and viral culture</td>
<td>Media, buffers, and solutions</td>
</tr>
<tr>
<td>United States</td>
<td>Pharmacopeia (USP)</td>
<td>Meets or exceeds requirements set out by the corresponding institute.</td>
<td></td>
<td></td>
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<tr>
<td>National Formulary (NF)</td>
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<tr>
<td>British Pharmacopeia (BP)</td>
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<tr>
<td>Japanese Pharmacopeia (JP)</td>
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<tr>
<td>European Pharmacopeia (PhEur or EP)</td>
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<tr>
<td>Multi-compendial</td>
<td>Meets or exceeds requirements set by more than one pharmacopoeia.</td>
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<tr>
<td><strong>Specialty Grades</strong></td>
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<tr>
<td>Molecular biology</td>
<td>Specifically manufactured for molecular biology applications. Tested for specific contaminants including DNase, RNase, and protease activity as well as bacterial contamination.</td>
<td>Suitable for molecular biology laboratory applications</td>
<td>Viral vector and plasmid production and purification</td>
<td>Polymerase chain reaction (PCR) and lysis buffers, buffers with poloxamers, glucose solutions, water for molecular biology, water for injection (WFI) quality water</td>
</tr>
<tr>
<td>HPLC</td>
<td>Specifically manufactured for the majority of high-performance liquid chromatography (HPLC) grade separations. Extremely high purity (generally &gt;99.9%) solvents, buffer salts, and mobile phase modifiers.</td>
<td>Suitable for HPLC, gel-permeation chromatography, and UV-spectrophotometric analysis</td>
<td>Monitoring capsid assemblies and product/reagent impurities</td>
<td>MES buffers; sodium acetate, sodium citrate, and sodium phosphate buffers; and Tris buffers</td>
</tr>
</tbody>
</table>
Drug Administration (FDA) and the European Medicines Agency (EMA) regulations require manufacturers to switch from RUO materials to those produced according to GMP. This transition may require validation, optimization, and comparative studies that ensure processes remain consistent—adding cost and time to the commercialization workflow. As such, using high-quality reagents in the initial stages and potentially switching to GMP reagents during early pre-clinical research can ease this transition.

While American Chemical Society (ACS), Reagent, and United States Pharmacopeia–National Formulary (USP–NF) grades are often interchangeable and offer the highest purity grades suitable for medicinal manufacture, each reagent must be scrutinized for every application. Selecting a reputable supplier with a sound understanding of cell and gene therapy manufacture will ensure appropriate reagents are used at each stage, saving time and money.

**Which supplier?** Choosing a known supplier is integral to a successful cell and gene therapy workflow. Reviewing a supplier’s processing and documentation procedures can help evaluate their expertise. Suppliers that have been certified through International Organization for Standardization (ISO) inspections confirm the presence of robust quality systems. For example, manufacturing facilities that are ISO 13485:2016 compliant and integrate extensive raw material analysis, bioburden testing, and quality-control processes into production of reagents can help enable a seamless transition from RUO to GMP manufacturing.

Additionally, using companies that already offer specialized products for cell and gene therapy workflows can be beneficial, because they can supply advice on the appropriate reagent for each application and stage. Moreover, they may be able to offer custom RUO and GMP products and services that are critical to meeting the complex nature of novel cell and gene therapy development and manufacture.

**Conclusion**

Although the manufacture of innovative medicinal products, including cell and gene therapies, represents a novel challenge, the basic principles that inform choices about reagent grades and when to transition to GMP materials still apply. The choice of raw materials can play a pivotal role in the manufacturing of cell and gene therapy products. Suppliers who conduct robust quality assessments to ensure that appropriate resources are used will help realize the promise of cell and gene therapies.
attention towards telemedicine, with the development of digital technologies being central to practice management, advanced therapeutics, and the wider clinical trial ecosystem. This shift has caused large pharma to refocus on digital health deals and has demonstrated the validity of digital investments. Now we can expect to see leading market participants release non-core business assets and instead focus on pursuing novel subsectors.

In particular, the biotech market will see substantial interest from investors and become a crucial M&A target, as companies continue to invest in innovation. For example, in June 2021, the German company MorphoSys announced a US $1.7 billion (€1.4 billion) deal to acquire the clinical-stage biotech company, Constellation Pharmaceuticals (5). According to PwC, biotech acquisition activity in the US $2–$10 billion (€1.7–€8.5 billion) range is accelerating, and funding will continue to trend as well, with companies looking for strategic deal making and partnership opportunities (6).

**Rise of new market players**

The ongoing digital transition is overhauling how industry players are assessing their business models and driving cross sector deals. Life sciences companies are increasingly acquiring or partnering with tech companies to enhance their market offerings. As rising valuations drive deal activity across the sector, companies are also becoming more introspective and taking a critical view on where they are coming up short. This is likely to prompt more cross sector transactions, particularly through bolt-on activity.

In 2020, bolt-on deals accounted for 82% of biopharma M&A activity, with companies spending US $17.8 billion (€15.1 billion) on these types of deals to mitigate financial risk (7). While we expect to see a rise in ‘mega deals’, bolt-on acquisitions of healthcare and pharma companies...
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will accelerate this year as businesses look to hedge risk and diversify at pace.

New players will also enter the market through bolt-on deals. Despite the turbulent market conditions, many participants have strengthened their financial position over the past 12 months and are now looking for suitable investment opportunities. The life sciences traditional position as a refuge for investors is now attracting the attention of companies that didn’t previously have a foothold in the industry. Private equity and venture capital investors are already taking stock of these new market opportunities to deploy capital and will become more active across the sector.

Still, there will be ongoing regulatory and legislative challenges for key market players to navigate.

**Implications of EC’s new merger controls**

In March 2021, the European Commission (EC) published a significant change to merger controls on cross-border M&A activity (8). Previously, a member state could petition the EC to review a cross-border M&A transaction under the provision that completion of the deal could have a detrimental impact on the ability for other industry players to compete fairly within European markets. However, the EC advised members against requesting reviews of deals that did not breach jurisdictional thresholds.

Now, under the updated controls, the EC is encouraging referrals to review M&A deals that do not meet the national filing threshold. In particular, they have announced interest in reviewing M&A deals within the pharmaceutical and biotech sectors, and, in April 2021, the EC accepted a petition to review a merger within the pharmaceutical sector for the first time (9). These new merger controls will now raise concerns for deals that previously would not have been reviewed within the EU and may impact the willingness of some companies to proceed with M&A transactions within the life science sector.

**The National Security and Investment Act 2021**

Expected to come into force later this year, the National Security and Investment Act 2021 will increase the powers of the UK government to scrutinize transactions on grounds of national security (10). The act is being introduced to prevent transactions that could hamper internal market competition and will trigger a significant change in the United Kingdom regarding the regulation of M&A activity.

With vaccine production and distribution becoming a crucial concern over the past year, transactions across the life science sector have fallen under the spotlight and many businesses in those areas will be classified within the mandatory notification sectors. Under the UK’s new act, even if actual government intervention turns out to be infrequent, life science companies will now face additional compliance challenges that could involve additional costs and extensive time delays.

According to the government’s impact assessment, up to 1800 transactions could be notified each year (11). This potential imposition will now need to be high on the agenda for life sciences companies when pursuing M&A deals. Moreover, any transactions since 12 November 2020 could be eligible to be called for review retrospectively, so there is the possibility that a deal that has already been completed may be subject to intervention (11).

Despite the acceleration of M&A deals within the life science sector, the introduction of this act is expected to impact market activity. From a regulatory perspective, there is also still a degree of uncertainty, and so one can expect to see executives act with reservations whilst the sector waits to see how the act will be enforced on the ground.

**Looking ahead**

Despite the market uncertainty triggered by the COVID-19 pandemic, M&A activity across the health industry in Europe, the Middle East, and Africa has recorded a significant recovery since mid-2020. Now, as markets adjust to this new COVID era and the sector re-focuses its priorities, large pharma companies will continue to re-evaluate their long-term strategy and look to invest in the assets that will drive operational growth.

Whilst there are a number of regulatory and legislative hurdles to consider, M&A deals offer a much quicker route to market. With investor demand and financial capacity on the rise again, we can expect to see a significant ramp up of activity across the life science sector, with new market players pushing valuations higher.

**References**

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Current Covid-19 mRNA vaccines consist of lipid nanoparticles (LNPs) The lipids used for this purpose are not part of the active principle but crucial for ensuring the efficacy of mRNA vaccines.

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With different kinds of vaccines, phospholipids also play a significant role, namely in the so-called inactivated vaccines. They often need an element to amplify their effect, an adjuvant. Frequently, these are packed into phospholipid-based particles, such as liposomes.

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Q. We have been tasked by management to improve our processes and to enhance compliance. To achieve this goal, we intend to significantly increase the use of automated systems, replacing manual paper-based processes. It is a well-known fact that IT projects can easily end up in disasters as an Internet search will tell you. We want to be diligent. Can you share some best practices that can help us prevent or at least mitigate automation project failures?

A. Some things still need to be done by hand, such as typing the answer to your question. But automation is a necessity in a regulated healthcare environment, not merely for business optimization reasons, but also for being able to operate in a compliant manner. The keyword here is data integrity. For example, every time someone performs a manual transcription of data (e.g., typing a measurement into a form), there is a chance of a typing error. Even when you check and double check, you will never be able to reduce the error rate to zero. That alone is reason enough to eliminate manual entries, wherever possible.

The following are some suggestions that can help you on your road to success when automating processes.

Follow best practices
Benefit from others’ experience and expertise. Well-known and widely used methodologies include COBIT (Control Objectives for Information and Related Technology) (www.isaca.org/resources/cobit), ITIL–The IT Infrastructure Library for IT Service Management (ITSM) (www.itsmf.co.uk/), and Good Automated Manufacturing Practice (GAMP) (https://ispe.org/initiatives/regulatory/what-gamp), to name but a few. In simplest terms, make sure you have a well-structured, carefully planned, and professionally executed project.

Always have a plan B. In IT terms this could be a roll-back option (i.e., you restore the status as it was before). It will be better to continue working the old ways than not being able to work at all.

Avoid these pitfalls
One should avoid transposing a manual paper-based process “as is” into an automated process flow. This will not really deliver an improvement. If we take the example of signing documents, then a piece of paper can only be signed by one person at a time. An automated process on the other hand should allow simultaneous signing by several signatories, using electronic signatures.

Automated systems almost always offer transactions that cannot be (easily) performed manually. Therefore, find out what the automated system will let you do that you could not have done on paper.

Avoid going live “big bang” style (i.e., stop any old process or system and use the new system only from day one). Yes, you will have tested the system and you have done dry runs, but the chances of things going wrong, users getting frustrated, clients becoming irate, and management being displeased are to be expected. So don’t do it. Use a phased approach; sometimes it is possible to switch on one module after another; use one site or one department as the trial site. This approach will limit the fallout from any system failures.

Avoid having user acceptance testing performed by the vendor or someone from the IT department, instead of the actual users. Invariably, users will do something totally unexpected and will stress test the system in ways that those who are experts in the system could never imagine. I vividly remember situations where I was told by IT “but this has never happened before”. The clue is in the expression ‘user acceptance testing’.

Don’t buy the sales pitch (“this is the all-singing, all-dancing system”), when all you actually need is one tool to handle one very specific process. Overly complex systems will only mean that users will find ways and means to bypass the system, and the benefits of having an automated system will be lost.

Of course, these are only a few suggestions, and there will be many more that can be found online and through other channels, such as industry organizations. Good luck with your endeavors. PTE
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