The Earlier the Better for Formulation Strategies

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Two years is a long time for an emergency. The US Food and Drug Administration and other regulatory bodies have given tremendous support and guidance for emergency use authorization whilst maintaining background duties such as inspections and evaluations. However, a majority of APIs now under development are considered poorly soluble and/or poorly permeable. Therefore, hard questions are currently being asked of formulators to develop new solutions. Lipid-based drug delivery is one of those answers. Immediately this causes another set of questions regarding both excipients and adjuvants. Some fingers at the recent the PharmSci 360 American Association of Pharmaceutical Scientists Philadelphia conference pointed tentatively toward polyethylene glycol (PEG) as being a problematic adjuvant. More questions are bound to follow.

Although new to vaccine applications, PEG is commonly used in many other formulations. It has been linked to rare instances of shortness of breath, low blood pressure, rash, and highly elevated heart rates. Despite some scientists pointing out prior exposure to PEG can create high levels of antibodies against PEG (putting these people at some small risk of an anaphylactic reaction), it was clearly the most effective choice given all conditions and considerations.

That choice does now throw light upon the last largely static decade of excipient and adjuvant advances. Proposals are now being accepted for a Novel Excipient Review Pilot programme at FDA. Universally welcomed, the pilot also carries a burden of very hard questions are currently being asked of formulators to develop new solutions. Lipid-based drug delivery is one of those answers. These unmet formulation needs are relevant for both small molecule and biologic drugs, for example, in poorly soluble drugs and in enhancing the stability of protein based therapeutics. I am hopeful that the pilot programme will be successful and a formal programme will follow, one that believes this will encourage innovation in developing and introducing new excipients specifically designed to help meet current and future drug formulation challenges. These unmet formulation needs are relevant for both small molecule and biologic drugs, for example, in poorly soluble drugs and in enhancing the stability of protein based therapeutics. I am hopeful that the pilot programme will be successful and a formal programme will follow, one that will consider all types of novel excipients in the future, including co-processed excipients and excipients used for different routes of administration.

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The Earlier the Better for Formulation Strategies

Investing in formulation strategies earlier on in development will maximize the chance of success.

Felicity Thomas

The bio/pharmaceutical industry is under more pressure than other industries to create innovative products because of the time limits placed on patents and exclusive licenses for drugs (1). However, pharmaceutical drug development also suffers from significantly high and variable rates of attrition, attributed to factors such as formulation issues, solubility and bioavailability challenges, alongside a lack of efficacy (2).

Expenditure on R&D is rising year-on-year, with estimates for this trend to continue into the future (1). Therefore, expectations to achieve greater success with each drug molecule in development are becoming more pressing. Complex and difficult to formulate molecules are ever more present in development pipelines, and an overarching industry trend toward niche therapeutic and specialized disease areas persists, so the importance of innovative formulation strategies implemented early in the development timeline is becoming alarmingly apparent.

Under pressure

“No matter the modality, there has been increasing pressure for a number of years to advance new medicines through development as quickly as possible,” says Andrew Lewis, vice-president of Pharmaceutical Sciences, Quotient Sciences. To achieve a rapid time-to-market, a successful formulation development strategy must be in place, and in order to do that, formulators must consider some key aspects, he adds.

Understanding ways to enable rapid first-in-human assessments while also meeting study objectives; transitioning to a drug product that is suitable for proof-of-concept studies in a time efficient manner; and working out time and cost-efficient strategies for scale-up as product development progresses are imperative, Lewis continues. “Some trade-offs may need to be made at different stages of development but viewing the programme with the next stage in sight, enables integrated development strategies to be developed to mitigate risks and accelerate molecules through development,” he says.

Jessica Mueller-Albers, strategic marketing director Oral Drug Delivery Solutions, Evonik, agrees that pressure to speed up drug development has been increasing. “This increased pressure is because many new drugs target small therapeutic areas, where it is essential for pharma companies to be first in the market from an economic perspective,” she notes.

“In recent years we have seen that many of the drugs approved are high-priced specialty drugs for..."
relatively small numbers of potential patients,” Mueller-Albers says. “This [trend] contrasts to the top-selling drugs of the 1990s, which were lower-cost and created for large patient populations. Regarding formulation, the trend towards more specialty drugs requires new formulation approaches that use enabling technologies.”

“…there has been increasing pressure for a number of years to advance new medicines through development as quickly as possible.”

—Andrew Lewis, Quotient Sciences

To illustrate how the industry trend is moving away from blockbuster-type drugs, Mueller-Albers highlights the messenger RNA (mRNA) technology platforms that came to prominence in 2020 through the launch and roll-out of certain COVID-19 vaccines. “This [technology] was a starting point for a new class of drugs, not only for prophylactic vaccines, but also therapeutic vaccines and other therapeutics for cancer and rare diseases,” she asserts. “Overall, mRNA has the potential to become a competitive modality across broad applications, especially as further advances in improving delivery and stability are made.”

Another example of a more specialized therapy is proteolysis-targeting chimeras (PROTACS), Mueller-Albers points out. “[PROTACS] are an emerging therapeutic modality with the potential to open a new target space via a degradation-based mechanism,” she says.

But in order to keep up with the time pressures, while developing specialty and niche therapies in particular, industry needs to improve R&D productivity, Mueller-Albers stresses. “The approach to improving productivity is reflected in the R&D budgets of different sized firms,” she explains. “Small companies generally devote a greater share of their research in developing and testing new drugs, which are ultimately sold to larger firms. Larger drug companies allocate a greater portion of their R&D spending to conducting clinical trials and developing improvements.”

Focusing on small companies, Stephen Tindal, director, Science & Technology, Europe, Catalent, emphasized the challenges they face regarding expertise. “One of the key challenges for any small pharma company is to hold sufficient expertise across the key disciplines of medicinal chemistry, material characterization, formulation and drug metabolism and pharmacokinetics (DMPK), in order to address all the possible combinations that could be required to progress a molecule from the modern discovery process,” he confirms.

If the trend of small companies developing APIs continues, then small teams will be required to navigate through the preclinical phase, which throws up resource and decision challenges, Tindal advises. “For example, in late-stage drug discovery, [the developer] may have a choice between four to six molecules, with each having its own unique potency, solubility, and API manufacturing challenges, and perhaps also the choice of whether to employ a salt form to improve poor solubility,” he says. “At this stage, the small team should choose to engage a formulator.”

Additionally, Sanjay Konagurthu, senior director, Science and Innovation, pharma services, Thermo Fisher Scientific, emphasizes the fact that between 70% and 90% of new chemical entities (NCEs) in development pipelines are poorly soluble. “NCEs often have bioavailability challenges when it comes to oral drug delivery, therefore, selection of the appropriate formulation technologies based on a deep understanding of the Developability Classification System (DCS) becomes important,” he notes. “A thorough understanding of the API physicochemical properties as it pertains to oral absorption is necessary to guide formulation strategies.”

The earlier the better

Generally, preclinical formulation development is focused on achieving a desired pharmacokinetic response in an animal model, while also keeping time and cost for formulation development at a minimum, Mueller-Albers confirms. “A structured approach starting at an early stage can help de-risk the drug development process and avoid costly late-stage failures,” she says.

“In order to properly triage a molecule in late-stage discovery, a formulator should be engaged to help provide a line of sight to the path for clinical evaluation and commercial development,” adds Tindal. “The assumption is that discovery molecules are precious, and formulation expertise will be able to progress any candidate, rather than discarding a molecule in favour of another with better properties at the end of a traditional API selection and development process.”

“A thorough understanding of the API physicochemical properties as it pertains to oral absorption is necessary to guide formulation strategies.”

—Sanjay Konagurthu, Thermo Fisher Scientific

For Konagurthu, it is critical for formulation scientists to understand the benefits of investing in scale-up in the early phase of development. “At this stage, formulation scientists should obtain as much information as they can about what is happening at the mechanistic level of a formulation process because it is much less expensive to identify and address manufacturability problems earlier in the process than later,” he
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emphasizes. “In addition, evaluating formulation and process impact on product critical quality attributes help to mitigate scale-up problems.”

“Companies need ‘early formulation’ teams with expertise in physicochemical characterization and biopharmaceutics integrated with colleagues in drug discovery and medicinal chemistry to advise on candidate optimization and selection to maximize chances of success of a molecule.”

—Stephen Tindal, Catalent

“Companies need ‘early formulation’ teams with expertise in physicochemical characterization and biopharmaceutics integrated with colleagues in drug discovery and medicinal chemistry to advise on candidate optimization and selection to maximize chances of success of a molecule” asserts Tindal. “But, it may not make sense to invest in a formulation technology until Phase I safety data is available, unless that study is performed in patients, where a finished dosage form may be desirable. As it can be challenging to fulfill both the clinical hypothesis and the long-term scale-up issues together, it is important to engage the formulator earlier to develop a long term strategy.”

Overcoming challenges

Very early on, when working with systemic oral small-molecule drugs, developers should consider delivering drug in solution to the gastrointestinal tract so that the drug can be absorbed, reminds Tindal. A positive to working in solution is that less API is required and is likely to provide more reliable data providing the API is at least reasonably stable. This could entail developing a solution, a powder, or a liquid that was in solution during processing and delivers a solution on dispersion, he adds.

“For these reasons, working with simple aqueous solutions, spray-dried amorphous dispersions, or lipid formulations, has turned the early development process on its head,” Tindal explains. “A formulator can accelerate API development, navigate through dose escalation studies, and use less API, all of which help to get more new chemical entities to Phase I proof of concept in healthy volunteers within an acceptable budget, with a focus on formulation development at a later stage.”

“The onus falls on formulation scientists to make sure they design a robust formulation that provides adequate bioavailability, stability, and manufacturability,” says Konagurthu. “This [responsibility] requires them to have proper knowledge about drug substance properties, how they interact, and any potential issues the scientist may face during formulation development.”

If the compound exhibits poor solubility or permeability for example, then the formulator should know to select a solubilization approach to improve oral absorption and bioavailability, Konagurthu continues. Some options available to formulators to overcome such issues include hot-melt extrusion, spray drying, coated beads, size reduction, lipid-based approaches, and so on, he notes.

“By far the most common challenge when formulating small molecular weight drugs is improving poor solubility to maximize bioavailability,” Lewis confirms. “In developing the formulation strategy, it is essential to understand the basis for the poor solubility—whether it is dissolution rate limited or solubility limited—informing by the preformulation data package.”

Particle-size engineering technologies, such as micronization and nanomilling, can be used to improve the solubility of a dissolution rate limited API, whereas amorphous dispersions, using spray drying or hot melt extrusion, might be better for APIs that are solubility limited, Lewis states. “Also, in recent years we’ve seen lipid-based drug delivery systems and complexes become increasingly important tools in the quest to improve the oral bioavailability of poorly soluble drugs. It is not unusual for several technologies to be evaluated head-to-head in a clinical study in order to select one for further development based on their performance and implications for later development,” he adds.

Poor solubility or bioavailability of an API can be problematic in drug development and can lead to an incomplete or variable absorption of the drug, a higher impact of pH and food on drug absorption, and poorly controlled pharmacokinetics, Mueller-Albers asserts. “It is therefore extremely important to develop a formulation that maximizes the chance of good exposure, even if doing so requires additional time and cost. This is especially true as the solubility of new molecules becomes more demanding,” she says.

There are advanced solubilization technologies available that can help overcome the challenges of poor solubility, Mueller-Albers continues. Using the example of lipid-based technology she states, “When drugs are orally administered, they can bypass first-pass metabolism through the lymphatic pathway. During intestinal lymphatic drug transport, long-chain and unsaturated lipids are assembled into chylomicrons (ultra-low-density lipoproteins) in enterocytes (intestinal absorptive cells). Chylomicrons are then exocytosed (excreted) from the cell and enter the lymphatic route. If lipophilic drugs are co-administered with these lipids, they are prone to incorporation into chylomicrons and can be delivered to the lymphatic system in the form of chylomicron–drug complexes. Thus, co-administration with lipids can
enhance the lymphatic transport of lipophilic drugs.”

**Novel approaches**
To be able to select the most appropriate solubility enhancement technology and excipients for a molecule without requiring extensive and unnecessary testing it is possible to employ diagnostic tools, highlights Konagurthu. Using Thermo Fisher Scientific as an example, Konagurthu points to Quadrant 2, which uses proprietary computer algorithms to select the most effective solubility enhancement for a compound and which excipients should be used for formulation and process development.

“Furthermore, Thermo Fisher has developed an ‘Engineered Solutions’ approach to pharmaceutical product development by building predictive models that understand the interplay between materials, formulations, process, and biopharmaceutics,” says Konagurthu. “These predictive tools can de-risk formulation impact on scale-up and technology transfer to enable accelerated product development timelines.”

For Mueller-Albers, a significant new development in oral solid drug delivery technology is an empty ready-to-fill enteric capsule, designed to optimize gastric resistance and improve absorption for drug products targeted for release in the upper small intestine. “The high-quality hydroxypropyl methylcellulose capsules feature a precisely tailored functional coating that is well accepted by key regulatory bodies around the world,” she notes.

Additionally, a pilot programme to review novel excipients has been launched by the Center for Drug Evaluation and Research that will provide new options for formulators to use in specialized drug products, Mueller-Albers discloses. “[The pilot programme] is intended to allow excipient manufacturers to obtain FDA [US Food and Drug Administration] review of certain novel excipients prior to their use in drug formulations,” she says.

“Recent advances in small-scale ultraviolet probe dissolution apparatus have really helped to unlock the solubilization of API in bio-relevant media,” adds Tindal. “I would really like to see more advances in *in-silico* prediction, but remain sceptical that the models could be properly trained with a meaningful data set. Nonetheless, they can be very useful, if only for beginning a thought experiment, which can be a very useful part of the planning phase.”

“It is not uncommon for preclinical data to not reflect the human situation, which can lead to the wrong formulation strategy being selected, or sub-optimal formulation performance,” emphasizes Lewis. At Quotient Sciences, integrated adaptive clinical trials are used to guide formulation development and selection in human subjects, which, Lewis confirms, accelerates development. “These Phase I trials in healthy volunteers can be used to compare technological approaches head-to-head and select formulations for later dosing periods (e.g., multiple ascending dose) based on their performance,” he says.

“We have also used these [trials] to bridge from a simple first-in-human formulation to a proof-of-concept ready formulation within study with a single regulatory approval.”

Furthermore, it is possible to obtain regulatory approval to dose any formulation within a design space that has been defined through the identification of a critical-to-performance formulation variable, Lewis continues. “The formulation to be manufactured and dosed can be modified, informed by the emerging clinical data (e.g., pharmacokinetic parameter) to ensure the target product profile is achieved,” he states. “This is all enabled by real-time adaptive manufacturing—products being manufactured immediately prior to dosing rather than months in advance of the clinical trial, accelerating development.”

**Final thoughts**
“Drug development is a balance between minimizing time to clinic and developing a promising formulation that meets pharmacokinetic targets,” reveals Mueller-Albers. “However, risk of failure of a molecule is not only related to its pharmacological and pharmacokinetic properties or its toxicity, but also to its manufacturability.”

“Drug development is a balance between minimizing time to clinic and developing a promising formulation that meets pharmacokinetic targets.”

—Jessica Mueller-Albers, Evonik

A thorough understanding of the target product profile is necessary to be able to build a robust formulation strategy, emphasizes Lewis. Additionally, referring to the objectives and end-goals of a programme is critical in order to ensure that the formulation developed meets the needs of each stage of development, he stresses.

“Formulators need to engage earlier, to overlap with the medicinal chemistry strategies, to partner with the medicinal chemists themselves in order to make decisions about API and drug product, and using formulation with API-sparing techniques that resolve any liabilities that the medicinal chemist cannot quickly fix without having to necessarily invest in a final formulation, but all the while, collecting data that move the project forward. Formulators also need to address all bioavailability factors and not just solubility,” concludes Tindal.

**References**
Lipids for Self-Emulsifying Drug Delivery Systems

SEDDS and SMEDDS improve solubility and permeability while expanding efficacy and applicability.

With the majority of APIs under development considered poorly soluble and/or poorly permeable, formulators have been forced to develop new solutions for overcoming these key issues. Lipid-based drug delivery is one of only a few methods effective for increasing both the solubility and permeability of APIs.

Formulations that are designed to spontaneously emulsify upon contact with aqueous media, including self-emulsifying drug delivery system (SEDDS) and self-microemulsifying drug delivery system (SMEDDS), are often preferred because they are relatively easy to formulate, can potentially decrease first-pass metabolism, minimize food effects (minimize the difference in API absorption in the fed and fasted states), and can protect APIs sensitive to degradation in aqueous environments. In addition, because the API is dissolved in a pre-concentrate and not subject to amorphous-to-crystal transitions, which can occur over time with other technologies, SEDDS formulations are relatively more stable.

The key to successful SEDDS formulation is the choice of the right combination of lipid excipients for the particular API and route of administration.

Some basic SEDDS properties

Lipid-based formulations are generally classified into four categories, according to Philippe Caisse, scientific director pharmaceuticals at Gattefossé. Type I are composed 100% of lipids. Type II are SEDDS without water-soluble components that consist of 40–80% oils and 20–60% surfactants with low hydrophilic-lipophilic balance (HLB) values, have a turbid oil-in-water dispersion aspect, and are easily digested.

Type III lipid formulations are SEDDS/SMEDDS composed of <20–80% oils, 20–50% high-HLB surfactants, and 0–50% hydro cosolvents that have water-soluble components, form clear of bluish dispersions, and are less easily digested. Type IV systems are composed of 0–20% low-HLB surfactants, 30–80% high-HLB surfactants, and 0–50% hydro cosolvents and able to form clear micellar solutions but may not be digested.

Typically, SEDDS are isotropic and kinetically stable (SMEDDS are thermodynamically stable) formulations of functional lipids containing one or APIs for systemic delivery, according to John K. Tillotson, pharmaceutical technical business director (Americas) for ABITEC. SEDDS compositions, adds Nitin Swarnakar, North America Application Laboratory manager within BASF Pharma Solutions, comprise precise combinations of oil, surfactant, and cosurfactants to yield low-viscosity, isotropic mixtures.

The nature and selection of each of these components will, Swarnakar says, significantly affect properties such as droplet size, speed of dispersion, digestibility of the droplets, and API absorption. For example, he notes that a less digestible mixture can be formulated by including a lipid with a long carbon chain or by increasing the concentration of a less digestible surfactant. “Depending on the goals of the formulation, an optimal composition can be targeted,” he states.

The key to successful SEDDS formulation is the choice of the right combination of lipid excipients for the particular API and route of administration.

Several common lipids

As of 2019, there were at least 15 commercially available small-molecule drugs formulated as SEDDS (1,2). The relatively simple need to make a small-molecule API soluble to improve drug delivery—rendering it orally available or capable of getting across the lining of the gut—involves differences in lipid structure, according to Jamie Grabowski, vice president, portfolio and sourcing at Curia (formerly AMRI).

The most common classes of lipids employed are solubilizers, emulsifiers, surfactants, and potentially co-surfactants, Tillotson
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comments. Medium-chain triglycerides serve as solubilizers; mono- and di-glycerides as solubilizers and emulsifiers; and pegylated esters, polysorbates, and ethoxylated oils as surfactants and co-surfactants.

Surfactants can be water-insoluble (e.g., propylene glycol esters), water-dispersible (e.g., linoleyl polyoxyyl-6 glycerides), or water-soluble (e.g., polyoxyyl-based esters), according to Caisse. Diethylene glycol monoethyl ether is the most common hydrophilic cosolvent.

Maintaining quality and consistency is a challenge with CGMP manufacturing of lipids.

“These functional lipids are preferred based on their efficacy with regard to solubilization and emulsification capabilities,” says Tillotson. For example, medium-chain triglycerides have a high solubilizing capacity for lipophilic drugs and are especially easy to emulsify using suitable surfactants, such as castor oil derivatives, according to Caisse.

A balancing act

SEDDS formulations start as isotropic mixtures that contain the API(s) dissolved in the functional oil, solubilizer, and surfactants. When the SEDDS formulation enters an aqueous environment, such as the GIT, the SEDDS forms API-containing droplets, with the API(s) contained in the hydrophobic interior and the emulsifiers, surfactants, and co-surfactants stabilizing the discontinuous oil phase inside the continuous aqueous phase.

For example, Tillotson notes that greater amounts of hydrophobic lipids tend to increase API solubility in the system for some APIs; in contrast, greater amounts of less hydrophobic lipids, such as emulsifiers and surfactants, tend to reduce globule size and generate micro-emulsions. “The challenge is determining the optimum concentrations of each functional lipid in the pre-concentrate with regard to maximizing API solubilization and emulsion performance,” he concludes.

Often SEDDS formulations may include three, four, or five excipients along with the API, according to Caisse. Formulating an optimal SEDDS may thus require numerous trials and formulation variations. He also notes that some all-in-one self-emulsifying excipient systems are available that can simplify the preparation of type II and Type III lipid-based formulations.

Multiple factors influence lipid selection

Generally, lipids with chain lengths of C8 to C18 are reported in the literature as being ideal for SEDDS formulations, according to Swarnakar. She adds that specific lipids are chosen based on the melting point and crystal lattice properties of the API in question.

Most poorly water-soluble drugs are lipophilic, and thus the solubility of the API in the lipid components of the system will be the first parameter considered, according to Caisse. For highly lipophilic drugs, oils or mixed mono, di-, and triglycerides are often used. For APIs with medium lipophilicity, low HLB (≤ 9) surfactants are often preferred, he says. For APIs with low hydrophilicity, high HLB (> 10) surfactants and hydrophilic solvents are often required.

Another very important consideration is the desired emulsion performance and characteristics of the SEDDS formulation, says Tillotson. “The ideal SEDDS formulation optimally balances the overall solubility of the API(s) while realizing the desired emulsion characteristics, such as globule size and dispersibility. The goal is to develop a system that provides for maximal API loading, while also generating a rapidly-dispersing micro-emulsion,” he explains.

SEDDS formulations should also take into account the type of API being delivered, according to Tillotson. For example, Biopharmaceutics Classification System (BCS) Class II APIs are poorly soluble but readily permeable. Therefore, the focus in a BCS Class II carrying SEDDS is on lipids that provide the greatest solubility/carryer capacity for the API.

In contrast, a BCS Class IV API is both poorly soluble and poorly permeable. In this case, the SEDDS needs to not only address API solubility in the functional lipids, but also, if possible, permeability issues.

For this reason, Tillotson says a BCS Class IV API-carrying SEDDS may include lipids that open tight junctions between enterocytes (functional lipids composed of C8 and C10 fatty acids) or lipids that inhibit the activity of P-glycoprotein (PGP) efflux pumps (certain mono- and di-glycerides and certain macrogolglycerides).

In addition to the nature of the API, lipids for SEDDS formulations are also selected depending on the delivery strategy, Swarnakar adds. With respect to the API, “like-dissolves-like” is the rule of thumb for choosing the lipid. “Generally, very hydrophobic drugs (log P > 5) can be solubilized in more lipophilic lipids with longer carbon chains,” he says.

Specifically, longer and fully saturated carbon chains are more stable and less digestible within the gastrointestinal tract (GT). “This less digestible nature can be beneficial to the absorption profile by providing a secondary, lymphatic route of absorption in addition to the standard portal vein absorption. This additional route of absorption can be used to enhance the bioavailability of specific APIs and increase API absorption times,” observes Swarnakar.

Other factors related to the API in addition to low in vivo permeability may also be of importance, observes Caisse, such as heat sensitivity and a high first-pass metabolism. “Hence the design of a self-emulsifying formulation as an efficient delivery system for a given API is also related to the targeted strategy for its bioavailability enhancement or physical limits of its manufacturing process,” he says.

The final dosage form should also be considered. Caisse notes that for soft-gel capsules and liquid-filled hard capsules, liquid/low-viscosity
formulations are best, while for solid-filled hard capsules, semi-solid/solid excipients are preferred as the main components, although up to 20% liquid excipient is feasible.

**Correlating in vitro and in vivo SEDDS performance**

Despite the general understanding of how different lipids impact solubility and permeability, formulators have always struggled to predict the best SEDDS formulation prior to costly in vivo and clinical work, according to Swarnakar. “Various reported in vitro methods, such as United States Pharmacopeia USP type 2 dissolutions, provide limited discrimination of SEDDS formulation behaviour. The interference of turbidity and biphasic media make conventional in vitro screening methods inaccurate for SEDDS formulations,” he explains.

To address this issue, BASF, in partnership with Professor Anette Müllertz at the University of Copenhagen, has recently established a robust in vitro-in vivo correlation of 10 ready-to-use SEDDS compositions using the MacroFlux device from Pion for determining the absorption potential of formulations and finished drug products in vitro. The ready-to-use compositions are categorized based on their compositional HLB values and performance-indicating target product profile attributes, including microemulsion droplet size and enzymatic digestibility.

“Through careful testing and consideration of the chemistries in these formulations, the formulator is able to pre-screen a range of formulations and select according to their preferred API absorption behaviour,” says Lindsay Johnson, global technical marketing manager—Pharma Solutions at BASF. She believes this tool will help formulators avoid costly pre-clinical studies and ensure continuity of product quality and performance during product development. “Overall, these tools will enable formulators to choose the best SEDDS formulation based on the API properties for preclinical and clinical trials and accelerate the product development timeline,” she asserts.

**Extending efficacy**

New developments with SEDDS are focused on extending the efficacy of the dosage form beyond simple improvements in solubility. Areas of research, according to Tillotson, include chylomicron signaling for tissue targeting, long-chain lipid inclusion promoting lymphatic transport and reduced first pass metabolism, and employing lipids as a delivery system for more specific targeting such as conjugated antibody targeting with APIs.

**Longer and fully saturated carbon chains are more stable and less digestible within the gastrointestinal tract.**

**Moving beyond capsules**

Liquid SEDDS formulations for oral administration are generally loaded into liquid-filled soft-gelatin or hard-gelatin capsules. “An ongoing challenge is how to administer SEDDS on higher throughput dosage forms, such as tablets,” says Tillotson.

There are many drivers for the development of solid or semi-solid SEDDS formulations in addition to the ability to easily incorporate them into tablets. They may also offer improved stability and enable sustained-release or abuse-deterrent formulations. Liquid SEDDS, according to Caisse, are susceptible to degradation during long-term storage and suffer from in vivo precipitation issues and handling complexity.

Research is ongoing in this application at multiple institutions. “The primary difficulty is generating tablets at industry tabletting speeds with minimum or no sticking to the punches that also release the SEDDS formulation,” he observes. Other solid SEDDS technologies are also being developed such as powder and granular SEDDS. SEDDS compositions formulated as solids can be achieved, according to Swarnakar, using a variety of methods, including adsorption onto solid carriers, freeze drying, spray drying, and melt granulation. Caisse adds that wet granulation and extrusion/spherization are other solidification techniques used for converting liquid SEDDS into solid SEDDS.

Of these methods, Johnson notes that adsorption onto an inert solid carrier is most common. In this case, a liquid SEDDS solution is mixed onto various solidifying agents such as mannitol, lactose, or calcium carbonate.

The key to this strategy is to retain the solubilization and dissolution enhancing properties of the SEDDS formulations once they are absorbed on the solid carrier materials, Caisse observes. The resulting powders, he says, can be subsequently filled into capsules or formulated as solid dosage forms such as tablets, granules, or pellets in sachets.

**The growing role of lipid nanoparticles**

Progress has been dramatic in the past few years particularly with respect to the development of lipids that facilitate the absorption of large molecules—notably biologics, according to Grabowski. “Driving the development of these lipids for SEDDS is the need for drug products with expanded methods of administration, notably oral. This is a big challenge for biopharmaceutical companies that want to offer patients the choice of an oral drug instead of an injectable,” he says.

Specifically, Grabowski notes that developers are moving away from relying on off-the-shelf lipids to get hydrophobic drug substances into solution or improve their stability. Instead, they are turning to complex cationic lipids that are actually helping with the functionality and efficacy of biologics by altering their bioavailability and pharmacokinetics, both in SEDDS and lipid nanoparticles (LNPs) such as those used in the formulation of mRNA vaccines against the SARS-CoV-2 virus, he says.

Cationic lipids improve the solubility, oral absorption, bioavailability, and
pharmacokinetics of biologic drug substances, according to Grabowski. In LNPs, which have a much more complex structure than SEDDS, they are used along with cholesterol, a minor lipid, and one other typically proprietary compound.

**Another challenge for lipid manufacturing is the need to find new ways to manufacture lipids with sustainable raw materials and more eco-friendly processes that leverage new classes of catalysts.**

Lipid nanoparticles such as cubosomes, adds Tillotson, contain both hydrophobic and hydrophobic regions and are readily absorbed by cells through typical lipidomic pathways. “The amphiphilic nature of these lipid carriers allows for the incorporation of proteins, RNA and both hydrophilic and hydrophobic APIs. For this reason, lipid nanoparticles composed of high-purity, functional lipids are ideal carriers for biologics and small-molecule actives,” he contends.

**Increasing focus on lipid design**

Across all research regarding lipid-based delivery, the main focus is on the purposeful design of lipids with specific structural and physiochemical properties. “Ultimately,” asserts Grabowski, “the industry will stop using off-the-shelf compounds such as cholesterol for LNPs and switch to carefully designed lipids with improved and diverse structures that enable fine tuning of the intended pharmacological impacts.”

For instance, Grabowski notes that assessing the structures of cationic lipids through structure-activity relationships will help improve the pharmacokinetics of drug delivery. “It will become less about simply being able to form micelles and more about making lipids that allow the drug substance to get across the gut lining and improve pharmacokinetics. That’s going to be the big issue,” he asserts.

Similarly, Tillotson sees emerging research on lipid-based drug delivery as being focused on the design and manufacture of high-purity lipids for specific applications, such as incorporation into LNPs for the systemic delivery of biological therapeutics. He also notes that ongoing lipidomics research seeks to identify novel lipids and lipid metabolites that can be potentially employed in biomarker discovery programmes for specific disease states.

**Greater expectations for GMP lipid manufacture**

In many advanced lipid-based formulations, including SEDDS/SMEDDS, the lipids are not inactive ingredients, but functional excipients that impact the efficacy of the drug product. Both drug manufacturers and regulators are responding by treating these types of functional excipients more like APIs, according to Grabowski.

“Increasingly drug manufacturers want lipids used in their drug formulations to be made according to [current good manufacturing practice] CGMP requirements,” Grabowski says. “While lipids may not need to be produced in a CGMP environment for early-phase research, if regulators potentially consider them to be additional ‘APIs’ because they affect the bioavailability of the drug substance or efficacy of the drug product, the lipid supplier will be expected to have the ability to produce GMP lipids.” As an example, Grabowski notes that there is movement toward treating cationic lipids as APIs.

One of the biggest challenges with CGMP manufacturing of lipids, observes Tillotson, is maintaining both quality and consistency. “This goal is achieved by maintaining consistent raw material stocks and tight specifications on manufacturing unit operations,” he says. That is important for SEDDS in particular, adds Johnson, because across one monographed chemistry, different manufacturer materials may ultimately perform differently in a final formulation. “For this reason, the sensitivity of formulations needs to be considered as the choice of supplier is weighed,” she comments.

Another challenge for lipid manufacturing highlighted by Caisse is the need to find new ways to manufacture lipids with sustainable raw materials and more eco-friendly processes that leverage new classes of catalysts.

Additionally, suppliers who start from certified sustainably sourced base raw materials, like palm kernel oil, coconut oil, corn oil, and others, can bring value and awareness to ethical and sustainable sourcing in the pharmaceutical industry, according to Johnson. For example, she observes that many of BASF’s lipid-based pharmaceutical excipients come with an external certification for being responsibly sourced.

**References**


**More on lipids**

For more about lipids, visit PharmTech.com to read the following:

- **Improving Solubility of Cannabinoids**
- **Overcoming Bioavailability ‘Roadblocks’ with LBDDS**
- **How Excipient Type Influences Self-Emulsifying Drug Delivery**
- **Developing Lipid-Based Formulations**
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With the COVID-19 pandemic, there has been a particular focus on the delivery of vaccines, which must be formulated to provide a sufficient immune response. This may also be a contributing factor to the increasing number of products targeting nasal drug delivery. In this case, formulations may be more focused on increasing retention and permeability of the nasal mucosa.

Additionally, there seems to be renewed interest in systemic drug delivery, which will drive formulation strategies for increased absorption. Increased awareness of the carbon footprint associated with pharmaceutical products and the replacement of high global warming potential (GWP) constituents used in the final product, or within the manufacturing process, may drive further diversification of formulation approaches in the future.

Promising approaches

PTE: Could you run through some of the alternative drug delivery formulation approaches that you believe are most promising at the moment?

Keenan (Vectura): Formulation approaches remain centred around the use of micronized dry powders, solutions, and suspensions, which are not always appropriate to achieve the desired target product profile. Liposomes are a proven formulation approach in parenteral drug delivery, which is increasingly being applied in lung delivery. These formulations are often well-tolerated in the lung and have been shown to increase lung retention and minimize systemic exposure, increasing the safety and efficacy of the product. Importantly, they have been successfully delivered into the lung using nebulization technology. Other formulation approaches are likely to offer similar benefits, including lipid-based and polymer-based nanocarriers. Additional functionality may be afforded through ligand targeting, enabling efficient uptake.
into target cells. What is particularly encouraging for these systems is that they can be readily translated into a liquid or powder dosage form for inhalation.

**Lenn (MedPharm):** One of the most promising areas for alternative formulation approaches is nasal drug delivery. This mucosal membrane, the entry way for the rest of the respiratory system, is appealing for many reasons. The nasal cavity is highly accessible offering an opportunity for local, systemic, and even direct to the brain drug delivery. Compared to systemic delivery, there are distinct advantages which include a relatively large surface area for drug absorption, convenience for patience compliance, avoidance of first-pass metabolism and harsh gastrointestinal conditions. Nasal delivery is also an ideal opportunity for vaccines, especially respiratory disorders like COVID.

**Potential beneficiaries**

**PTE:** Are there specific diseases/therapeutic areas or patient populations that would significantly benefit from alternative drug delivery approaches to formulation?

**Allen (MedPharm):** Patient compliance will always be an area of focus for pharmaceutical and biotechnology companies. Patient populations where easy-to-use and non-invasive self-administration is required, or where there is hesitancy for needles, are ideal target markets for alternative drug delivery approaches such as the nose and other mucosal membranes.

Intranasal vaccination will be an area of intense research as we continue to struggle with the pandemic and appearance of new variants. Infection with SARS-CoV-2 initially attacks the upper respiratory tract; therefore it’s interesting to explore vaccines or protective treatments of the nasal passage. This could be a potential opportunity to block infection or, at the very least, improve protection of the mucous membranes of the nose and throat. It also presents an opportunity for self-vaccination and/or an easier way to introduce mass vaccinations by less skilled persons.

Localized nasal delivery has been and continues to be an area of development for conditions such as congestion, rhinitis, sinusitis, and other allergic conditions. In addition, the nasal cavity is highly vascularized offering opportunities to exploit rapid onset of action for analgesic effects (e.g., morphine and ketamine).

Finally, the nose offers an opportunity to deliver drugs directly to the brain or central nervous system (CNS) via the olfactory pathway. Two relatively recent commercializations for intranasal delivery are naloxone nasal spray to treat suspected opioid overdose emergencies and diazepam nasal spray for short term rescue treatment of seizure clusters.

**Keenan (Vectura):** Alternative drug delivery approaches may benefit therapies that need to overcome significant barriers resulting from the disease itself. For example, in cystic fibrosis, the overproduction of mucus and alteration of mucus properties, represents a challenge for effective drug delivery by inhalation alone. The treatment of infections within the lung may also be improved by the use of alternative formulations, particularly when coupled with an inhalation device that can achieve efficient lung deposition. Maintaining an elevated local dose above the minimum inhibitory concentration for anti-infectives is likely to result in better treatments while minimizing the risk of bacterial resistance, as well as limiting systemic exposure. Treatments that specifically target cancerous cells within the lung may also show significant benefits, particularly in light of the number of nano-therapeutic formulations already approved for the treatment of cancer by the parenteral route. Therapies that are used in an acute setting, such as pain relief, may benefit not only from delivery to the peripheral lung, which can be achieved using efficient delivery devices, but through rapid systemic uptake achieved by alternative drug delivery formulations.

It is far more likely that the nature of the therapeutic and the target disease drives consideration of alternative formulation strategies than the patient group. However, selection of an inhaled drug delivery approach over more invasive options, such as by injection, may be preferred by some patients. Examples include severe asthmatics requiring antibody therapy or Parkinson’s patients receiving treatment for “off” periods.

**Formulation challenges**

**PTE:** What are the challenges facing formulators when developing an alternative drug delivery formulation? How are these challenges overcome? Are some challenges insurmountable at the moment?

**Keenan (Vectura):** There must be a clearly demonstrable benefit for implementing an alternative formulation strategy over a conventional approach because of the increased complexity. The number of excipients approved for lung delivery is particularly limited; therefore, there may be additional requirements to demonstrate safety and tolerability in the lung. If the excipient is novel, then qualification is likely to further increase both costs and timelines, although this must be considered against the potential benefits associated with new intellectual property. In many cases, alternative formulations are not suitable for direct delivery to the lung and must first be translated into a respirable powder or liquid that is compatible with an inhalation device. At each stage, it is essential that the stability, integrity, and functionality of the formulation is preserved, which requires implementation of an appropriate testing strategy. Justifying the investment required to translate a novel formulation approach that has shown promise at bench scale into a marketed product remains a significant challenge.
Lenn (MedPharm): There are some unique challenges associated with developing an intranasal topical, transdermal, or vaccine formulation. These types of medications are unique in that they require the formulator to think about the physiochemical properties of the drug, the vehicle, and the device throughout product development. In addition, targeted delivery to different regions of the nasal cavity and the biology of the nasal epithelium present opportunities and challenges.

The nasal epithelium is composed of mucus secreting, ciliated, non-ciliated, and basal cells, thus the formulation needs to be designed for this type of epithelium. The general formulation approach of prioritizing drug solubility and stability remain paramount and should be developed while keeping in mind the anatomy of the nose and the engineering of the device. To aid in the development and optimization of intranasal formulations, MedPharm has developed a testing model that uses regrown human nasal epithelia cells to recreate a 3D living nasal epithelium. The model allows prototype formulations to be applied topically to measure the permeation of the drug from either active or passive transport. To account for the influence of the device, MedPharm has developed a nasal cast model that allows the device to spray the formulation and measure the concentration of the drug to the different compartments of the nose.

**Regulatory pathways**

**PTE:** Are there clear regulations for alternative drug delivery approaches currently? If not, what should be done in your opinion to rectify this situation?

**Allen (MedPharm):** MedPharm’s formulation approach would be to use excipients that have been used in approved products for the route of delivery that are listed on the FDA [US Food and Drug Administration] Inactive Ingredient Database (IID).

**Keenan (Vectura):** The regulatory pathways are well documented and when coupled with a continual dialogue with the regulators, alternative drug delivery formulations can be successfully implemented. Even in cases where the approach is truly novel, building this relationship with the regulators will help ensure agreement between both parties. Provided there is a strong rationale that is supported by robust scientific data. Regulators consider hazards relating to lung exposure as different to those via other administration routes and, therefore, unless safety in the lung has been previously demonstrated, the registering company will be expected to provide a robust preclinical and Phase I inhaled safety package. These additional studies significantly increase the cost and complexity for any alternative drug delivery development pathway. In addition to the increased cost and time, large preclinical studies can create ethical concerns unless sufficiently justified.

**Raphael Bar,** consultant at BR Consulting in Ness Ziona, Israel.

Ultimately, it is the cost and impact of alternative formulation approaches on the development timelines, together with the additional risks, that limit their implementation. Only in cases where a novel approach has the potential to be truly product-enabling, or transformative in terms of unmet medical need, can alternative formulations be sufficiently justified. PTE

Editor’s Note: Practical SPC Rules in the Real World of an Ongoing Process Verification Plan: Part 2. Practical SPC Rules to Apply on Pharmaceutical Process Data

A peer-reviewed article, “Practical SPC Rules in the Real World of an Ongoing Process Verification Plan: Part 2. Practical SPC Rules to Apply on Pharmaceutical Process Data” has been published in the November 2021 issue of *Pharmaceutical Technology* North America and is available on PharmTech.com.

In the paper, which is the second part of a two-part series, the author overviews some suggestions of tools or measures that can be used to reduce the extent of false signal alarms by relaxing and adjusting conventional statistical process control (SPC) rules. Additionally, the author provides further measures and consolidates the topic within the framework of the pharmaceutical regulatory setting, while also providing real process data examples.

Within the paper, the author details 10 tools that have been applied on real-life process data, to be considered by manufacturers in efforts to minimize process false alarms. The 10 tools are use of global standard deviation, implementing a selected number of Nelson rules, three-way chart, setting limits as $k \cdot \sigma$ with $k > 3$, setting limits based on acceptance control charts, avoiding truncated reportable results, setting normal-equivalent limits to a fitted distribution, determining limits based on non-parametric tolerance intervals, determining percentiles of data as limits, and setting a limit as a fraction of the specification tolerance. Furthermore, the author provides real-life process data plotted on charts to illustrate each tool.

It is concluded by the author that the tools discussed in the paper are capable of reducing “the number of futile investigations of apparent and innocuous deviations of a process that is in fact maintained in a state of control.”

**Article Author**

Raphael Bar, consultant at BR Consulting in Ness Ziona, Israel.

—Felicity Thomas
From physical twins to digital twins

In the late 1960s, the concept of a “digital twin” was introduced by NASA as part of the Apollo programme. Researchers developed two identical space vehicles, one of which was used as a “twin” to simulate the real-time behaviour of the counterpart that was sent to space (2). Coincidentally, it was during these times the first CFD algorithms were developed to model flow over airfoils, ship hulls, and aircraft fuselages. These algorithms, in a sense, were sophisticated calculators that evaluated a time-averaged solution to the fluid velocity and pressure field across a simulation domain. Relevant output included the time-average shear stress/strain field across the fluid as well as the average force on any solid objects with the domain. The success of these models to aerospace and naval hydrodynamics led to the commercialization of many CFD packages in the 1980s and 1990s, which were initially targeted to users in the automotive, defense, and energy industries.

From 1990 to 2010, commercial CFD packages trickled into the pharmaceutical and biopharmaceutical industries, according to a 2017 article in *Microbial Biotechnology* (3). Many of the initial applications focused on predicting impeller power numbers, calculating the maximum shear stress in a vessel, and examining flow fields through piping networks and tanks (3). Models were later extended to include predictions of blend time and residence times, using the mean-flow field as input to the scalar advection equation (3). The applications of CFD also extended to rotor/stator systems, chromatograph columns, and orbital shakers. For each individual process test, the cost savings from using CFD in the experimental design space were estimated to be between US$500,000–$1 million (€431,000–€862,000) (4).

Although these time-average models provided sufficient fidelity for single-phase/single-fluid systems, extending the models to handle the
multi-phase, transient, and multi-fluid systems typical of the pharmaceutical manufacturing process proved difficult. For example, because these original CFD implementations were focused on steady-state flow fields, they provided little insight into the turbulent structure and flow field driving reactions, mixing, and cell damage processes (4). Additional challenges were presented by topologically complex systems, which often required CAD geometry clean-up and careful volume meshing. Moreover, although some academic circles could extend these traditional CFD tools to handle multiphase flows, the industrial application of CFD to generalised bioreactor design and process simulation was not widespread. Thus, although time-averaged CFD could provide insights into aspects of a process, it was not a practical tool for simulating processes.

In the 2010s, two important trends converged to present a step-change in process simulation capabilities. The first trend, as motivated by advances in transport physics theory, was the development of new algorithms for solving the fully transient fluid flow and particle transport equations (5, 6). These modern algorithms, which are based on the Boltzmann transport equations, provided a multiple order-of-magnitude speedup in runtime relative to approaches applied in earlier commercial algorithms. The second trend, as motivated by advances in computer hardware, was the development of graphics processing units (GPU) dedicated to scientific computing. Originally developed for graphics rendering, GPUs are highly parallelised computing architectures that present a superior paradigm for machine learning, data analysis, and artificial intelligence applications. For the modern CFD algorithms developed in the past decade, a single desktop GPU can model physics faster than hundreds (or thousands) of CPUs operating in parallel (7).

The combined effects of these algorithmic and hardware advances have presented an important advancement in process simulation. In contrast to time-averaged single fluid calculations, these modern approaches can be used to run fully transient, time-accurate three-dimensional process simulations. The physics in these simulations are fully coupled such that changes in rheology due to blending inform real-time changes in the fluid flow, or the combined effects of individual bubble break-up and pairwise coalescence events inform fluid flow and mass transfer in an agitated bioreactor. These approaches enable the development of time-accurate digital twins with a self-consistent linkage between fluid flow, species transport and free surface dynamics, and drug product growth. In this sense, entire processes can be developed, transferred, and/or scaled up entirely in silico (8).

**Recent industry applications**

Earlier this year, researchers demonstrated how a digital twin running on a multi-GPU workstation could reproduce the real-time blending properties of a high viscosity/low-density buffer excipient solution within a water-like drug substance solution (5). Because the flow field evolves in time due to ongoing changes in the fluid viscosity, the notion of a time-averaged flow field is not appropriate. Using a three-dimensional time-accurate simulation, however, the coupling between blending and fluid flow was immediate and the predicted blend time was in line with measured data at multiple impeller speeds. Following this validation, the twin could be used to optimize how the excipient solution could be added to the solution to minimize blend times and how the process would scale at different operating volumes. Using the digital twin, process scale-up strategies were identified in hours/days as opposed to the months/weeks typical of empirical testing.

In a *Chemical Engineering Science* article, researchers used a digital
twin—also running on a multi-GPU workstation—to predict the oxygen transfer rates of sparged bioreactors (6). Agreement between the predicted and measured data was realised across 5 L to 2000 L working volumes with no model reparameterisation or recalibration between scales. Using this model, researchers could identify variations in mass transfer rates across the vessel and how these lead to variations in dissolved gas concentrations across different scales. The success of the model across these scales and operating conditions was linked to the fundamentality of the physics evoked during development. The computational requirements of this modelling approach were, admittedly, beyond the capability of steady-state solvers. When these physics are solved using algorithms tailored for GPUs, however, they provide mechanistic insights into the link between operating conditions and oxygen transfer rates.

**Emerging trends and outlook**

As the past year of vaccine production has demonstrated, the need for more efficient process scale-up and optimisation strategies is pressing within the pharmaceutical and biopharmaceutical manufacturing industries. The use of CFD-based digital twins to enable smart manufacturing is emerging in different phases of process development, process prediction, decision-making, and risk mitigation. A key component in the development of this class of digital twins is the ability to reduce simulation time to achieve near real-time computations at a relatively low computational burden. Reduced order modeling approaches and hybrid modelling (e.g., artificial neural network + CFD) seem promising but can be computationally complex and may not be suited for wider application in the industry.

Fortunately, in the past decade, important advances in modelling algorithms and hardware architectures have enabled a step-change in the fidelity, utility, and efficiency of the CFD models for addressing these needs. These models present researchers with the ability to build real-time, three-dimensional digital twins with output that can be validated directly against transient measured data. To help troubleshoot problematic unit operations, researchers can use these models to understand the underlying physics governing process outcomes. Perhaps more importantly, because the models are time-accurate, they can be used to run ahead of real-time and forecast possible problems in process design. In this sense, to minimize the number of physical experiments, an entire unit operation can be designed, tested, and optimised in silico. The approach presents tremendous reductions in development costs and schedules.

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Labelling efficiently: Machine and material innovations yield more efficient, sustainable processes for pharmaceutical packaging, including vaccine vials.

Labelling equipment and materials continue to evolve with onboard serialization and inspection capabilities, adoption of radio frequency identification (RFID) technology, ever-improving performance and speed, and higher levels of connectivity that include remote access for troubleshooting, servicing, and training. Materials offer better performance as well as sustainability advantages.

Demand for labelers is strong for both new installations and line upgrades. “Labellers and Related Equipment” is among the top six categories of new equipment purchases for the pharmaceutical industry, according to a report published in November 2020 by PMMI, The Association for Packaging and Processing Technologies (1).

Forces driving purchases of labelling equipment include automation, growth in self-administration of medication and personalized pharmaceuticals, digitalized packaging that communicates directly to patients, the need for flexible production, and sustainability concerns (1). According to the report, built-in connectivity is important, and remote troubleshooting is becoming a necessity. As requirements for traceability and serialization take hold, the need for efficient labelling operations grows. The report notes, “Facilities are increasingly leveraging the Internet of Things (IoT), connecting equipment with computers and devices to maximize productivity, control operations, and maintain quality. Companies are finding that they need these systems more within the serialization process, and this trend is expected to continue as more regulations get implemented and more tracking data is required throughout the supply chain” (1).

Vial Labelling
Speed, accuracy, quick changeover, and flexibility are important attributes for labellers on today’s pharmaceutical packaging lines. Designed for COVID-19 vaccine packaging applications, the modular, servo-driven VR-72 labeller from WLS, a ProMach product brand, can run faster than 600 vials/min. The flexible, continuous-motion unit applies wraparound, pressure-sensitive film or paper labels to any cylindrical container and accommodates different code printing methods and inspection systems.

Products enter the labeller via a synchronized feedscrew and are held in place during label application by a vertical trunnion roller assembly for accurate, repeatable placement. A vacuum drum label dispenser holds each product at three contact points to minimize label skew. The continuous motion of the vacuum drum maintains tension on the label web to minimize web break and expand label and web material options. WLS’s patented label reconciler automatically tracks and removes out-of-tolerance labels from the vacuum drum before application. Options include redundant label heads to eliminate downtime and United States Code of Federal Regulations (CFR) 21 Part 11 compliance with audit trail, domain authentication, and various types of data collection (2).

Maximizing speed and uptime for vaccine vial labelling is the goal behind an upgrade of the high-speed HERMA 132M HC wraparound labeller. Designed for efficiency, the wraparound labeller features digital position indicators and format sets that provide tool-less changeover and integrated control for the entire machine, including the camera and printer. The labeller now can operate continuously via retrofittable EasySplicer and EasyCutter modules, which make it possible to change or remove label and liner reels without stopping the machine and halting production, as shown in Figure 1. Considering that reels require replacement approximately every 10 minutes, the result is reduced downtime and significantly improved output.

The EasySplicer module arranges two label reels vertically, one above the other. The active label web is guided over a splicing table, where it is fixed at the end of the label web. The flexible, continuous-motion labeller is designed for COVID-19 vaccine packaging applications, ensuring high-speed, accurate, and flexible labelling operations.

Labelling equipment and materials continue to evolve with onboard serialization and inspection capabilities, adoption of radio frequency identification (RFID) technology, ever-improving performance and speed, and higher levels of connectivity that include remote access for troubleshooting, servicing, and training. Materials offer better performance as well as sustainability advantages.

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- Unmatched total cost ownership
- Abbreviated design timelines using standard PODs or turnkey solutions

G-CON is fulfilling the needs of reliable and fast deliverable capacities for the biopharmaceutical industry. G-CON provides comprehensive prefabricated and prequalified CGMP compliant cleanroom environments and platforms for uses ranging from laboratory, clinical and commercial production for a variety of therapeutic applications.
Manufacturing

the buffer runs out. Meanwhile, the EasyCutter module vacuums up the empty liner and chops it into shreds that are collected automatically and can be recycled. The add-on eliminates the need for manual removal of rewound backing paper (3).

RFID labels

As the deadline for unit-level serialization approaches, RFID is viewed as one way to carry data through the supply chain. RFID labels on vials, bottles, tubes, syringes, and devices can lock in select variable data while allowing other variable data to be updated through the life of the product. This technique simplifies inventory control and confirms product authenticity. However, applying RFID labels can be tricky. Label paths must be designed to prevent damage to tags or antennas to ensure readability for the life of the product. This challenge has been overcome, and pharmaceutical manufacturers have a growing number of equipment options so RFID labels can be adopted with minimal disruption.

For example, WLS offers three choices: RFID-Ready labellers, RFID-Enabled label application systems, and RFID-Ready print stands. RFID-Ready labellers apply pressure-sensitive labels with embedded RFID inlays. The RFID labels are read, written (encoded), locked or unlocked, verified, applied to the product, and re-verified as needed. Options include variable data printing with vision inspection, rejected label reconciliation, and rejected product removal.

RFID-Enabled label application systems consist of dual label heads that feed a single applicator. The first label head releases a standard pressure-sensitive label onto the vacuum drum while the second label head centres and releases an RFID tag onto the label, so the vacuum drum applies an integrated tag and label. Prior to being married with the label, the tags are read, written, locked or unlocked, and verified. Once applied, the RFID label can be re-verified.

RFID-Ready print stands are designed to digitally print pressure-sensitive labels embedded with RFID inlays, providing an off-line solution for incorporating RFID labels with variable data print-ing or whole-label printing. The offline, on-demand unit makes it possible to adopt RFID labelling without altering or upgrading existing labellers. The high-speed RFID-Ready print stands incorporate full-label vision inspection with rejected label removal and verification and also verify the printed label and the encoded RFID tag (4).

Digital label printing

Digital label printing provides quick turnaround, production planning flexibility, real-time variable data application, and inventory reduction, supports multilingual label printing, reduces waste, and decreases costs associated with ordering and maintaining an inventory of pre-printed labels. Digital printing can be integrated with the labeller to create a printer/applicator. An integrated system from United Automation combines an Epson ColorWorks C7500 on-demand colour label printer with robotic automation. The desktop label printer/applicator prints standard matte or glossy labelstock on-demand in full colour, and a high-precision robot performs feeding and application functions. The desktop system allows pharmacies to upgrade from black to colour labels to highlight warnings, logos, and branding on prescription bottles (5).

“Colour not only enhances safety by enabling the inclusion of photo identification, colour-coded warnings, and colour-highlighted information but also helps improve readability and reduce errors,” says Andrew Moore, product manager, Commercial Label Printers, Epson America.

Although targeted to pharmacies, the systems can be integrated on pharmaceutical packaging lines. “The process is very similar to our prescription labelling applications,” explains Jeff Runge, project manager, United Automation. “An on-demand, colour label printing solution allows companies the flexibility to incorporate colour for safety, reduce errors, and implement overall process improvements,” adds Moore.

The printer/applicator model with a six-axis robot offers expanded functionality: printing, loading, labelling, peel labelling, inspection, verification, and unloading. Capable
of printing and applying up to 600 unique colour labels/hr, the first-in/first-out flow and inspection and verification technologies ensure each bottle receives the correct label. The system is flexible enough to handle wraparound or folded labels and bottles of varying heights and diameters. Label height is adjusted dynamically based on bottle specifications, and label position is verified at two points in the cycle (5).

In many printing processes, colour comes with an upcharge. However, Moore says, “The cost of ink does not vary by colour for Epson. So, there is no impact to cost, (which) makes using colour even more attractive.” Durable pigment-based inks result in smudge-proof labels that can withstand exposure to gamma sterilization and chemicals such as hand sanitizers. “The [return on investment] is evident in a very short period of time,” concludes Runge.

**Auxiliary equipment**

Auxiliary equipment also must be considered. For cold-chain products like temperature-sensitive vaccines, serums, and tests, labelling can be a challenge because condensation affects adhesion. Yet conventional conditioning methods can mean a challenge because condensation, and/or renewable materials. Two paper-based release liners from Mondi offer a renewable material plus source reduction or recycled content. EverLiner labelite release liner is a lightweighted 47 g/m² alternative to standard 58 g/m² glassine. The EverLiner M R release liner is said to be the first to use recycled base paper. The machine-glazed paper with 70% Forest Stewardship Council-certified recycled content reduces the amount of virgin fiber consumed. “Our aim is to create sustainable alternatives with no need to change the silicone system in order to offer products that are effective in usage, work for our customers, and ultimately help protect the environment,” said Andrea Lackner, R&D director Release Liner at Mondi, in a press release (9).

**Label innovations**

With new materials and designs constantly arriving on the market, pharmaceutical manufacturers have an ever-growing array of labelstock options. To make it easier to identify the proper material, FLEXcon has organized its PHARMcal line according to application requirements, such as container diameter, cover-up capability, extreme storage conditions, tamper evidence, and secondary blood bag labelling (7).

Another application-oriented product, the Pharma-Tac Plus label for infusion bottles, was developed by Schreiner MediPharm to simplify international clinical trials. The label combines a multipage booklet label with Schreiner MediPharm’s hanger label, creating ample space for comprehensive product descriptions in multiple languages. The paper booklet label firmly adheres to the base label and can be opened and reclosed via a tab. The customizable combination can be adapted to various vial and bottle sizes, and the number of booklet pages can be tailored to suit specific requirements (8).

Sustainability ranks as another important consideration, pushing the adoption of source reduction and use of recyclable, recycled-content, and/or renewable materials. Two paper-based release liners from Mondi offer a renewable material plus source reduction or recycled content. EverLiner labelite release liner is a lightweighted 47 g/m² alternative to standard 58 g/m² glassine. The EverLiner M R release liner is said to be the first to use recycled base paper. The machine-glazed paper with 70% Forest Stewardship Council-certified recycled content reduces the amount of virgin fiber consumed. “Our aim is to create sustainable alternatives with no need to change the silicone system in order to offer products that are effective in usage, work for our customers, and ultimately help protect the environment,” said Andrea Lackner, R&D director Release Liner at Mondi, in a press release (9).

**References**


FIGURE 2. A multipage booklet label provides space for product descriptions (Pharma-Tac Plus, Schreiner MediPharm).
Detecting and Determining Quantitation Limits for Impurities

Different methods give different answers when calculating limits for impurities. The prediction interval method may be the best option.

Chris Burgess
is managing director, Burgess Analytical Consultancy Limited, Barnard Castle, Co Durham, UK.

Regulations require drug manufacturers determine the detection limit (DL) and quantitation limit (QL) of impurities in APIs and drug products. There are multiple ways of doing so, some of which are described in the International Conference on Harmonisation (ICH) guideline, ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology (1). Primarily, these methods are based upon the statistical uncertainties from a linear least squares regression calibration curve. However, different calculation methods give different answers. The following describes an example and a recommended best practice method.

ICH Q2(R1) lists several possibilities for DL & QL calculations based on the following five approaches:

- visual examination
- signal-to-noise ratios
- the standard deviation of a blank
- the residual standard deviation of the least squares analysis of the calibration curve
- the standard deviation of the intercept of the calibration curve.

As the calibration response function with concentration is a regulatory requirement for assay and impurities, this article will only discuss the last two options—residual standard deviation of the least squares analysis of the calibration curve and the standard deviation of the intercept of the calibration curve—and a proposal regarding the prediction interval.

There are more possible methods, and for a comprehensive discussion, read Section 5.6 in reference (2). This column focuses on a linear model with small molecules; however, the principles apply to non-linear models also.

Linear least squares regression model

In this example, a calibration experiment for an impurity with seven concentrations over the range 0.01–0.20% is performed. In addition, three measurements are made at each concentration level giving a total of 21 (k) data pairs. These data are shown in Table 1.

The linear least squares regression model for a calibration fits the individual response data, as the dependent variable, \( Y \), to the independent variable (assumed error free), concentration \( X \), shown in Equation 1,

\[
\hat{Y} = a + bX + \epsilon
\]

[Eq. 1]

where the best estimates from the regression model are \( \hat{Y} \), the predicted value the independent variable, \( a \) is the \( Y \) intercept when \( X = 0 \), \( b \) is the slope of the regression line, and \( \epsilon \) is the error component. An earlier article has discussed some aspects of this methodology (3).

This functionality is widely available in statistical packages and Excel. Minitab 19 was used to illustrate the plots and values for this article.

For the data set, the Minitab 19 output is shown in Figure 1. The best fit regression line is shown in red, and the 95% confidence interval contours of the model are shown in the dashed green lines. The values for the intercept, \( a \), and the slope, \( b \), are 0.4090 and 148.8, respectively. The error term in Equation 1, \( \epsilon \), is shown as \( S \), 1.1217.

DL and QL from ICH possibilities 4 and 5

Based upon either the residual standard deviation of the regression line (Equation 2) or the standard deviation of the intercept (Equation 3), the equations are:

\[
DL = 3.3 \frac{S}{b}
\]

[Eq. 2]

\[
QL = 10 \frac{S}{b}
\]

[Eq. 3]

The values derived from the residual standard deviation of the regression line are immediately obtainable from the regression plot and are in Equations 4 and 5:

\[
DL = 3.3 \frac{1.1217}{148.8} = 0.025\%
\]

[Eq. 4]
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### Table 1. Impurity response data for the linear model example. CONC is concentration.

<table>
<thead>
<tr>
<th>i (1 to k)</th>
<th>CONC% (X)</th>
<th>Response Function (Y)</th>
<th>((X_i - \bar{X})^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.01</td>
<td>0.80</td>
<td>0.00470</td>
</tr>
<tr>
<td>2</td>
<td>0.01</td>
<td>1.77</td>
<td>0.00470</td>
</tr>
<tr>
<td>3</td>
<td>0.01</td>
<td>2.60</td>
<td>0.00470</td>
</tr>
<tr>
<td>4</td>
<td>0.02</td>
<td>2.81</td>
<td>0.00383</td>
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<tr>
<td>5</td>
<td>0.02</td>
<td>1.96</td>
<td>0.00383</td>
</tr>
<tr>
<td>6</td>
<td>0.02</td>
<td>3.19</td>
<td>0.00383</td>
</tr>
<tr>
<td>7</td>
<td>0.03</td>
<td>6.44</td>
<td>0.00205</td>
</tr>
<tr>
<td>8</td>
<td>0.03</td>
<td>4.58</td>
<td>0.00205</td>
</tr>
<tr>
<td>9</td>
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<td>5.57</td>
<td>0.00205</td>
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<tr>
<td>10</td>
<td>0.05</td>
<td>8.25</td>
<td>0.00082</td>
</tr>
<tr>
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<td>0.05</td>
<td>9.00</td>
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<td>14</td>
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<td>12.52</td>
<td>0.00000</td>
</tr>
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<td>0.08</td>
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<td>0.00000</td>
</tr>
<tr>
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<td>21.00</td>
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<tr>
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<td>0.16</td>
<td>24.00</td>
<td>0.00663</td>
</tr>
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<td>0.16</td>
<td>25.07</td>
<td>0.00663</td>
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<tr>
<td>19</td>
<td>0.20</td>
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<tr>
<td>20</td>
<td>0.20</td>
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<td>21</td>
<td>0.20</td>
<td>31.44</td>
<td>0.01474</td>
</tr>
<tr>
<td></td>
<td>[\sum_{i=1}^{n}(X_i - \bar{X})^2]</td>
<td></td>
<td>0.09832</td>
</tr>
</tbody>
</table>

### Figure 1. Linear calibration model for the data set in Table 1.

It is now apparent that different calculation methods yield different answers on the same dataset. In addition, the standard deviations are only estimates derived from one particular calibration. Therefore, if the calibration was repeated, different values would result. Such is the nature of errors.

### Calculation equations for DL and QL from the prediction interval

The prediction interval of the calibration provides a confidence estimate for future measurements. One of the main reasons for using the prediction interval is that it uses all the data from the calibration model together with the intended number of

\[
QL = 11.1217 \frac{1}{148.8} = 0.075\%
\]

\[\text{Eq. 5}\]

The factor of 3.3 in Equation 2 for the DL has a statistical basis. When probability curves overlap, there is a chance that one could conclude that they have detected the impurity when it is, in fact, due to the blank signal. This is a false positive, \(\beta\) error, or Type 1 error. Alternatively, one can conclude that an impurity is not detected when it is, in fact, present. This is a false negative, \(\alpha\) error, or Type 2 error. To limit the probabilities of both these errors at 5%, the distance between the mean blank signal and the mean sample response is 3.3. This is illustrated in Figure 2.

On the other hand, the value of the factor for the QL of 10 is empirical.

Two further points need to be mentioned:

- The regression range of concentration should not be too large and a maximum range of up to a factor of 100 has been suggested (2). In this example, the concentration range is 20 (0.20/0.01).
- There is also the possibility that the variation from pure calibration standards will underestimate the variability of the procedure in routine use because of matrix effects. If this is a possibility, then the calibration curve should be derived using standards containing the matrix. This would be essential for many biopharmaceutical procedures where matrix effects are almost always present.

If one chooses to use the standard deviation of the intercept, \(s_x\), the calculations would use Equation 6:

\[
x_c = \frac{1}{\sqrt{n}} \left[ \frac{1}{\sum_{i=1}^{n} (Y_i - \bar{Y})^2} \right]
\]

\[\text{Eq. 6}\]
determinations for routine analyses. This feature is also widely available in statistical packages such as Minitab 19 and is shown in Figure 3.

The prediction intervals are more complex to calculate. However, direct calculation of DL and QL is possible and is illustrated in the Equations 7–10 (4) for the current data set. The original source is only available in German, but it is also abstracted in English (2).

\[
DL = 2t_{(0.05,2)}S \sqrt{\frac{1}{n} + \frac{1}{m} + \frac{(a + \bar{Y} - T)^2}{b^2 \text{SS}_{(a,T)}}} = 0.032
\]  
[Eq. 8]

\[
Y'_1 = a + 2t_{(0.05,2)}S \sqrt{\frac{1}{n} + \frac{1}{m} + \frac{(Y'_1 - \bar{X})^2}{b^2 \text{SS}_{(a,T)}}} = 5.3037
\]  
[Eq. 9]

\[
QL = Y'_1 - a - 2t_{(0.05,2)}S \sqrt{\frac{1}{n} + \frac{1}{m} + \frac{(Y'_1 - \bar{X})^2}{b^2 \text{SS}_{(a,T)}}} = 0.049
\]  
[Eq. 10]

Note again, that the calculated values using this calculation method are different from the ones calculated from the standard deviation methods from ICH.

One important feature is the inclusion of factors \(n\) and \(m\). The factor \(n\) is the number of data pairs for the calibration model and is 21 in this example. The factor \(m\) is the number of determinations that will be used in routine use of the analysis. In this example, \(m\) has been assumed to be 1. As \(m\) increases, both the DL and QL will decrease. Hence, the use of the prediction interval is more reflective of "in use" values.

**Prediction interval graphical method**

The necessity of calculation can be avoided for \(m=1\) using a simple graphical interpretation of the 95% prediction interval (PI) plot from one of the many available statistical packages. Only four lines need to be drawn resulting in two perpendicular interpolations to the concentration axis to yield the DL and QL.

The method is as follows:

1. Generate a regression plot showing the best fit regression line and the upper and lower 95% prediction intervals.
2. A horizontal to the X-axis line is drawn from the

Figure 2. Statistical basis for the detection limit (DL).

Figure 3. Linear calibration model for the data set in Table 1 showing both the confidence contours of regression and the prediction interval for future analyses at 95% confidence. CONC is concentration.

Impurity data
Response (Y) = 0.4090 + 148.0 CONC % (X)
intercept of the regression line to the intersection of the lower 95% PI of the regression line. This is actually the upper PI of the blank.

3. A vertical line is drawn from this PI intersection point upwards to the upper 95% PI of the regression line.

4. A second horizontal line is drawn through the intersection of the regression line with this vertical line to intersect with the Lower 95% PI. The point of intersection represents the DL and is directly obtainable by perpendicular interpolation to the concentration axis.

5. A third horizontal line is drawn from the point of intersection of this vertical line of the upper 95% PI across to the lower 95% PI. The point of intersection represents the QL and is directly obtainable by perpendicular interpolation to the concentration axis.

**Figure 4** illustrates this graphical process with the example data using Minitab 19.

**Conclusion**

As shown, the values of the DL and the QL are dependent on the method of calculation. For this reason, ICH Q2(R1) requires that the method selected for determining the detection limit and the quantitation limit should be documented. In any event, the QL should be verified during routine testing as part of system suitability testing.

The values from each of the four methods for the example data set discussed are shown in **Table II**.

However, the prediction interval method that makes best use of all the calibration data and the intended number of determinations for future use and is recommended. The graphical procedure generates values for a single future determination (m=1). Increasing the number of determinations reduces both the DL and QL, in this example the values for m=2 are 0.023% and 0.036%, respectively.

If the calculated DL or QL are close to the required values, it may be preferable to calculate the 99% prediction interval instead of 95% for a more conservative estimate. These 99% PI values are close to the much more complex tolerance interval approach [5].

**References**

1. ICH Q2 (R1), Validation of Analytical Procedures: Text and Methodology, Step 4 version (2005).
"AVI systems are installed end-of-line, typically before labelling and packaging in order to have the products as close as possible to end-user conditions but with the greatest amount of uncovered surface to facilitate a complete inspection of the product," says Luisari. "Infeed and outfeed for AVI machines can be completely in-line, either belt-to-belt or by means of infeed and/or outfeed trays. Products can be loaded and unloaded manually or automatically."

For the visual inspection process to best be incorporated into manufacturing, John Shabushnig, principal consultant, Insight Pharma Consulting, LLC, shares that identifying particle types early is key. This identification aids in reducing the inherent particle load in the formulation.

Shabushnig says, "This carries into manufacturing with similar goals to identify and reduce sources of particle contamination. Visual inspection further supports stability studies during development and routine manufacture to assure the product and process function as intended."

Visual inspection installation
Compared to manual systems, AVIs are usually installed before labelling and packaging, according to Luisari.

"[AVI machines use] a system of high-resolution cameras, illuminators, and computers that receive and process data to record a series of images of the product, photographed in 360° and in motion. Specialized software identifies any defects in the container and any particles or contaminants in the product," says Luisari. "Products are classified as conforming or non-conforming: non-conforming packages are automatically rejected. The processing unit generally uses algorithms to determine compliance."

The best visual inspection is non-destructive and inspects every manufactured product, Luisari adds. In addition, visual inspection can be either manual or automatic:

- **Manual visual inspection**: Performed by one or more trained operators following strict procedures.
- **AVI**: A machine performs the same tests done by manual operators. However, these machines often have equal or better performance in terms of detecting defects, false rejects, and speed.

**Visual inspection guidelines**
According to Shabushnig, the guidelines for visual inspection in the United States, Europe, and Japan are as follows:

- **United States**: United States Pharmacopeia (USP) General Chapter <790> Visible Particulates in Injections and the supporting information chapter USP <1790> Visual Inspection of Injections.
- **Europe**: European Pharmacopoeia (Ph. Eur.) 2.9.20 Particulate Contamination: Visible Particles and the information chapter 5.17.2 Recommendations on Testing of Particulate Contamination: Visible Particles.
When it comes to best practices, Shabushnig recommends manufacturers drive process improvement by using particle characterisation and identification information. It would be ideal if particles never entered the filled containers (rather than requiring inspection after filling), as proactive prevention is more reliable and can reduce cost as compared to reactive prevention. Shabushnig adds that this applies to container and closure defects as well.

Moreover, advances in artificial intelligence (AI) and deep learning—according to Shabushnig—may allow AI to better detect defects and have a reduction in false rejects from automated systems.

It's essential for manufacturers to first perform an adequate risk analysis when defining their product, according to Davide Luisari.

“The application of AI is increasing day by day, including visual inspection for pharmaceutical products. It is particularly beneficial to apply neural networks to visual inspection because the testing machine ‘learns’ from its mistakes, becoming more precise and reliable over time,” says Luisari. “Bonfiglioli Engineering utilizes neural networks and AI for the most challenging AVI applications, such as detecting defects in lyo cakes (lyophilization cakes) or finding cosmetic defects on a container. Over time, AI analysis refines the definition of ‘acceptable’ and ‘defective’ products, to generate an improved ‘defects directory’ and deliver better more refined results.”

The challenge, according to Luisari, is to continuously research advances in software and hardware, which are technologies that are constantly changing and improving.

“[I]t’s essential to be able to create the best conditions for product handling and lighting/optical setup, to fully emphasize the product features that facilitate the neural networks’ operation in defining a compliant or non-compliant product: there is no visual system in the world that can identify an unseen defect,” says Luisari.

Best practices and artificial intelligence

When it comes to best practices, Shabushnig believes that one of the most common misconceptions is the belief that visual inspection assures 100% probability of detection. Defect size, shape, colour, and location have significant influence on detection probability,” says Shabushnig. “I would also add that many consider inspection to be primarily concerned with visible particles. A wholistic approach, including the primary container and closure, is also needed to address the full range of defects of greatest concern.”

What manufacturers should know

No process or practice in manufacturing is error-proof nor does it guarantee a particular result. However, meticulous upfront design and planning can significantly impact the visual inspection of injectable drug products.
"While the inspection process is not perfect, a well-designed and operated inspection programme provides valuable information on the performance of the manufacturing process and contributes to the assurance of product quality," says Shabushnig. "It is part of a larger quality system and relies on good process design (both inspection and manufacturing). It also provides valuable information on process and product stability and can be used to drive continuous process improvement to reduce or prevent future defects and product loss."

Designing a detailed visual inspection programme upfront that includes proactive prevention, keeping up to date with advances in software and hardware, incorporating AI technology, and shifting from a manual process to an automated one that combines machines together has the potential to significantly improve the visual inspection of parenterals—thereby, ensuring both safety and product efficacy. 

**Learn more: automatic visual inspection system**

A mandatory practice for injectable manufacturers, automatic visual inspection (AVI) is used to inspect and detect foreign particulate matter (FPM). According to a Bonfiglioli article, AVI machines detect (1):

- Fibres
- Dust
- Agglomerates
- Undissolved material
- Rubber
- Glass
- Plastic
- Metal
- Outside particles
- All types of particle contamination.

FPM can originate from the environment or from packaging materials as well as from product formulation or the drug manufacturing process (1). In addition, visual inspection technology searches cosmetic or packaging defects, such as rubber stopper absence, flip-off absence, non-conforming flip-off shape, dented aluminum ring, non-confirming container color, non-conforming fill level, and general cracks, scratches, burns, spots, or shape defects.

To learn more, visit the international regulations for visual inspection (1):

- *United States Pharmacopeia (USP) General Chapter <1>: "Injections"
- *USP General Chapter <1790>: "Visual Inspection of Injections"
- *European Pharmacopeia General Chapter 2.9.20: "Particulate Contamination: Sub-visible Particles"
- *EU GMP Annex 1: "Manufacture of Sterile Medicinal Products"
- *World Health Organization: Annex 6 – GMP for sterile pharmaceutical products #13.8

**Reference**


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GMP/GDP Inspections: Challenges and Opportunities from COVID-19

An annual survey on inspections and audits has revealed opportunities to use more flexible approaches to optimize processes.

Stephan Rönninger,* sroennin@amgen.com, is director, Quality External Affairs, Amgen (Europe) GmbH; Andrea Kurz, is vice director, External Collaboration Europe, F. Hoffman-La Roche Ltd.; and Francisco Raya, is quality assurance head, Almirall.

*To whom all correspondence should be sent.

This paper presents the most recent results from the European Federation of Pharmaceutical Industries and Associations (EFPIA) annual survey and their conclusions. The year 2020 demonstrated the ability of the pharmaceutical industry and regulators to be agile whilst maintaining the same high standards as previous years because of the COVID-19 pandemic.

Inspections of a firm’s manufacturing operation are essential to evaluate commercial manufacturing capability, adequacy of production and control procedures, suitability of equipment and facilities, and effectiveness of the quality management system in assuring the overall state of control (1). Notably, pre-approval inspection (PAI) includes the added evaluation of authenticity of submitted data and link to dossier (1).

Since 2003, EFPIA has conducted and reported an annual survey of good manufacturing practice (GMP) and good distribution practice (GDP) inspections and related International Organization for Standardization (ISO) audits to monitor inspection activity and trends in research-based industry (2–4). The annual survey is performed to shape the future based on data. Companies can compare the results with their own situation.

Based on the outcome of the survey results, the efficiency and reliance approaches can be demonstrated. The conclusion of the data assessment supports promoting alternative approaches to inspection with physical (on-site) presence. Harmonizing requirements and expectations will maximize effectiveness and reduce uncertainties for companies and inspectorates. Furthermore, the annual survey intends to demonstrate the benefits of Mutual Recognition Agreements (MRAs) and Pharmaceutical Inspection Co-operation Scheme (PIC/S) membership in optimizing use of inspection resources while maintaining patient safety (5).

Scope of the survey
As in previous years, the scope of the EFPIA regarding the 2020 regulatory GMP/GDP inspections and related ISO-certification audits included inspections by regulatory authorities and Notified Bodies at manufacturing sites and commercial affiliates for both manufacturing of investigational medicinal products (IMPs) and commercial products. The scope included inspections inside (i.e., domestic) and outside (i.e., foreign) the regulatory authority’s country or region.

EFPIA asked companies in the survey to specify all inspection tools (or a combination of them), including on-site, virtual (‘remote’), or paper-based, as well as reliance and recognition approaches used. The product type manufactured at the site and the duration and outcome of each inspection were reported. Companies also reported the type of inspection and whether inspections were scheduled or unannounced. EFPIA also asked a set of questions related to how inspections had been performed and about the impact of the restrictions during the pandemic.

Results and trends
The 2020 survey received responses from 25 global research-based pharmaceutical companies (EFPIA members) and eight local companies reported by National Trade Associations. Full results are available on the EFPIA website (4). As expected, there were significantly fewer inspections overall in 2020 (approximately –40%, 1106 inspections, compared with 1733 inspections in 2019 and 1748 inspections in 2018 [4]) while the number of manufacturing sites included in the survey was comparable with previous years.

The total number of foreign inspections in 2020 was reduced by approximately 50%. However, the number of manufacturing sites without an inspection (domestic or foreign) was in the same range as in previous years (36% in 2020; 26% in 2019; 31% in 2018 [4]). Therefore, the regulatory oversight of manufacturing sites is consistent.

Domestic Inspections. Domestic inspections are defined as inspections performed in the country/region of the inspectorate. In 2020, the number of domestic inspections at manufacturing sites were nearly reduced by half for 2020 when compared with 2019 (453 versus 709). The number of days an
Inspection Trends in the Data

In 2020, the pandemic revealed the range of tools available to inspectorates and the flexibility offered by the toolbox for conducting inspections using physical presence, document review, virtual presence, and experience, recognition, and trust. Inspectorates used a variety of tools in 2020. GMP is good manufacturing practice, GDP is good distribution practice, PAI is pre-approval inspection.

Some data remained unchanged, however. For example, the proportion of unannounced versus scheduled inspections has been unchanged since 2015, and the outcomes of both unannounced and scheduled inspections are comparable, since these data were collected in 2015.

Some key company responses from the survey questions include the fact that there was no change in the number and severity of observations reported; no significant differences in the outcome of GMP/GDP inspections or ISO-audits were reported; more than 90% of companies stated that there was no change in the number or type of observations; some shifts in observations were described by individual companies; and no challenges regarding drug shortage prevention measures were reported.

Efficient application of inspection process and tools

In 2020, the pandemic revealed the range of tools available to inspectorates and the flexibility offered by the toolbox for conducting inspections using physical presence, document review, virtual presence, and experience, recognition, and trust. Inspectorates used a variety of tools as standalone and in combination (4). Each approach has challenges and opportunities (Figure 1).

Physical presence. The COVID-19 pandemic impacted the ability of inspectorates to be present on site to perform inspections. While more than 80% of the domestic inspections had at least partial on-site presence of the inspectorate; however, less than a quarter of foreign inspections were conducted with on-site presence. Inspectorates that did use on-site presence for foreign inspections included Belarus, EU, and United States.

Virtual presence. The virtual tool offered a logical alternative for inspectorates mostly adopted for performing foreign inspections in 2020 (6,7). Implementation of this tool varied: it was used, for example, mainly by EU inspectorates (that employed virtual and...
on-site tools in a 50:50 ratio), Republic of Korea, and Russia.

Some inspectorates used a hybrid approach, with a combination of on-site presence and the virtual tool. This combination was used mostly for domestic inspections. Use of the virtual tool alone was reported for domestic inspections by EU inspectorates (including Belgium, France, Germany, Ireland, Poland, and UK), the US, and Brazil.

Feedback provided by companies on the use of the virtual tool varied. Some companies reported technological and privacy issues, and difficulties with time zone management. The point was made that certain inspectorates (e.g., Russia) did not make it clear that the inspection had finished. Companies reported that a defined agenda would be useful. Other companies reported that a longer time was needed when preparing for a virtual inspection, with many more documents being requested in advance than with other tools. It seemed that both industry and regulators were on a learning curve with the application of the virtual tool. Nevertheless, inspections proceeded at a time when travel was severely restricted.

Note that there was uncertainty in the 2020 data evaluation about the number of inspector days used for virtual inspections. If a company named more than 10 days for a virtual inspection, we set the value to 10 days to account for the fact that not all days would have been full days when the inspection was performed. Similarly, with paper-based inspections, some companies reported the start and end date of a paper-based inspection, even if the days in between were not used. Thus, the duration of paper-based inspections was not accounted for.

**Document review.** Documents to be submitted prior to an inspection continued to be used as a tool in 2020, when there were 139 paper-based inspections (compared to 62 paper-based inspections in 2019) reported, primarily involving inspectorates from Japan (40%), US (10%), Republic of Korea (7%), and Turkey (7%).

Although document reviews without virtual interaction or physical presence of the inspector can be less time-consuming for a company and inspectors, provision of documentation still uses resources, and the document request process is not currently harmonized. Companies can be asked to provide documentation in advance not just for paper-based or virtual inspections, but also for all inspections with physical presence. In addition, translations may be required with the risk of misinterpretation. Data from a separate survey in 2020 revealed that up to 700 documents of a broad variety, have been requested before an inspection with a physical presence (4).

**Experience, recognition, and trust.** In 2020, there were seven inspections (five foreign, four of them as of an MRA or Memorandum of Understanding [MoU], and two domestic) reported where it was indicated that licences had been renewed without performing an inspection ("waived" inspections). EFPIA advocates the use of waivers and leveraging the benefits of fully implemented MRAs. An effective risk management process adopted by the inspectorate (8) allows for waivers. Waivers are being increasingly granted for sites in countries where a formal MoU is established, or the inspectorate is a PIC/S participating authority.

Inspections by the EU in the US have dropped by 80% since 2017 (4). The survey data revealed that there were 50% fewer foreign inspections by the US in the EU compared with 2019. However, this lower number may be an effect resulting from the general reduction of foreign inspections in 2020. It is expected that this trend will continue going forward, and the observed reduction of inspections is not just a reflection of pandemic restrictions or government shutdowns due to the budget situation in the US.

**Recommendations for the future**

The COVID-19 pandemic caused a significant reduction in the number of inspections in 2020, but there was no discernible drop in oversight of manufacturing facilities ensuring that industry maintained high standards of quality, safety, and efficacy of medicines. The authors feel that lessons learned from this year’s survey could be permanently implemented, in compliance with existing legislation (9).

**Risk-based approach for inspection planning.** A risk-based approach to planning and conducting inspections was used more effectively in 2020, and the authors advocate that it is continued in future years, using the PIC/S guidance on risk-based inspection planning (8). This approach facilitates planning of inspections by regulators by providing risk ranking of sites, along with a suggestion for the number of inspectors and scope (including focus and depth) of the next surveillance inspection.

**Best use of the different inspection tools.** The pandemic drove companies and inspectorates to seek new, innovative tools to provide alternatives to inspection with physical presence. The virtual tool was used extensively, although companies reported certain difficulties. It was an enabler for an informed compliance decision by the inspector. Some companies found it difficult to interact virtually, especially if they experienced technological problems or if an interpreter needed to be used. In this case, the involvement of local affiliates in foreign virtual inspections may allow better communication. Hybrid approaches could be valuable in future years. Application of virtual tools can confirm compliance while replacing a physical presence or a document assessment by issuing a GMP-certificate to guarantee continuous patient access, for example. It is most important that in the end, patients continuously receive good quality medicines (9).

Inspectorates also made more use of existing tools, particularly paper-based inspections. Supporting document reviews as part of inspections, EFPIA recommends that a standard set of documents could be agreed upon the various harmonization
initiatives to be available for each site to the inspector (5). The use of such a globally aligned and consistent list of required documents in English, would enable advanced preparation and ensure consistent documentation reviews, simplifying the process by eliminating variability.

Potential differences in terminology could be harmonized, for example by PIC/S, that local regulators could use to develop a specific glossary linking local terminology with these harmonized terms. This standardized package would allow streamlining of efforts so that companies and inspectors could be more focused and effective.

Reliance for reducing redundancies. Although the number of inspections overall was reduced significantly, the proportion of sites of inspections overall was reduced eliminating variability. We believe that the legal requirements for GMP/GDP inspections can be fulfilled with increasing application of reliance approaches based on the positive experience gained during the pandemic, because there was no negative impact observed on the oversight of compliance of manufacturing facilities (13).

Conclusion

The following opportunities to optimize the inspection process based on the EFPIA 2020 survey outcome could be considered: reliance on available information about inspections at a manufacturing site; standardization of the package of documents; and a focus on domestic inspections and sites that have never been inspected before. Agencies’ risk-based inspection planning approaches could recognize all available inspection tools, review of and reliance on documents, or considering combinations of those tools. Furthermore, EFPIA suggests leveraging existing MRAs and accepted comparable standards like inspections conducted by an inspector from a PIC/S participating authority as an opportunity to simplify the inspection process (4,11). The results from the survey on the 2020 data reveal that inspectors ask for many documents, especially since the pandemic, to be submitted prior to the inspection, which is very time- and resource-consuming for industry (4). Inspections with virtual presence increases knowledge, which can provide better bases for decision-making, rather than just requesting and reviewing paper documentation. Finally, a regulatory decision on GMP capability and compliance of the manufacturing site will support a smoother regulatory approval process leading to earlier and continuous access of medicines to patients (14).

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Lessons learned from GMP/GDP inspections during the pandemic.

The COVID-19 pandemic showcased opportunities for future adoption in the GMP/GDP inspection practices, such as remote (desktop) reviews, increased reliance on recognized inspectorates, further use of MRAs, and inspection waivers.

We believe that the legal requirements for GMP/GDP inspections can be fulfilled with increasing application of reliance approaches based on the positive experience gained during the pandemic, because there was no negative impact observed on the oversight of compliance of manufacturing facilities (13).

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The Remote Audit– A Tongue-in-Cheek Memo

Siegfried Schmitt, vice president, Technical at Parexel, comments on the new paradigm of remote audits.

Because of the COVID-19 pandemic, many companies no longer permit on-site audits. This has many advantages for the audited company (the auditee). This article tells how a company could explore this opportunity to its maximum advantage.

**Memo to all staff**

In order to make customer audits as efficient and effective for us, we have decided to update the respective standard operating procedure. Here we summarise the key elements:

- From now on, we will only allow virtual audits or questionnaire audits, but no on-site audits.
- These audits are limited to normal office hours (i.e., between 9 am and 4.30 pm with a one-hour lunch break from noon to 1 pm). Extensions are not possible.
- We will only participate in Microsoft TEAMS video conferencing sessions that we have set up.
- We do not allow parallel sessions (e.g., for more than one auditor).
- There will be only one person from our company (the moderator) participating in the audit.
- Any questions from the auditors that the moderator cannot answer, will be forwarded to the relevant subject matter experts (SMEs). The audit will be paused while the moderator types the emails to the SMEs.
- The moderator will relay answers from the SMEs to the auditors as and when these are received.
- If the moderator has been in contact with a person infected with COVID-19, the audit will be cancelled. Cancellations should not be sent out more than 24 hours before the start of the audit.
- Documents can be reviewed in a data room during audit hours only.
- For data protection reasons, anything we put in the data room, like the company presentation, will be non-editable, non-printable, and the “print screen” function will be disabled.
- Documents will only be shared with the auditors through the data room.
- Auditors can either access the data room to look at the documents, or they can access the video conference with the moderator. Parallel sessions are disabled.
- For privacy reasons, we cannot switch on video on our side.
- Virtual site tours cannot be conducted live. We will prepare pictures that will serve as a site tour.
- For privacy reasons, the pictures for this virtual site tour cannot show any personnel.
- The pictures for this virtual site tour will be available in the data room. No other pictures can be provided.
- Only questions received during the audit will be answered.

**Summary**

Audits can be so much more relaxed and enjoyable because virtual audits have become commonplace. If this memo seems familiar, then this is pure coincidence. **PTE**
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