Pharmaceutical Technology®

JANUARY 2022

Transforming IMP into Clinical Supply: An Integrated Approach

- Planning Ahead: Using Phase 1 to Anticipate Phase 2 Clinical Supply Challenges
- Unique Molecules Push Formulation Boundaries
- Putting the Patient at the Heart of Dosage Form Design
- Who, When, Where & How? The Key Clinical Supply Issues Sponsors Should Consider with their CRO

This custom ebook is sponsored by Catalent and presented in partnership with *Pharmaceutical Technology*.

Catalent

Planning Ahead: Using Phase 1 to Anticipate Phase 2 Clinical Supply Challenges and Solutions

Ann McMahon and Matthew Rota

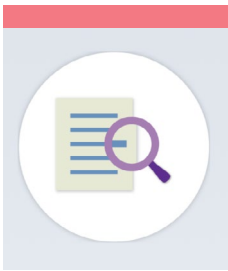
Early collaboration with an integrated solutions partner mitigates challenges.

Introduction

Early phase clinical studies are typically less complex than late phase studies, but they lay the groundwork for a successful program as the molecule progresses toward commercialization. This article explores how to prepare for increasingly complex clinical trials, as well as highlights how integrated solutions providers can streamline operations and ensure a smooth transition from Phase 1 to Phase 2.

CMC Aspect of the Supply Chain

The integrated drug development approach—where drug substance, drug product, clinical supply, and packaging development activities overlap and are handled in tandem by a single, integrated team—has numerous benefits to sponsors from pre-clinical stages through to commercialization:



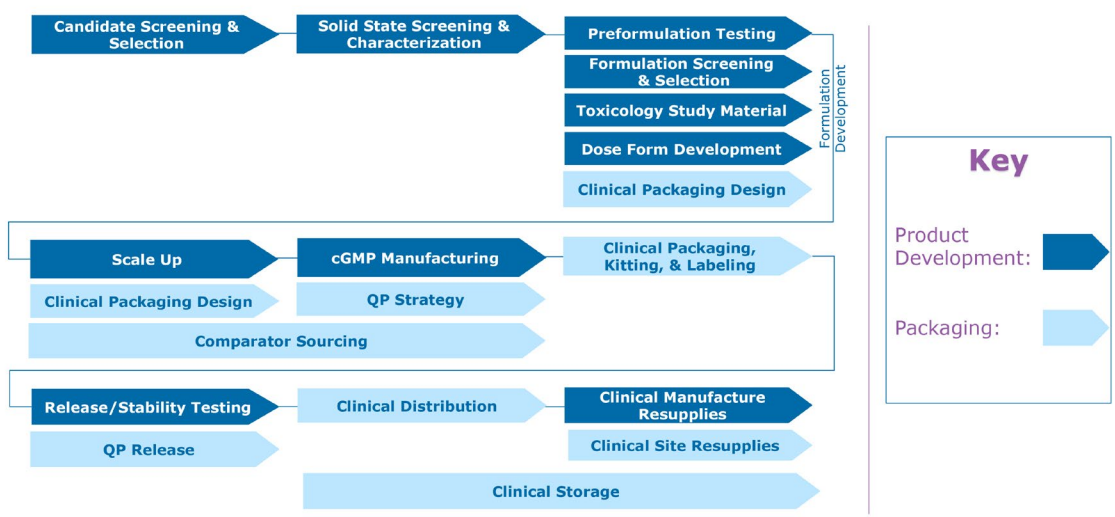
- Faster development timelines
- Better knowledge transfer using robust internal systems that are aligned to share data and avoid rework
- Reduced time burden thanks to one point-of-contact project management

Integrated drug development can start with candidate screening and solid-state screening and characterization, and move into formulation development (e.g., pre-formulation testing, formulation screening, toxicology assessments, and dosage form development). At this point, an experienced integrated services provider can start layering in support on the packaging side for clinical supply.

As the program progresses, FIGURE 1 highlights how critical packaging design work can be completed in parallel with product development using the same service provider. For instance, in parallel with scale-up activities, packaging experts can work on comparator sourcing for clinical trials—a critical activity that can threaten to delay a program if it is not done properly and at the right time.

There are clear advantages to having both CMC and clinical supply teams working together earlier to achieve success for the program. When pharmaceutical scientists are isolated from clinical supply services associates, or when clinical supply is only considered after the drug product is manufactured, it can lead to delays and

FIGURE 1: Integrated drug development.



inefficiencies. The opposite is true of an integrated drug development approach.

Moreover, communication between the manufacturing and packaging teams and the teams suppling the drug product is critical to reducing the risk of breakdowns in the supply chain and unavailable or out-of-stock drug product (resulting in better inventory management), as well as optimizing problem solving.

Early versus Later Phase Work

With the goals and budgets for early and late stage development being very different, how can companies best use Phase 1 to prepare for Phase 2 and beyond?

What follows are several examples of the differences between early and late phase work:

- In early-stage development, **toxicology-related information** for safety assessment is limited. In later stages, the mechanism of action is defined, and safety data becomes available for better informing handling requirements.
- In terms of the **active pharmaceutical ingredient (API),** suitable polymorphs and salt forms are investigated in the early stages, whereas in later stages the manufacturing process for the desired polymorph or salt form of API is well defined and controlled.
- **Dosage forms** for early phase studies are often selected for expediency in getting the materials to clinical study sites. For this reason, powder in bottle, liquid in bottle, and powder in capsule might be chosen. Meanwhile, in later stages, the dosage form is designed for patient compliance, manufacturability, and cost-effectiveness.
- From a **process** perspective, a wide range of dose strengths are explored in early phase studies, and thus there will not be a product-dedicated process train. By late phase, dose strengths are well-defined and can be made with a large-scale multiproduct process train.
- In early stages, **test methods** are qualified as suitable for their intended use, whereas in later stages, and certainly at the time of the NDA submission, these methods should be fully validated.
- Lastly, in early phase studies, typically just one or two scientists have all the institutional **knowledge**. Sponsorship of the molecule might change hands, so it is therefore important to have good documentation early on. In later phases, there is a well-studied design space, risk assessments, and the development history to reference and build upon.

Of all these areas, there are three important considerations for Phase 1 that could make a significant positive impact on later phase work. First, understand the API. Make sure to obtain a professional toxicology assessment for safety; determine the DCS (developability classification system) classification to help guide whether bioavailability enhancement techniques will be needed; and identify critical material attributes through solubility/

stability testing, physical characterization, and forced degradation studies.

Second, formulate for the future by performing excipient compatibility testing and developing a formulation that is easily scaled up. For instance, if time and resources permit, consider developing a formulated capsule or tablet that will allow you to seamlessly scale from several thousand units to tens of thousands of units as your program needs.

Lastly, for analytical method development, start by reviewing and utilizing the critical material attributes collected previously, this will help you save time and conserve API. When developing early phase methods consider method "qualification" rather than full method "validation." Qualifications keep the method parameters more flexible and validation can and will be performed when the process and product are better defined. With that in mind, document any shortcomings of the method not covered during method development and qualification. Be sure to communicate and account for these gaps when looking to validate, which will help the follow-on teams fine-tune method validation. The availability of this documentation also contributes to the easier preparation of phase-appropriate regulatory submissions (CMC) documentation.

The optimized integrated team structure and efficient internal processes allow for rapid and efficient transfer of programs and adherence to shortened timelines. This strategic mindset starting in early development also conserves API, helps reduce risk, creates efficient knowledge transfer, provides holistic teamwork, and avoids rework (FIGURE 2).

FIGURE 2: Benefits of integrated drug development.

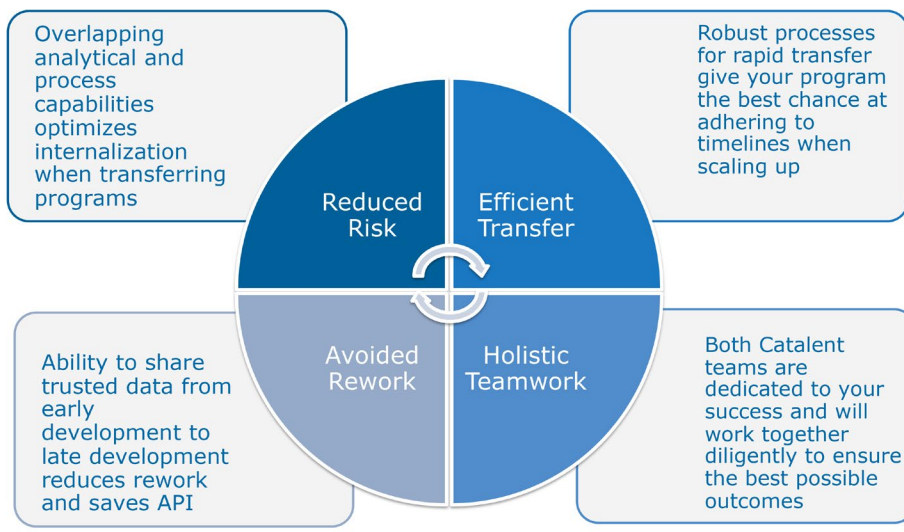
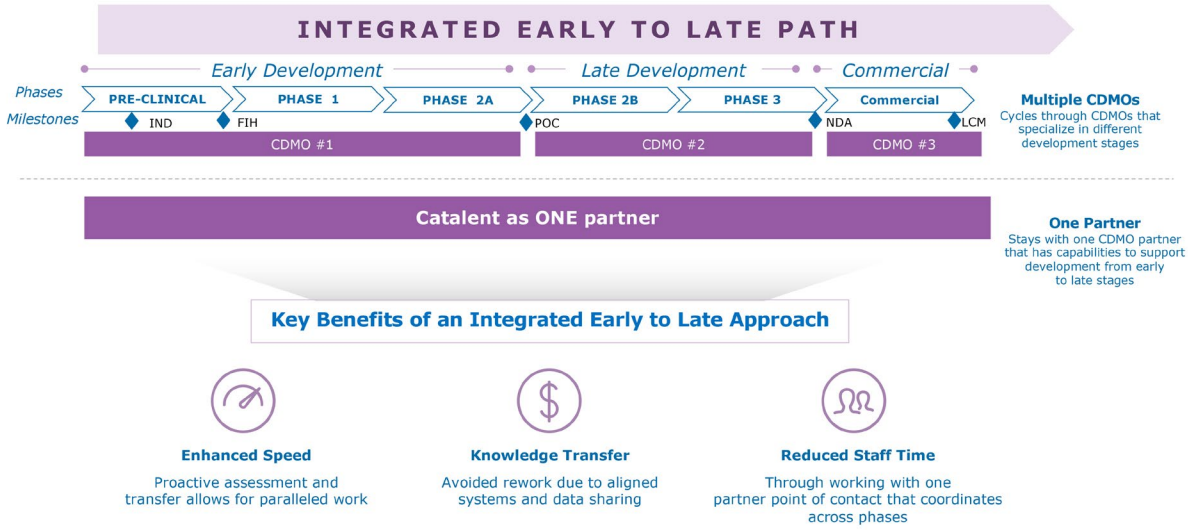


FIGURE 3: Accelerate timelines and reduce risk with an integrated early-to-late solution.



Integrated Packaging Services Create Efficiency

Formulation development can benefit from packaging solutions being designed in parallel. For instance, a partner that can offer formulation development, manufacturing, and packaging/labeling expertise can bring the right experts together to design the best container closure system for a product. This might be particularly helpful for protecting moisture-sensitive APIs with a protective blister component or adding a coating step (if feasible). Likewise, this approach can ensure ease of dosing with pediatric formulations such as using stick-pack technology, for instance.

By using a partner that offers these integrated supply chain and packaging services, the overall time burden can be significantly reduced (FIGURE 3). For example, with one development partner, only one contract and quality agreement needs to be negotiated for all services rather than many contracts and quality agreements that are necessary to do business with many vendors. This connects with another advantage: seamlessly sharing safety information within one development partner, rather than providing the same information to many partners, also helps to reduce bottlenecks.

Additional efficiency elements built into an integrated supply chain include packaging and shipping under quarantine and leveraging the ability to perform some parallel processing. Instead of waiting for those analytical results to be available before starting the packaging operation, the integrated approach saves time by being able to package materials while some of the analytical release testing and certificate of analysis is completed and generated.

Other advantages to this integration involve labeling and kitting activities. In Phase 1, packaging and labeling for open-label studies is straightforward. As clinical studies progress through to later phases and the number of study sites and subjects grows, the volume of packaging activities also increases as does the complexity of labeling and kitting. Leveraging a single integrated services partner that offers packaging, labeling and kitting support can pay off in later stages. Some examples of the synergies in later clinical phases include developing multi-language booklet labels, implementing country-specific labeling requirements, creating kits for multiple treatment arms, comparator sourcing and blinding.

Real-world examples

A customer required a small quantity of drug product to be primary packaged and labeled to support an early phase trial. In this instance, the packaging activities could be performed at the manufacturing site, but the labeling requirements were complex. The drug product manufacturing team reached out to their clinical supply colleagues to assist in the label design and printing. Labels were then shipped to the contract manufacturer for application.

Because the clinical manufacturing team was able to leverage their integrated clinical supply team, the label design and printing activities were completed in time to meet the customer and clinical timeline.

In another example, formulation development and clinical manufacturing needed to be done on an extremely compressed timeline with some complexities in the supply chain. The customer also needed to file some regulatory documents in parallel with the formulation development activities. This posed some challenges with the importation of the API and subsequent conversion to drug product.

In addition, the supply chain for the drug product was complex and required a third-party depot to support some of the distribution activities. Thus, project managers for manufacturing and clinical supply were engaged from the very start of the project. Time was of the essence and nothing could be spared due to the complexities of working across different suppliers. Because project managers were working efficiently and engaged in the planning, the final finished product was released and shipped to the clinical site to meet the important clinical milestone of first patient initiation.

Summary

Though packaging, labeling, distribution, and resupply are at the very end of drug development and clinical supply chain process flow, considering these elements and planning for them early on in the project plan is essential for success. Experience has shown that communication between teams throughout the process is incredibly important. Engaging early and often with the right subject matter experts within the organization can help a sponsor evaluate a wide range of solutions for clinical supply concerns. For the sponsor, this integrated

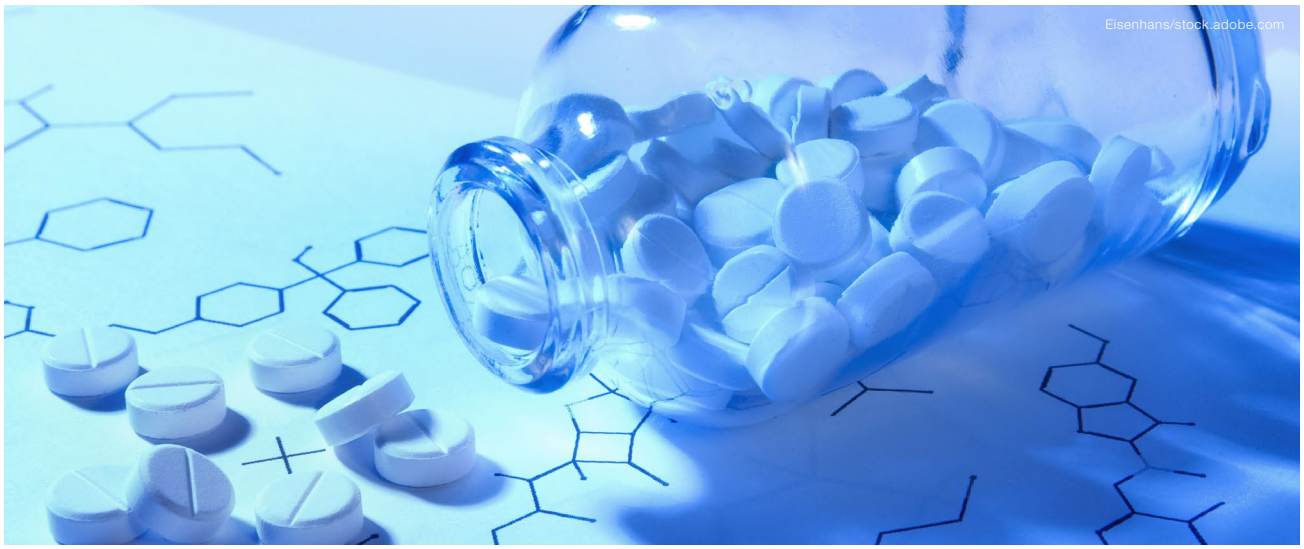
approach coupled with dedicated project managers reduces the overall number of people involved in the project and improves overall collaboration and communication, resulting in less complex and more streamlined supply chain.

Ann McMahon

General Manager, Commercial and Integrated Development Operations
Catalent

Matthew Rota

Commercial Operations Manager
Catalent



Unique Molecules Push Formulation Boundaries

Felicity Thomas

More complex and challenging compounds require a more tailored approach to formulation strategies.

Increasingly challenging and complex molecules entering the development pipeline are changing the way formulation development is approached. Furthermore, time and cost are considered to be at a premium, and demand for products to be commercially viable in the shortest time possible within a limited budget is ever more apparent.

According to market research, formulation is a key opportunity in drug development as formulation issues or challenges can readily lead to project failure or significant delays (1). "New molecule formats and extreme concentrations demand tailored formulation strategies instead of platform approaches now," explains Andrea Hawe, co-founder and chief scientific officer of Coriolis Pharma.

Challenging Compounds, Enabling Technologies

"The biggest trends that have been observed in formulation strategies over the past few years are that pharma companies

are more open to complex technologies to address pipeline issues," notes Jim Jingjun Huang, founder and CEO, Ascendia Pharmaceuticals. "Additionally, the increasing application of enabling technologies for use in challenging compounds, such as BCS [Biopharmaceutics Classification System] II and IV, is trending."

This latter point, on challenging compounds, is of utmost importance for Sanjay Konagurthu, senior director, science and innovation, Pharma Services, Thermo Fisher Scientific. "Small molecules are still the largest segment of drug development in the industry. Oral and injectables dominate the pharmaceutical pipelines," he adds. "In terms of oral drug delivery, it is currently estimated that 70–90% of small molecules in the pipelines have solubility and bioavailability challenges. This number has doubled compared to over 10 years ago."

As a result of these solubility and bioavailability difficulties, conventional formulation approaches do not necessarily suffice, Konagurthu continues. "Depending on the physicochemical properties of the drug molecule, appropriate technologies and formulation strategies will have to be identified and evaluated," he says.

For Hawe, the majority of trends that have been seen by industry in the area of formulation strategies has resulted from the increased diversity of biopharmaceutical molecules. "While monoclonal antibodies are still important, new formats—such as artificial peptides, fusion molecules, antibody fragments or bi/tri-specific antibodies—require new formulation concepts and novel analytical approaches," she asserts. "This holds true also for advance therapy medicinal products (ATMPs), such as viral vectors for gene therapy or cell-based products, which are emerging rapidly, and where a lot of movement in the years to come is expected."

Additionally, Hawe emphasizes that there is a trend toward high-concentration protein products, even beyond 200 mg/mL, of late, which has been sparked by the rising use of autoinjectors for subcutaneous self-administration and intravitreal administration. "For such products, formulation development needs to focus on viscosity and aggregation, next to chemical and conformational stability," she says. "On the contrary, products that require ultra-low concentration formulations, for example bispecific T-cell engager, are also being developed. Here, surfaces adsorption and the development of suitable analytical methods are the challenges that formulation scientists must deal with."

As a result of molecular and route-of-administration demands, project-specific approaches are now required, and for Hawe, these approaches should be based on existing, FDA-approved generally recognized as safe excipients, as there is a clear hesitancy by the pharma community to use novel excipients. "The analytical methods need to be developed so that they preferably measure the sample as-is," she notes. "Thus,

it is good to see a constantly increasing analytical portfolio including new submicron and micron particle characterization techniques and multi-attribute mass spectrometry methods."

Considerations and Practical Tips

Both clinical and business objectives are important to consider when evaluating the most appropriate formulation strategy, according to Konagurthu. "Once the clinical and business objectives have been established, however, it is important to identify the quality target product profile (QTPP) of the drug and a phase-appropriate strategy that can accelerate drug development," he says. "Special focus on performance, manufacturability, and stability is of course ultimately required for a drug to be commercially viable."

The most appropriate formulation strategy will vary depending on each specific situation, emphasizes Hawe. By way of example, she specifies situations where there may be a small amount of material available or where the product is in preclinical trials, for which, she explains, it could be useful to develop a first reasonably stable, but not yet fully optimized formulation. "At later stages, when more material is available, but timelines are more aggressive, the strategy can include a parallel development of liquid and lyophilized formulations, for example," she says.

When the project is in the early phase, the probability of success to test in first-in-human or first-in-patient is the most important consideration for evaluating formulation strategy, stresses Huang. "Once the project has successfully transitioned to the market formulation development (Phase IIb/III), then market acceptability or commercial aspect, scalability, intellectual property protection, and cost all become equally important," he adds.

In terms of practical tips for developing a formulation strategy, Hawe highlights the importance of a reasonable chemistry, manufacturing, and controls (CMC) formulation development package early on in development. "Approaching clinical trials with a suboptimal formulation and facing stability issues or other challenges in later stages is, in the end, more time consuming and expensive," she states.

For Huang, "following the science" when developing a formulation strategy is a requisite for a successful development program. "A rational design of tox and human formulations for the precious ingredients is critical to ensure a successful proof of concept in humans," he says. "The key aspects for successful tox and early-phase formulation development consist of preformulation of the drug

candidate, biopharmaceutical evaluation, analytical method development, formulation development, and [current good manufacturing practice] CGMP manufacturing for clinical trials."

"Each drug molecule is unique, and it is critical to understand the physicochemical properties of the API and interactions with various excipients that are used in formulations," asserts Konagurthu. "Also, excipients are not always inert and an understanding of how they might impact physiological targets should be considered. Building expertise and internal knowledge databases can be used to build predictive formulation tools."

Hurdles and Common Mistakes

A major hurdle in developing the best formulation strategy, in Hawe's opinion, is the compromise between being as fast as possible to the clinic and performing sufficient studies so that a high quality and stable product is developed. "Oftentimes, customers approach partner companies too late or with unrealistic timelines for full-scale formulation development but we then aim to find a satisfying middle ground," she says.

Time and cost are also considered to be major issues for Huang, who comments that it is common for contract development and manufacturing organizations (CDMOs) to be expected to provide proof-of-concept for a customer's compound from preclinical to in-human trials as quickly as possible and for a limited budget. "Therefore, it is important to come up with very efficient formulation strategies to meet these demands," he adds. "In some cases, for very challenging compounds, it is possible to encounter a choice between developing the best formulation and being able to meet the budget and time demands."

Moreover, there are hurdles to overcome in terms of the characteristics of drug molecules. "Some drug molecules can be very labile and, as a result, can provide significant chemical and physical stability challenges to the formulator," continues Konagurthu. "Constraints on dose, drug loading in the dosage form, size, and weight can also present challenges."

However, oftentimes companies do not allocate sufficient time and resources to developing an optimal formulation strategy for challenging compounds, stresses Huang. "The main goal for early-phase development is to test the compound's safety and efficacy for the intended therapeutic indications in animal and humans," he says. "Tremendous efforts need to be placed in improving the pharmacokinetic properties of compounds and ensuring bioavailability in animal models and human Phase I and II studies. A desired compound's systemic exposure in testing subjects is prerequisite to meet the goals of early development. Otherwise, the drug program could be at a higher risk of costly failure in first-in-human and at later stages of development."

Konagurthu also emphasizes that significant delays in timelines and overuse of critical

resources can result when companies employ an empirical trial-and-error approach toward formulation, process development, and scale-up. "Lack of a thorough understanding of the *in-vitro* and *in-vivo* performance, process design space, and stability can lead to delays and program re-starts," he explains. "Having an in-depth understanding of performance, manufacturability, and stability is important at all stages of product development and eventual commercial launch."

In Hawe's experience, there are three common mistakes that are made when developing a formulation strategy. "First, using excipients that are not FDA-approved and are not available in the required pharmaceutical quality. This can easily be omitted but happens surprisingly often," she says. "Second, not considering the target product profile (TPP) and the requirement for a later manufacturing when starting formulation development. Third, skipping certain analytical methods and with it being blind for certain instabilities. Sometimes orthogonal approaches might seem like an overinvestment, but each technology has its blind spots and we need orthogonality to compensate for that."

Technological Advancements and Trends

Although there may not be a single, magical technology that can make formulation development both quick and easy, Hawe notes that there are many small improvements that, in combination, can facilitate the process. "The application of

"Sometimes orthogonal approaches might seem like an overinvestment, but each technology has its blind spots and we need orthogonality to compensate for that."

artificial intelligence (AI) and improved statistical methods, for example, may reduce the number of experiments; better method automation/throughput and lower sample consumption will deliver more insights in less time or with less material; and advanced scientific understanding will improve decision making and reduce failures," she says.

Technologies that enhance the solubility and permeability of drug candidates are important in the facilitation of formulation design for Huang. Optimization of solubility and bioavailability is achievable through using suitable delivery systems by screening a set of technology platforms that address different compound challenges in hydrophilicity, lipophilicity, permeability, and melting point, he explains.

"The use of predictive models can provide insights into formulation and technology selection based on the API's physicochemical properties," Konagurthu adds. "Use of a comprehensive material property database facilitates the development of predictive models that serve to guide formulation development. Advanced techniques such as

compaction simulation can guide a rational, material-sparing formulation strategy."

Additionally, when using predictive models, such as thermodynamics, discrete element method, or computational fluid dynamics for process development, it is possible to gain valuable insights into formulation design, Konagurthu continues. "Accelerated stability assessment programs can rapidly guide excipient selection in formulations and packaging design," he says. "Use of physiologically based pharmacokinetic models to understand in-vivo performance can also aid in guiding formulation strategies (e.g., modified/controlled release)."

Moreover, Hawe believes that predictive methods, along with prior-art experience, will become ever more important for formulation development. "New and better predictive indicators, for example, for protein stability as well as base formulation development, will lay the foundation of future formulation strategies," she states. "On top of that, data science in combination with AI will allow the required experiment to be narrowed down and to focus on the formulation corridor. While the development strategy will still be tailored to the specific product and situation, I expect development programs to become more efficient."

An emerging trend that has the potential to help companies with the increasing pressures on quality, pricing, and productivity, is in the form of continuous manufacturing, remarks Konagurthu. "Continuous manufacturing can deliver higher quality oral solid-dose products, with greater flexibility and a reduced total cost of supply," he says. "Formulation strategies for continuous manufacturing will require adopting a materials science-based approach."

Benefits of Partnerships

Outsourcing partners should play a crucial and integral role in formulation strategy, notes Huang. A partner can provide expertise in CMC, technology, and regulatory affairs, or can act as a traditional pharmaceutical R&D department for the sponsor company, he states.

"A knowledgeable CDMO partner can help bolster product knowledge throughout all phases of a program lifecycle," adds Konagurthu. "A CDMO with hands-on experience with a host of compounds and formulations can help build quality-by-design (QbD) into a product, as they will have deep knowledge to draw on for addressing problems that arise during development."

Application of QbD principles early on in development, along with predictive models and risk assessment tools, are useful in mapping the design space for the formulation and processes, and ultimately, developing commercially viable formulations and processes, Konagurthu notes.

"The biggest benefit of having a specialist partner for formulation development is the experience and scientific knowledge that can be applied to the benefit of our clients,"

Hawe summarizes. “However, formulation development is not just a strategy. Specialized analytics, dedicated methods, and excellent scientists to run them are all required and are assets an experienced partner can provide.”

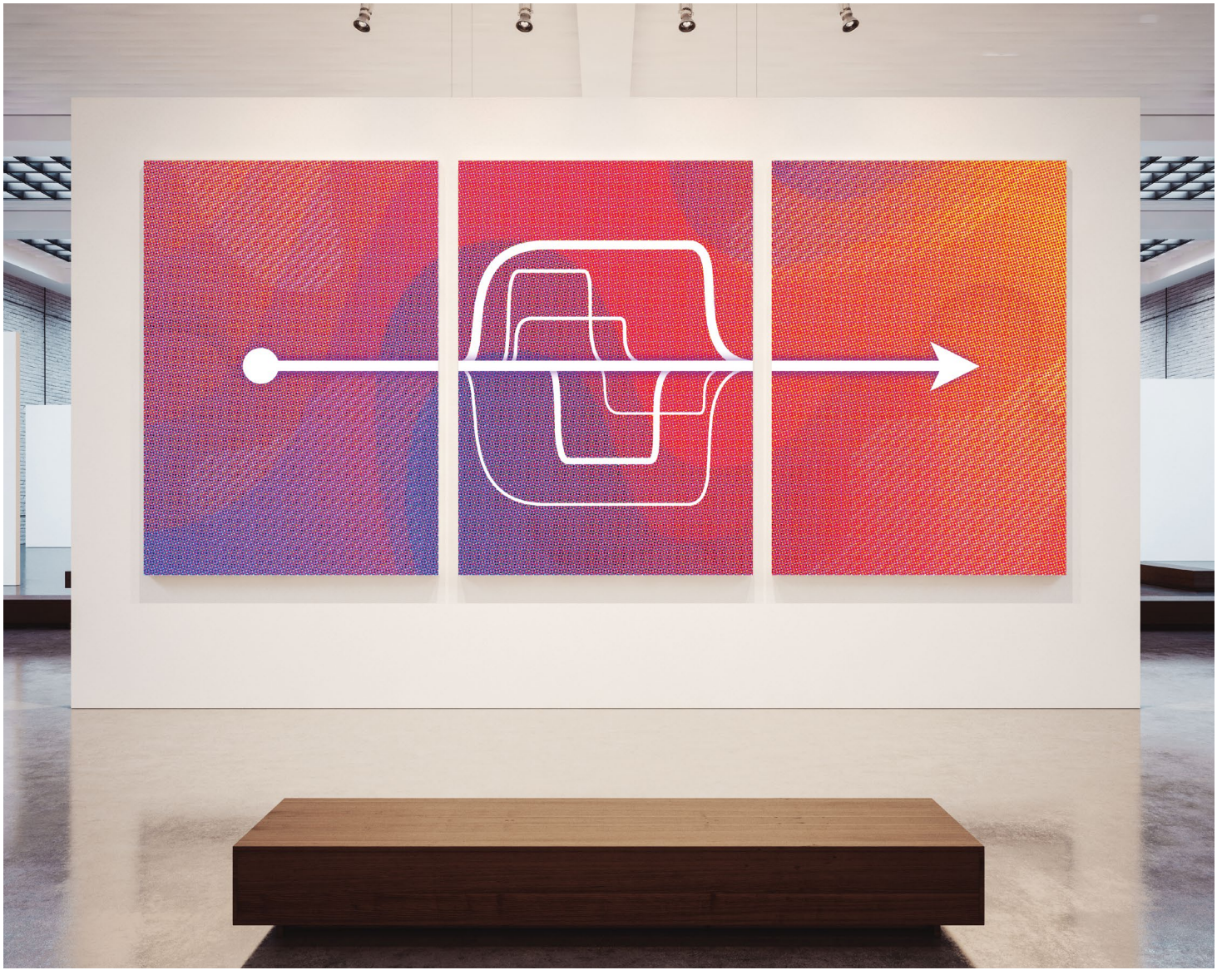
Reference

1. Rentschler Biopharma, “2018 Survey: Formulation in the Drug Development Process,” Industry Insights, rentschler-biopharma.com, Nov. 6, 2018.

Felicity Thomas

European Editor
Pharmaceutical Technology

This article was first published in *Pharmaceutical Technology*, 44 (10): 16–19 (2020).



BRINGING NEW DRUGS & THERAPIES TO CLINIC IS SCIENCE. SOLVING COMPLEX CLINICAL SUPPLY CHALLENGES IS ART.

Bringing tomorrow's innovative treatments through successful clinical trials takes robust pharmaceutical science and the art of successfully orchestrating complex and dynamic clinical manufacturing, supply and logistics across the globe.

Catalent's integrated single-source solutions, global network and comprehensive capabilities will simplify, accelerate and de-risk your unique trial needs for small molecule treatments, biologics, or cell and gene therapies.

CLINICAL SUPPLY MANAGEMENT | COMPARATOR | MANUFACTURING & PACKAGING | STORAGE & DISTRIBUTION

Catalent® CLINICAL SUPPLY

WHERE SCIENCE MEETS ART.

US + 1 888 SOLUTION (765-8846) **EUR** 00800 8855 6178 clinical.catalent.com

Putting the Patient at the Heart of Dosage Form Design

Felicity Thomas

Dosage form priorities are shifting to focus on user-friendliness, leading to greater engagement with outsourcing partners earlier in development timelines.

Research investment in the global biopharmaceutical market helps to drive innovation and development of novel therapeutic products to treat many diseases and illnesses. According to recent figures highlighted by the International Federation of Pharmaceutical Manufacturers and Associations, there are currently more than 8000 compounds in development around the world (1).

"A recent market report has shown that there was an influx of new products in the pipeline at all stages of clinical development during the 2020/2021 period (2), especially of early-stage clinical products," notes William Chin, manager, global scientific affairs, Catalent, citing recent research studies. "Moreover, cancer, infectious diseases, and diseases of the central nervous system came up as the top areas of clinical trial activity last year. The number of people suffering from these chronic conditions is expected to rise as population growth is anticipated in many developing countries (3). The development of

complex dosage forms is also expected to grow in parallel to increased diversity in the drug pipeline."

Key Trends

Over the past five to 10 years, the low water solubility of new molecular entities (NMEs) has been a major drug product development challenge, emphasizes Julien Lamps, product manager, Lonza Capsules and Health Ingredients. "Knowing the solubility performance attributes for the compound is important as it will aid selecting the right dosage technology," he says.

"There have been numerous developments and innovations in drug delivery over the last few years to overcome challenges with products and formulations, such as biologics and complex entities like larger molecules," adds Jnanadeva Bhat, head—formulation R&D (Pharma and Nutra), ACG Group. "Other trends that have evolved are prefilled syringes, wearable injectors, and needleless syringes, each of which have a niche market."

Considering the route of delivery, Chin states that injectable dosage forms are dominant in the development pipeline. "The intravenous route [is] seen to offer more advantages in early-stage studies as a means to quickly deliver the desired concentration of drug to the target via systemic circulation, and to achieve the required pharmacological response," he confirms. "However, simply having injectables may no longer be sufficient anymore because of the growing demand for more patient-friendly formats, such as oral solid dosage (OSD) forms."

Bhat concurs that even though the sector for specialty products has witnessed growth, OSD forms have remained steady throughout the past decade. "There is demand for continuous innovation to improve efficacy, efficiency, and competence in [oral solid] dosage forms," he says. "Developing novel and more efficient oral delivery routes also helps brands reach a larger audience. Thus, development scientists prioritize OSD forms because not only are they key to patient compliance, but they also have broad application."

The growing demand for OSD forms has driven innovators to focus on patient-centricity early on in development, Chin continues. "This [trend] is especially true in the past year, where there has been an expectation to increase both the convenience of use and the therapeutic efficacy of the drug product, as well as ease of deployment without the need for cold-chain considerations, especially given the current focus on oral COVID-19 vaccine development," he states.

"In biologics and small molecules, the trend shifted towards patient centricity," adds

Tatiana Nanda, director and program leader, The Center for Breakthrough Medicines. "Historically, the sole focus for drug product development was effective treatment of the disease while now additional emphasis is put on patient experience and quality of life during treatment."

Focusing Priorities

"As innovators are focusing more on solutions that allow them to develop patient-centric drug products, the priorities of drug development are expected to not only demonstrate clinical efficacy and safety in patients, but also to address key challenges such as improving usability, bioavailability, stability, and palatability, while eliminating any variability due to food effects," confirms Chin. As a result of this shift in priorities, advanced dosage forms, such as modified-release products, multiparticulates, ODTs, or new fixed-dose combinations, are increasingly in demand, he adds.

Dosage form priorities have certainly been adjusted, Lamps specifies, with the deployment of common strategies and platforms that help to enhance drug oral bioavailability, such as cosolvents, salts, surfactants, particle size reductions, polymorphs, lipid-based systems, amorphous solid dispersions, and so on. "Additionally, it is becoming a best practice to evaluate the end dosage form earlier in the development cycle," he adds.

"Drug product design is more focused on meeting patient-centric target profiles and has become the goal for drug companies," agrees Nanda. "Previously drug product profiles were a derivative of what upstream/downstream capabilities allowed. Now the selected profile and dosage form drive the required API process, needed concentration, and purity."

The priorities of pharmaceutical companies have shifted as a result of the drive toward patient centricity, Bhat concurs, with manufacturers seeking the most patient-friendly form that supports maximum therapeutic efficacy and safety of the formulation. "Regulatory bodies also encourage patient-centric dosage forms, which fuels this new focus," he says.

Additionally, the change of priorities for development have led to the integration of patient-centric design early on in the development cycle, Bhat continues. "The physicochemical properties of an API usually point the formulator to the most suitable route of administration, as well as dosage form. The solubility of APIs specifies approaches for dose selection, excipient selection, and stability of the final product," he says. "Bigger challenges are observed for larger molecule oral absorption, which need to be addressed adequately by formulation scientist."

Discussions between innovators and contract development and manufacturing organizations (CDMOs) on dosage form design are taking place relatively early on now, Chin states. Furthermore, manufacturability of the dosage form is

being addressed earlier on by innovators, which is an aspect that has received less attention historically speaking, he notes. "Innovators have recognized that a druggable molecule alone does not automatically imply successful commercialization of a pharmaceutical drug product, but that there is also a need at an early stage to establish all other key considerations that will meet the target product profile covering patient and manufacturing requirements," Chin says.

Taking patient opinions and assessments of dosage forms into consideration during design and development can also help to create user-friendly products, Bhat highlights. As patient-centricity is becoming more prominent, so too are tailored dosage forms, which directs the industry away from a one-size-fits-all approach in terms of dosage forms, he explains. "With this trend, dosage forms will perform more effectively for individuals, and this is shifting pharma R&D towards new pathways," Bhat says.

Important Innovations

For Bhat, some of the most important innovations in drug dosage forms have been seen in the area of inhalation. "Local inhalation administration delivers sufficient levels of drug to the target organ, the lungs, while minimizing systemic exposure and side effects (primarily due to the reduced drug dose needed as compared to oral administration)," he says.

"Additionally, there is mounting interest in the inhalation segment, where conventional molecules are converted into inhalation formulations," Bhat continues. "In this area, dry powder inhalation formulations via hard capsules is a trend formulators and manufacturers are showing great interest in. Capsules are not only robust and easy to use, but also help with effective delivery through the inhalation devices."

Capsule-based dry powder inhalation (cDPI) formulations offer an affordable option that incorporate characteristics—such as reduced dosing frequency and side effects—and easy administration, which are preferable for patients, Bhat asserts. "The most impressive developments taking place in this field go beyond conventional respiratory therapeutic segments," he says. "Many leaders are exploring cDPI for other therapeutic segments like Parkinson's disease, migraine, tuberculosis, cystic fibrosis, and lung infection."

Techniques, such as particle size reduction, spray-dried dispersions, and lipid-based formulation platforms, have helped overcome solubility-related issues, Lamps states. Additionally, as the techniques are complementary, they are applicable to a broad compound space, he says.

For large molecules, being able to reach high protein concentration and co-formulating with dispersion enhancers, such as hyaluronidase, has been a significant advancement, reveals Nanda. "[This innovation] allowed delivery of a high volume—up to 20 mL—of drug product as a single injection into subcutaneous space," she stresses.

"A rising demand for tailored or customized formulations and precision medicine will greatly impact drug dosage form development in the near future, according to Bhat."

However, it is also important to consider innovation from the perspective of manufacturing, rather than just on new technologies that are centered on the discovery and development path, Chin emphasizes. "For example, one of our core expertises is in manufacturing softgel dosage forms for both immediate- and modified-release applications. The typical development option for a modified-release softgel is through the formulation of the fill content followed by the coating of the capsules," he says. By using a proprietary modified-release softgel capsule, which combines pectin and gelatin, a separate capsule coating step can be avoided, Chin adds.

"The capsule technology allows innovators to design the delayed-release profile to be incorporated directly into the softgel capsule shell, thereby making a separate capsule coating step unnecessary," Chin continues. "This [innovation] reduces manufacturing time and yield loss and eliminates potential quality issues associated with coated softgels."

Market Drivers

"An important driver that could steer the dosage form market is the increasing demand for solutions that could overcome cold supply chain bottleneck constraints, especially given the current focus on vaccine development for COVID-19, as most vaccines are available as solution for injection that require ultra-cold chain storage," Chin asserts. "A lot of effort and investment will be made to develop an alternative dosage form that could effectively deliver such biomolecules via the oral route. If this alternate dosage form could not only overcome enzymatic and permeability barriers, but also ensure stability and biological activity without the need for ultra-cold storage solutions, this could be expected to positively impact the global pipeline in the coming years."

A rising demand for tailored or customized formulations and precision medicine will greatly impact drug dosage form development in the near future, according to Bhat. "The increased focus on patient centricity will certainly lead the development pipelines away from a generalized approach to more individualized treatments," he stresses. "[This shift] will also allow for the creation of more innovations in combination delivery to achieve better dose compliance by minimizing the number of medicines that need to be taken separately."

For example, combining dosage forms in one hard capsule is a possible option, Bhat adds. "Pellet technology, or minitablets, are a great example of converting conventional technology into personalized solid oral dosage form," he says. "Minitablets can be

filled in capsules as it is relatively easy to blend them together to attain combinations of multiple drugs in accurate doses and with different release profiles, if required. This solution is customized and user-friendly as it will reduce the dose regime."

In Lamps' opinion, lipid-based formulations will continue to impact dosage form developments in the future by addressing the solubilization challenge. "As [the technology] maintains solubilization during the dispersion/digestion step in the gastrointestinal lumen, it's favoring efficient diffusion through the mucus layer to reach the intestinal epithelium," he explains.

Additionally, amorphous solid dispersions (ASDs), which dissolve rapidly to higher concentration than crystalline forms and maintain supersaturation in the intestine, promoting drug absorption, will impact dosage forms in the future, Lamps continues. "[ASDs] broad applicability, flexibility, and quenching rates makes them amenable for high-dose compounds," he says.

A high priority effort for many drug developers is the creation of an appropriate dosage form for cell and gene therapies (CGT), Nanda specifies. "Formulation and manufacture of CGT drug products represents specific challenges not encountered by small molecules and biologics," she says. "Early-phase clinical trials for advanced therapies are rather complex and include wide dose ranges. It becomes extremely important to introduce a proper, robust formulation for CGT therapies early on, to be able to accommodate an intended route of administration, indication, and dose level."

"A high priority effort for many drug developers is the creation of an appropriate dosage form for cell and gene therapies (CGT), Nanda specifies. "

Although CGTs are still only administered in a clinical setting, the requirement for an optimal dosage form is just as critical as it is for therapies (large and small molecule) that are administered at home, Nanda emphasizes. "Both healthcare professionals and patients greatly appreciate using a therapy that allows a streamlined and simple administration, reduces the number of doses, or does not require specialized surgical instrumentation for delivery," she says. "CGTs will require significant development in the container closures most suitable for efficient storage and shipment and convenient withdrawal for administration. Continued innovation of novel devices and adaption of existing platforms will also help enable advanced (tissue specific) therapy delivery."

References

1. IFPMA, "The Pharmaceutical Industry and Global Health: Facts and Figures 2021," ifpma.org (April 2021).
2. K. Sedo, "2020 Global Drug Delivery & Formulation Report: Part 4, The Drug Delivery

and Formulation Pipe-line," PharmaCircle LLC (June 2021).

3. PricewaterhouseCoopers, "Chronic Diseases and Conditions Are On the Rise," pwc.com [Accessed July 12, 2021].

Felicity Thomas

European Editor
Pharmaceutical Technology

This article was first published in *Pharmaceutical Technology*, 45(8): 16–20 (2021).

Who, When, Where & How? The Key Clinical Supply Issues Sponsors Should Consider with their CRO

Karl Buer

A discussion of the key issues sponsors should consider to help their CRO or partner of choice better understand their clinical supply needs.

The global contract research organization (CRO) market is expected to grow by over 8% (CAGR, 2019-2024) to reach $63.83 billion.[1] As sponsors increasingly look to CROs to support their clinical studies, many of which have evolved over the last 25 years from simple, single-country studies to become progressively global and complex, understanding the clinical supply considerations which need to be addressed at the outset can reduce the risk of unforeseen delays and cost overruns later.

Roles and Responsibilities

Clear communication between sponsors and their CRO, or partner of choice, is necessary so that all parties understand and acknowledge the role each will play. For example, sponsors should be able to identify who will act as their project's Clinical Supply Manager (CSM) and be responsible for managing the outsourcing of clinical supplies, demand forecasting and oversight throughout the study.

SPONSORED CONTENT

Questions You Need To Ask About Clinical Supply

Sponsors should also ensure they understand which party will act as Importer of Record (IoR) and therefore be held responsible for ensuring the importation of goods complies with all applicable local trade laws and regulations, as well as managing the related documentation. As studies become increasingly global, it's particularly important for sponsors to understand who will be the IoR as eligibility to perform this role can vary—some countries stipulate that only the sponsor may act as IoR while others will permit a third party to act as IoR on the sponsor's behalf.

Additionally, it is important to determine which party will oversee the Interactive Response Technology (IRT) set up. The CSM should be involved in this process as early as possible as well. Simulation tools used in the planning of the study should be interfaced with the IRT system as it is important to ensure that both systems use common data, language and terminology. For example, problems can arise if the systems use conflicting date formats, as the dates logged in each system could inadvertently appear to be different. Making sure the language is mirrored in both systems is of fundamental importance in ensuring the study timelines are not negatively impacted due to miscommunication or misunderstandings. Early and frequent communication during the IRT set up process can prevent unnecessary rework later.

Protocol Design

Clinical trial supply management can be challenging due to its many moving parts. As trials become more global, supplies need to be divided among many regions and countries. Added to this, the studies themselves are becoming increasingly complex; studies that were separate in the past are being combined into a single study or utilize advanced protocol designs. Accordingly, sponsors should understand that study design can have a major impact on deciding which clinical supply strategy should be used and that this must be taken into their planning and discussions with their CRO or other partners. For example, for adaptive trial design, which "allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial,"[2] sponsors should ask their CRO or partner what potential clinical supply changes would be needed during the study. For instance, if the interim data in an adaptive trial suggests that patients require a 5mg daily dose, will there be sufficient product to support the patients for the remainder of the study? However, if the interim analysis instead shows that the patients require 10mg, consisting of two 5mg tablets daily, at what point would an additional packaging campaign be required? Failing to consider the potential changes resulting from a sudden

"Sponsors should check with their CRO that sufficient lead time has been built into the project plan for clinical supplies as manufacturing and procurement times need to be factored in, too."

shift in supply needs could incur the sponsor additional costs or time delays, sometimes significantly so.

At the beginning of a study, it is not uncommon for the list of countries and planned clinical sites to still require finalization. As the study progresses it may reveal certain important trends that can have direct correlation with supply needs, such as the enrollment rate—the rate at which clinical sites and countries are able to enroll patients. Though a relatively rare occurrence, the enrollment rate may prove to be faster than expected, so the sponsor should check that their CRO or partner is able to ensure there is a timely resupply of the drug product available at the depots and clinical sites to maintain an uninterrupted supply. Equally, if the enrollment rate is slower than expected, additional sites and countries may be added and underperforming sites shut down, which could impact the depot inventory in a given region. A common strategy to mitigate some enrollment risk and avoid unnecessary cost is to take a staggered approach to activating clinical sites so as to avoid opening them all at the same time. In this instance, the sponsor should ensure their CRO or partner will undertake a thorough examination of the drug product and expiration dates, to determine if additional product will be required to replace the existing product if there is significantly more or less demand in a particular country or region.

Project Management

Clinical trials are becoming increasingly global and complex, driving the need for increased control and management of supplies. Poor or little advance planning can cause unnecessary delays to project timelines, which can be particularly disastrous for drugs that have the potential to be a first-in-class therapy, giving the sponsor a competitive advantage and more importantly, hope for patients without other therapeutic options. For simple projects, a minimum of 90 days is generally recommended to establish a clinical supply plan and deliver the initial shipments to clinical sites, but more complex projects may require lead times of six months or more. Sponsors should check with their CRO that sufficient lead time has been built into the project plan for clinical supplies as manufacturing and procurement times need to be factored in too. This is particularly important if comparator and reference products are to be used as they may have limited availability, short expiration dates, or long lead times—the latter is especially true for biologics. Similarly, there may be other components with long lead times such as booklet labels. Aside from the expected

impact to the overall project timeline, failure to give these components appropriate consideration can also impact the budget or have regulatory or logistics implications.

Clinical supply management is a continuous balancing act with managers needing to avoid unnecessary waste while also ensuring that supplies are available in sufficient quantities when and where needed. Services such as forecasting and demand planning can create a better-informed supply strategy. However, sponsors should discuss whether these services are needed for their specific study with their CRO as early as possible, to minimize any additional impact to their budget or timelines. Additionally, to increase its value to the study, any forecast should be conducted early, even before the clinical protocol is finalized. A pre-study forecast will provide the initial demand planning, help to identify critical path items and areas of risk that need to be proactively addressed and determine the overall supply requirements and necessary timeline for execution.

As trials become increasingly complex, sponsors may need to use newer, more advanced clinical supply models such as a demand-led approach, of which forecasting is a critical component, but it is important that sponsors check with their CRO as to the specific requirements of their study as early as possible. To avoid any potential impact to their budgets, delays to project timelines or logistical or regulatory issues, sponsors should work with their CRO to ensure they understand who will assume the required roles and responsibilities, key dates and milestones, the services required and the supply chain implications of the trial designs that may be used. Identifying any potential challenges early on will help to ensure projects get off to a good start and are able to run as smoothly as possible.

References

1. Frost & Sullivan. (2021). Hybridization of Clinical Trial Designs Reviving Global CRO Market Postpandemic; 2019-2024. http://frost.ly/4h3
2. U.S. Food and Drug Administration. (2019). Adaptive Designs for Clinical Trials of Drugs and Biologics: Guidance for Industry. https://www.fda.gov/media/78495/download

Karl Buer

Regional Sales Director,
Clinical Supply Services
Catalent

Catalent®
CLINICAL SUPPLY

supplying clinical trials of the future.
ready today, innovating for tomorrow.

We have the passion to reliably supply comprehensive clinical trial solutions with flexibility & speed around the world.

Small Molecule & Biologics | Forecasting & Planning | Manufacturing | Packaging & Labeling | Logistics & Cold Chain | Comparator Sourcing

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™

US + 1 888 SOLUTION (765-8846) **EU** 00800 8855 6178 clinical.catalent.com