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Bio/Pharma Outsourcing
Innovation 2022

Analytics
Analytical Methods and Bioassays

Development
Method Development
Formulation Expertise

Manufacturing
Expanding Capacity
Spray Drying

Quality/Regulations
Orphan Drugs
OPTIMIZED DRUG SOLUBILITY AND STABILITY
Captisol is the trade name for Ligand’s solvent-free processed modified cyclodextrin preparation. Captisol is a patent-protected mixture of chemically modified cyclodextrins with a modifying structure to optimize drug solubility and stability. Captisol was invented and developed by scientists at the University of Kansas’ Higuchi Biosciences Center specifically for drug development and formulation.

Captisol overcomes solubility and stability hurdles faced during each phase of development. Captisol can make a substance more soluble and an agent more stable. Captisol can convert a solid to a liquid or an oil to an aqueous solution. Combinatorial chemistry, high throughput screening (HTS), and molecular genetics have led to an increase in the number of insoluble and unstable molecules, peptides, and proteins being investigated for their therapeutic activity. There are currently more than 50 Captisol-enabled products in clinical development. This unique technology has enabled several FDA-approved products, including Amgen’s KYPROLIS®, Baxter International’s NEXTERONE®, Gilead’s VELCLURY®, Acrotech Biopharma L.L.C.’s and CASI Pharmaceuticals’ EVOMELA®, Melinta Therapeutics’ BAXDELA™ and Sage Therapeutics’ ZULRESSO™. There are many Captisol-enabled products currently in various stages of development.

SEAMLESS TRANSITION TO CLINICAL TRIALS
Captisol may increase systemic exposure for toxicology studies of investigative compounds and has a proven clinical safety record. In early development, captisol formulation can lead to a seamless transition from nonclinical safety to clinical trials. Captisol-enabled products are approved in more than 60 countries.

MULTIPLE ADMINISTRATION ROUTES ENSURE TARGETED DELIVERY
Captisol’s chemical structure was designed to create new products by improving solubility, stability, bioavailability, and dosing of active pharmaceutical ingredients. Routes of administration investigated include parenteral, oral, ophthalmic, nasal, topical, and inhalation products. Once inside the body, captisol releases the drug agent, which then travels to its target. The interaction between captisol and the agent is not permanent, and captisol is safely expressed from the kidneys.

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Of all modified cyclodextrins, Captisol is an ingredient in the most approved products in the U.S. Manufactured under cGMP, at multiple locations, using a patented and validated all-aqueous process, annual manufacturing capacity is being increased to 500 MT. Captisol is supplied in ultralow endotoxin, ultralow bioburden, low-chloride forms in 100g, 1kg, 5kg and 20kg packages for R&D use. Commercial pack sizes include 1kg, 5kg, and 20kg, with the ability to fill metric-ton orders.
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A nalytical methods and bioassays require a well-thought-out manner of evaluating method validity (truthfulness) and systems suitability (a known positive control) to ensure the method is correct, reliable, and can be used to determine the value of the unknown test article. This paper recommends and explains methods for evaluating system suitability as well as validity criteria. Further, the paper discusses practical and phase-appropriate methods for setting limits for systems suitability and validity criteria.

In alignment with guidances such as International Council of Harmonisation (ICH) Q2 (1), United States Pharmacopeia (USP) <1033>, <1032>, <1225>, and ICH Q6B (2), method development, validation and method understanding is a critical element of product measurement and control. Systems suitability should be understood to be separate from validity criteria. Systems suitability is defined as a known positive control that can be demonstrated to be within a defined set of limits. Validity criteria typically includes signal control for bioassay criteria for parallelism and linearity, and criteria for repeatability. It may further include a fixed number of outliers for data management.

**Systems suitability**

There are two methods for systems suitability. The first method involves adding a positive control to the assay run. The positive control is a known standard at a fixed concentration. By adding the known standard to the plate and checking if it is within a defined limit, one can trust that the method is running correctly, and the test article may be reliably determined. The second method requires use of a standard curve. A standard curve or calibrator has a known value and is placed on the plate at three or more concentrations; a curve is then fit to the data. By measuring the concentration at a fixed position on the standard curve, one can use that data for systems suitability. The standard curve approach has a distinct advantage in reducing the analytical error of the quantitation of the positive control. It is not recommended...
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to use a calibrator and then add the positive control to a plate, however, as this doubles the analytical error. Figure 1 shows the systems suitability back-calculated from a fixed position on the reference standard.

Validity criteria for signal control
Before relative potency of a test article to a reference standard can be calculated, it is crucial to verify that there is a clear signal from the dose response for the reference standard. There are two methods for verifying a reliable signal: the dose response test and curve depth.

Based upon health authority input, the dose response test is a standard approach to show signal-to-noise control. The dose test measures the effect of analyte concentration, which is used to generate a statistically significant signal (alpha = 0.05, two-sided). A regression model may be linear, square root, log, three parameter exponential model, or four parameter logistic regression (4PL), depending on the method.

The curve depth of the reference standard is another method to demonstrate a clear signal. Curve depth is the mean signal for the highest concentration subtracted from the mean signal from the lowest concentration. For assays using 4PL fit, curve depth is calculated by subtracting the lower asymptote of the standard from the upper asymptote of the standard (Figure 2). Normally the limit is set at 50% of the curve depth from qualification or validation assay runs.

R² of a fitted curve is not recommended for a validity criterion, but should be for report-only. Confidence intervals (CIs) of the reportable value are a more reliable indication of the errors in quantitation due to curve fitting.

Systems suitability should be understood to be separate from validity criteria.

Validity criteria for bioassay parallelism
USP <1032> defines parallelism as the following:

“A quality in which the concentration–response curves of the Test sample and the Reference Standard are identical in shape and differ only by a horizontal difference that is a constant function of relative potency” (3).

Parallelism must be evaluated as a validity criterion because parallelism between the test article and reference standard demonstrates that the two are similar, and, therefore, relative potency may be determined. F-tests for parallelism are not recommended because they are too sensitive and may cause a high degree of invalid results.

Demonstrating parallelism in a bioassay is done for a sigmoidal curve and may be evaluated using the upper asymptote ratio (UAR). The UAR is compared to a two-sided limit. If the ratio of the upper asymptote for the reference standard and the UAR for the test article is within defined limits, then the curves can be constrained, and relative potency can be calculated. UAR only checks parallelism at one point on the sigmoidal curve. Slope ratios may be used for a parallel line analysis of the reference and test article. A highly recommended method for determining parallelism is the absolute difference between the relative potency of the unconstrained model and the constrained model. This measures how the forcing function of constraining the curves changes the reported relative potency.

An equivalence test may be used in evaluating the UAR. If the slope ratio is outside of the equivalence bounds, the assay run fails parallelism and is invalid. Figure 3 is a parallelism test example with a resulting slope ratio of 0.993.

Linearity ratio calculation for bioassays
A bioassay also has a requirement to be linear in the dose response. The Linearity Ratio method of analysis uses a measure of curvature relative to the linear line rather than a measure of probability by comparing the effect size attributed to the quadratic term (curve) to the effect size attributed to the linear term in the full model. In practical terms, the question of linearity is, what percentage of the linear line is curvature?

A scaled estimate for the linear term is half the change in the signal over the range (distance from center). To determine the full change over the range linear effect of concentration, it must be multiplied by two. The quadratic term is curving and ½ the range is the full curvature, which is then divided by full change in the linear signal.
In order for an analytical method to be validated, it must be shown to be repeatable at the moment of measurement (4). Before evaluating repeatability, outliers should be removed from the assay run or run of the analytical method. Jackknife $z$ is the preferred method of outlier identification within each dose. Jackknife $z$ is calculated independently for each concentration in the dose response for both reference and sample type. Jackknife $z$ evaluates the influence each point is having on the curve fit where each point is removed from the model; the model is regenerated and evaluated, iteratively, for each data point. Jackknife $z = (\text{measurement} - \text{dose mean} (\text{measurement removed}))$ - Standard deviation (measurement removed).

CIs should be included when reporting the results for any and all test articles. CIs control for sample size, variation in the method, and risk (95%). CI range is calculated by taking the difference of the upper confidence limit of the constrained relative potency and the lower confidence limit. A narrower CI range indicates that the assay is less variable and, therefore, more repeatable. Excessive CI range may not make the assay run invalid; it demonstrates that additional assay runs are required to tighten the error. Normally, the CI range is reported as a percent of tolerance (Equation 2):

$$\text{CI Range} \% \text{ of Tolerance} = \frac{\text{CI Range}}{\text{USL} - \text{LSL}} \times 100$$  \hspace{1cm} [\text{Eq. 2}]$$

where USL is upper specification limit and LSL is lower specification limit. The coefficient of variance (CV) is often used to evaluate repeatability of the dose response. CV is not recommended for use because it incorrectly scales the analytical error by concentration; high concentrations appear to have low error and low concentrations seem to have high error.

**Setting systems suitability and validity criteria limits**

When setting specification limits based on the representative sample, risk must be considered. The wider the interval,
Tolerance intervals were developed to provide a correction for
the Y response. K sigma is used when the sample size is 30
or more, and tolerance intervals are used when the sample
size is less than 30. Before setting limits, a representative
data set must be available. Systems suitability and validity
criteria limits are normally set post-qualification and review
and finalized post-validation of the method (5).

The curve depth of the reference standard
is another method to
demonstrate a clear signal.

K sigma or tolerance interval approach.
Tolerance intervals were developed to provide a correction for
limited sample sizes and scales. The interval of risk is based
on three considerations: sample size, confidence interval, and
proportion of the population to be described.

Tolerance intervals should be used under the following
conditions:
• No transfer function is available and/or possible
• No adverse nor unacceptable results are associated
  with the parameter or response
• When n => 30, use K sigma in setting limits
• When n < 30 use tolerance intervals
• Sample data are stable (use a control chart or regres-
  sion analysis to evaluate stability)
• Distribution is either normal or nonnormal.

The procedure for setting limits are as follows:
• Generate a distribution histogram (Figure 4)
• Make sure there is a representative sample of the assay
  validity or systems suitability measurement.
• Check data for outliers. Jackknife z and three sigma
  cut point is typical.
• Determine the distribution that best fits the data, nor-
  mal or nonnormal distribution, use a goodness of fit
  or second-order Akaike’s information criterion
  (AICc) functions to determine the best fit.
• Avoid using Johnson or Sinh-Arcsinh (SHASH) distri-
  butions when fitting nonnormal tolerance intervals as

Figure 4. Distribution-based limits.
they set limits excessively wide. Normal, Gamma, Weibull, Lognormal, Normal Mixture are preferred and should all work well to set limits.

- Use Table I to determine the risk and associated tolerance interval and margin.
- Use a K Factor calculator (6) to determine K for the interval (sample size, confidence level and population) for any tolerance interval.
- Set Spec using K sigma to define the limits.
- Examine results and document limits, update any standard operating procedures or calculators with the defined limits.

### Conclusion and summary

Using the correct methods for evaluating systems suitability and acceptance criteria is critical to ensuring that the analytical methods is fit for use. Setting specification limits as described is statistically rigorous, scientifically sound, and defensible upon regulatory review. Table II is a summary table of all criteria and recommended limits.

### References

1. ICH, Q2(R1) Validation of Analytical Procedures: Text and Methodology, Step 4 version (November 2005).
2. ICH, Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, Step 4 version (March 1999).
5. USP, <1033>, "Validation of Biological Assays,” (Rockville, Md., 2010).
According to market research, the size of the outsourcing sector serving the pharmaceutical and biotechnology industries is expected to expand, reaching $99.4 billion by 2028 (1). Demand for outsourced services is being driven by several factors, such as high demand for biologics and small molecules, a lack of in-house expertise, and rising costs associated with in-house development capabilities.

To find out more about how demands have changed for outsourcing partners providing method development services and the trends affecting this sector, Pharmaceutical Technology spoke with Jerry “Jr.” Mizell, senior director, Analytical Services, Metrics Contract Services.

**Changing demands**

**PharmTech:** Could you provide a brief overview of how the demands have changed over the years for outsourcing partners in terms of method development services?

**Mizell (Metrics Contract Services):** Nowadays, there is an increased demand for sound methods to be developed early in the product life cycle. More customers want rugged and robust methods in place as early in the development process as possible, and they want methods that require minimal changes as their programs advance to commercial phases.

Based on the experience of Metrics Contract Services, customers also want to develop quality control (QC)-friendly methods that help maximize laboratory efficiency in the commercial phase. Across various methods developed in recent years, dissolution, in particular, has been in the spotlight. A comprehensive approach to dissolution should produce a discriminating method that can demonstrate that an adequate drug product has been manufactured. Current customer expectations also demand a detailed dissolution method development report describing how the dissolution procedure was derived. This is especially important for new drug applications (NDAs).
COVID-19 disruptions
PharmTech: How has demand of outsourced services for method development been impacted by the COVID-19 pandemic?
Mizell (Metrics Contract Services): While we haven’t experienced a direct uptick in development services requested because of the COVID-19 pandemic, we have experienced supply chain challenges as a result of it. The delays and disruptions to key supplies have made it imperative to execute method development in the most effective means possible to align with clinical timelines.

“There is an increased demand for sound methods to be developed early in the product life cycle.”
—Jerry “Jr.” Mizell, Metrics Contract Services

Choosing a method development partner with vast experience and a proven track record becomes invaluable to customers who need to deliver treatments to patients at speed, while also ensuring that key project deliverables are met.

Call for experience
PharmTech: Have there been changes in expectations as to what an outsourcing partner should be able to provide or accomplish with method development services?
Mizell (Metrics Contract Services): The outsourcing partner, or contract development and manufacturing organization (CDMO), should have a vast array of development experience in solid oral dosage formulations. This experience will allow for expedited development services, especially when challenging formulations are being developed. These challenging formulations may include API loaded on resin or beads and molecules that do not contain chromophores, requiring alternative modes of detections.

CDMOs with experience in charged aerosol detection, evaporative light scattering detection, and refractive index detection for challenging molecules can be the deciding factor in awarding a project. Outsourcing partners with mass spectrometry (MS) capabilities are also at an advantage when impurity issues arise and identification is needed. Cost can be a primary focus for some programs; however, quality assurance and the ability to meet deliverable timelines are also very important qualities, which can often outweigh price differences.

Present and future trends
PharmTech: What other trends have impacted outsourced method development in recent years?
Mizell (Metrics Contract Services): Over the past few years, there has been an increase in the development of poorly soluble small-molecule drug products, which can be extremely challenging when developing a dissolution method. This type of program is challenging because introducing two APIs into the same formulation and combining products, with significantly differing physical and chemical characteristics, means that method development can take on a new level of difficulty.

From a safety perspective, highly potent APIs (HPAPIs) introduce additional challenges, as developers want user-friendly methodologies in place without jeopardizing laboratory staff safety.

PharmTech: In your expert opinion, what trends might we expect to see in the future and why? Also, how might outsourcing partners be best prepared for future demands/industry trends?
Mizell (Metrics Contract Services): There should be more and more Biopharmaceutical Classification System Class II and IV molecules being discovered for evaluation. Customers should seek outsourcing partners with extensive experience in dissolution development and alternative mode of detection in the event that a molecule does not contain a chromophore. Instrumentation must remain compliant with current industry standards to ensure method expectations are met.

“There is an increased demand for sound methods to be developed early in the product life cycle.”
—Jerry “Jr.” Mizell, Metrics Contract Services

There is also an expectation that future demands will call for methodology development for nitrosamine assessments, and the ability to meet FDA (and other regulatory bodies’) requirements for NDA filings and current commercial products on the market. This methodology requires MS, which if not currently available at a CDMO, may become a worthwhile investment to offer to customers. As with elemental impurities, this requirement will not go away and will only face increased scrutiny as time passes.

Reference
By the year 2026, the global outsourcing market for formulation development is expected to reach a value worth $12.65 billion, growing at a 7.2% compound annual rate (1). Factors driving this market growth include the rising demand for innovation of novel drugs due to the increasing number of patent expirations for major drugs and the fact that many pharmaceutical and biotechnological companies are trending toward outsourced services for formulation development (1).

To learn more about outsourced formulation development services, including various industry trends impacting the sector, challenges for outsourcing partners, and key benefits for outsourcing formulation development, Pharmaceutical Technology spoke with Lynn Allen, vice-president of Business Development at MedPharm.

Industry trends
PharmTech: Could you provide insights into industry trends that have affected the formulation development outsourcing market?

Allen (MedPharm): The pharmaceutical industry continues to adapt to new business conditions. Life cycle management continues to drive the need for outsourced formulations, often in developing products for alternate routes of delivery.

Companies that are looking to improve patient compliance or reduce systemic side effects can look at new formulations for local delivery through topical dosing. Based on MedPharm’s experiences, there have been increases in the demand for formulation services of ophthalmic preparations and respiratory delivery, primarily intranasally. An increase in the number of biologics with targeted topical delivery routes has also been a trend. As a contract development and manufacturing organization (CDMO) that specializes in dermatological, nail, eye, airway, mucosal membrane, and otic product development, MedPharm continues to support topical formulation development services for local delivery market needs.
Additionally, proprietary nonclinical models that test formulations for effectiveness at early stages continue to be an asset to the company’s client base. For example, MedPharm’s reconstructed human nasal epithelia model is a living representation of the nasal membrane, and allows formulations that are targeted for the different regions of the nose (local, systemic, or brain) be tested to evaluate formulation parameters such as delivery, irritancy, mucoadhesion, and effectiveness.

**Growth areas**

**PharmTech:** What type of formulation work is more commonly outsourced currently?

**Allen (MedPharm):** There is continued growth in product development by specialty and virtual pharmaceutical companies. As large pharma looks for investments in late-stage assets, start-up companies that effectively deliver well-developed products with effective clinical data are highly sought out for licensing and acquisition deals.

Consequently, start-up companies require formulation expertise at the earliest stages of development and often do not have extensive research labs to perform critical assessments such as screening multiple APIs. Outsourcing of these early research activities continues to grow, and MedPharm continues to invest in these services to support both early start-up and specialty pharma companies.

**Biggest challenges**

**PharmTech:** What are the biggest challenges for outsourcing partners when working on a formulation project?

**Allen (MedPharm):** In the fast-paced environment of drug development, it can be challenging to ensure that all stakeholder needs are being articulated at the start of formulation activities and continue through the development process. When sponsors have not conveyed all needs or if they are not prepared to make decisions on formulation priorities when challenges arise during development, it can often mean repeating activities or delaying timelines.

**PharmTech:** How do outsourcing partners overcome these challenges?

**Allen (MedPharm):** One key aspect that must be stressed at the start of any program is the necessity of a well-defined target product profile. The key attributes of what the formulation should achieve and, particularly in the topical space, how it should feel when applied or how it should be packaged and used by the patient are critical considerations of development. Internal expertise is also critical which includes program management, development, or regulatory resources.

**Benefits of broad experience**

**PharmTech:** What are the key benefits of outsourcing formulation development?

**Allen (MedPharm):** When formulation development is not an internal strength or if the delivery route is outside of in-house formulation expertise, the broad experience of a service provider dedicated to these services can save time, money, and avoid the pitfalls of an ineffective, poorly developed formulation. CROs [contract research organizations] and contract development and manufacturing organizations, particularly those focused on niche markets like MedPharm, have broad experience and can pull from decades of experience and current real-time learnings to guide development activities in the constantly changing regulatory environment. Service providers can also offer more dedicated resources when companies need to prioritize critical programs.

**Reference**


**Evolving Demands of Process Development Services**

Over the years and in light of various industry trends, the demands for outsourced services have increased and evolved. In this interview, *Pharmaceutical Technology* discusses how process development demands have changed for service providers with Xiaoyong Fu, PhD, chief technology officer and head of API Business, WuXi STA.

**Trends impacting process development services**

**PharmTech:** How have process development demands evolved over the years for outsourcing partners?

**Fu (WuXi STA):** Molecules are getting more complex, pipelines more diverse, and at the same time, increasing numbers of targets are on accelerated pathways. Put these factors together and there is a need for contract development and manufacturing organizations (CDMOs) that can handle integrated and accelerated pathways with a full suite of technologies from biocatalysis and flow chemistry through to crystallization and spray drying. Integrated models provide much greater flexibility and enable API and formulation teams to work side by side.

Phase-appropriate development is also often asked of many CDMOs, and this usually means running pathways sequentially. Another way timelines can be accelerated is by developing an ‘end-in-mind’ process strategy to seamlessly connect discovery, development, and commercial API needs from milligram to metric ton scale. But the CDMOs will need a large R&D team with the right expertise and a broad technology platform to ensure the most appropriate chemistry at every scale.

The final trend that is being seen and, in some ways is linked to the challenges of the pandemic, is the requirement of a partner who can ensure supply chain stability with a robust continuity business plan including multiple facilities available, technologies to avoid or minimize the use of scarce material, or even the ability to manufacture them in the event of shortages. This means forward-looking innovators are seeking backing by a contract partner that has a solid network of vetted vendors and a large chemistry organization and a diverse manufacturing and technology platform that can react and adapt quickly.

—Felicity Thomas
What Outsourcing Partners Wish You Knew

Meg Rivers

Industry experts share their top outsourcing tips from both the perspective of companies offering outsourcing services as well as for companies looking to outsource.

In the modern bio/pharmaceutical industry, countless services are outsourced, including manufacturing, process development, scale-up, regulatory compliance assistance, analytical services, software and cloud services, and much more. But what should companies looking to outsource know prior to selecting vendors and partners? In addition, what should the companies that are outsourcing services be aware of?

Pharmaceutical Technology interviewed David Heiger, associate VP, Agilent CrossLab Group; Nandu Deorkar, vice president of R&D production, Avantor; Sébastien Ribault, vice president and head of end-to-end solutions, Life Science business of Merck KGaA, Darmstadt, Germany; Angelo Filosa, PhD, portfolio director, professional and technology services OneSource, PerkinElmer; and Christoph Zehe, research fellow, advanced cell biology, Sartorius Corporate Research, on what outsourcing partners wish you knew.

What companies offering outsourcing services should know

PharmTech: What are your top recommendations for companies offering outsourcing services?

Filosa (PerkinElmer): Clearly define what you want to outsource and why. Classify activities as core to your work and non-core and then identify partners that have expertise in the non-core activities that are a strategic aspect to how you run your business so your internal team can focus on the science you are advancing.

Decide whether to insource or outsource. Once you have identified the non-core activities, then you need to decide whether they are outsourced or insourced and what needs to be supported on-site or can be done remotely. Certain activities are non-core but still must be done onsite for various reasons. This process is part of defining your outsourcing strategy and identifying the correct partners.

Determine if a vendor can grow with you. Make sure to properly evaluate vendors and understand their expertise and how they can grow with you as you evolve your out-
sourcing strategy. You might look at one service today, but [you will] likely expand the scope in the future; so, it’s important that the provider can grow with you.

**Ribault (Life Science business of Merck KGaA, Darmstadt, Germany):** *Determine the end goal and assess the team.* It is important for companies looking to outsource to define their end goal and determine their key experts and resources to reach that goal.

**Develop a step-by-step strategy.** By defining a step-by-step strategy early in the development process in alignment with quality and regulatory requirements, companies looking to outsource can foresee potential risks and challenges before they arise and help determine the best course of action to help mitigate these risks.

### Understanding what your company does best, current workload, and manpower should all be considered.

**Heiger (Agilent):** *Think ‘core vs. context.’* If what you require is absolutely core to your business, be cautious about outsourcing. But don’t build what you can buy. It’s important to distinguish between the ‘core’ and the ‘context’ from the outset. If something is core to your business, then it might be more cost-effective, efficient, and reliable to think about sourcing this yourself. Part of deciding whether to outsource will be influenced by your timeframe—are you looking for a short-, medium-, or long-term solution? This way you can determine whether it’s worth making a large investment up front to handle the operation in-house. If it’s something that is readily available and other suppliers have years of skill in that area, then outsourcing is the right option.

*Think through your business objectives to ensure you are selecting an appropriate partner or vendor for the long term.* Take the time to remind yourself of what you are trying to achieve in the first place and how these relate to your core business objectives. Having transparent conversations to ensure your vendor understands your objectives can give you a good head start. The last thing you want is to be tied into a contract if it’s wrong for your core business objectives. These objectives can be aligned with a broader vision for your business and brand. For example, you may want to partner with a vendor with similar commitments to sustainability to make your business greener. If you are committed to offering your customers highly innovative solutions, you’ll need to ensure your vendor is continuing to invest in the latest technologies the market has to offer.

**Deorkar (Avantor):** *Companies need to look beyond just unit cost.* To provide total value, a service provider’s capabilities should be understood. Like choosing a contractor, companies shouldn’t make a decision based on the cost alone. They need to make sure that the service provider can meet their needs to complete the project.

**Expectations should be clearly communicated to the service providers as early as possible.** The project requirements change over the progression of the project. Open dialogue with your service provider on any changes sooner than later would help to overcome potential delays.

**Zeh (Sartorius):** *Choose a provider with proven performance and expertise …* The capabilities and experience should be proven by a track record, which gives insight into the number of successful projects, experiences with different product types (antibodies, complex molecules, etc.), and regulatory acceptance (projects that have reached clinical phases, market approval, etc.).

**Choose a provider offering a comprehensive service and product portfolio.** It is important to keep the whole drug development process in view. A good partner should not only offer individual isolated services but provide more holistic support … Such complete solutions ensure higher success rates, shorter timelines, and simplified project management and communication.

### What companies outsourcing should know

**PharmTech:** What are your top recommendations for companies seeking outsourcing partners?

**Heiger (Agilent):** *Do what you do best.* Stay close to your core competencies and ensure a best-in-case experience for your clients.

*Consider reviewing where your team is spread too thin and not able to support what is key to your business.* Look at outsourcing as a way of taking care of operations. This is important because business can be a stressful, high-paced environment, and handing over operations to a service provider can really help to focus the team.

**Ribault (Life Science business of Merck KGaA, Darmstadt, Germany):** *Be transparent.* The customer’s molecule is often ‘the life of their company’; so, they place a significant amount of trust when handing it off to a contract development and manufacturing organization (CDMO). They want more transparency in their molecule’s complex development and manufacturing process. A key element in creating transparency is communication, and excellent partners should also be excellent communicators. This includes access to its experts when urgent matters come up, as they will.

*Become technically excellent.* A key element in the outsourcing relationship is relying on your partner to possess distinct scientific insight and expertise for your molecule’s unique journey.

*Be flexible.* A good partner should be flexible to help meet their customer’s needs so that they are successful in achieving their milestones. Having the right capabilities, capacity, and scale to meet the client wherever they are in their molecule’s journey, when and where it is needed, is critical. It sounds pretty straightforward, but many CDMOs today don’t have enough capacity or capabilities to meet their customers’ timelines.

Contin. on page s21
The COVID-19 pandemic highlighted the potential of an array of modalities within the biopharmaceutical industry. In particular, the success of messenger RNA (mRNA)-based COVID-19 vaccines has encouraged biopharmaceutical companies to explore and utilize these technologies for other diseases and look to rapidly expand their capacity and capabilities in response to an upsurge in demand.

At the end of 2019, the combined market capitalization of the five publicly listed companies focusing on mRNA platforms was $15 billion, and as of August 2021, that value of capitalization reached more than $300 billion (1). This significant boost in market valuation reflects the optimism that mRNA technology can deliver much more and go beyond the current prophylactic COVID-19 vaccines.

Preparation for this new wave of technology brought new challenges. The continued growth of biologics pipelines magnified limitations in internal manufacturing capacity, driving drug developers to partner with contract development and manufacturing organizations (CDMOs) to enlarge the manufacturing network.

CDMOs needed to expand capacities and facilities to serve the dynamic market changes. More robust technologies and cold chain capabilities had to be offered to meet the demand too.

By increasing capacity and preparing for the multi-modalities of new technologies, CDMOs have put themselves in good stead for new therapeutics on the horizon, such as mRNA treatments targeting advanced cancers and heart disease. Preparing for these advancements will ease transitions into supporting the production of cell and gene therapies (C&GTs), another key growth area for the industry in the future.

Challenges faced by CDMOs
Prior to the past decade, mRNA technologies were slow to advance and there was little investment into the area.
EXPERTISE AT EVERY STAGE OF DRUG DEVELOPMENT

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With gradual innovations, mRNA began to be considered a safe and efficient therapeutic tool in vaccine development. However, it was not until recently, with the onset of the COVID-19 pandemic, that the mRNA vaccine field quickly expanded. The need for a rapid response drove the swift adoption of these new technologies in vaccine and treatment development.

CDMOs were increasingly becoming more heavily relied upon to support the development and manufacturing of these new drug technologies. This necessitated CDMOs to rapidly prepare for improvements to accommodate mRNA manufacturing and overcome any challenges they faced in an unprecedented amount of time.

The pandemic has highlighted that foresight, careful preparation, and agility continue to be essential traits for CDMOs.

Adapting existing capabilities quickly. With an upsurge in demand for this new wave of technology, manufacturers needed to make necessary changes to their facilities and processes for them to be optimized to the product characteristics.

Cold chain capabilities had to be expanded and optimized to suit the temperature-sensitive nature of mRNA molecules. This has been achieved by investing in different types of capabilities, from blast rate freezers to control rate freezers, and offering a wide range of container storage types to best fit the needs of the product. The necessary standard operating procedures (SOPs) have also had to be put in place for each new storage capability.

The lipid nanoparticles used to encapsulate the mRNA were also unfamiliar to many manufacturers that predominantly worked with water-like solutions. Time was needed to determine how the nanoparticles would behave and how processing conditions could impact the characteristics of the mRNA products.

Balancing new and existing projects. Not only did CDMOs need to accommodate and support COVID-19-based projects, including vaccines, but they also needed to maintain the production of other medications requiring similar facilities. Ensuring sufficient capacity was, therefore, one of the greatest challenges to CDMOs during the COVID-19 pandemic.

Careful management was needed to avoid delays due to bottleneck processes and ensure sufficient capacity for the increased level of demand. Balancing these requirements also necessitated both flexibility and scalability to successfully support the development of a wide variety of essential products.

Accelerating speed to market was essential. Speed was essential in the delivery of products to patients in a short time frame, especially during the COVID-19 pandemic, and presented another challenge to manufacturers. To facilitate speed to market, regulatory approaches to accelerate the availability of vaccines and treatments were heavily relied upon. These included FDA’s Emergency Use Authorization (2) and Priority Review (3) approaches and emergency conditional market authorization in the European Union (4).

To successfully shorten timelines and meet capacity demand, CDMOs needed to expand facilities to offer improved scalability and increase efficiency of existing processes. This required all aspects of development and manufacturing to be highly optimized. Throughout this process, the high quality had to be balanced with delivering at an unprecedented speed.

Managing supply chains to avoid disruptions. Manufacturers had to also ensure they maintained a reliable supply of raw materials and consumables. Many projects, both COVID-related and not, relied on much of the same equipment, processes, and raw materials. However, with the onset of the COVID-19 pandemic, biomanufacturers were waiting up to a year for supplies and equipment. Despite vendors responding to increased demand by expanding capacity, projects still took months to come online (5).

Essential materials for making vaccines were in short supply—exposing how the supply chain is reliant on only a handful of countries, and even companies when it came to the sterile bags used for cell cultivation in bioreactors (6). Despite the rise of globalized supply chains in the past decade, the COVID-19 pandemic has highlighted the need to proactively monitor and quickly react to potential delays.

Manufacturers had to identify several potential sources of equipment and consumables to have alternative options in the event of delays from their primary source. Identifying alternative suppliers close to the production facility for localization of materials helped to minimize risks associated with delays. Additional time also had to be taken to ensure that the alternative equipment and consumables identified were suitable and optimized for the manufacturing needs.

The potential of mRNA

The growing interest in mRNA technology is in part because of its ability to be easily edited, providing the potential for it to be used in the treatment of countless possible diseases. In this way, mRNA technologies have the ability to be used as a “plug-and-play” platform, offering unprecedented versatility. Recent advances in mRNA vaccine technologies have further improved translatability. Carriers have also been developed to prolong antigen expression in vivo, further increasing its potential.

Additionally, vaccines that rely on mRNA technologies provide the added benefit of having the potential
for inexpensive, rapid, and cost-effective scalable manu-
facturing. As mRNA can be synthesized using relatively simple in vitro transcription reactions, high yields can be achieved with a small, good manufacturing practice (GMP) facility footprint.

As a result, mRNA technologies are being used in abundance in drugs currently at clinical trial. As of July 2021, there were more than 70 mRNA therapeutics in clinical pipelines globally and many more assets in early development (7). The therapies in development are to be used in an array of therapeutic areas. These include drugs for cancers (ovarian, lymphomas, melanomas, and glioblastomas), ischemic heart disease, rare diseases (caused by Zika virus, Chikungunya virus), and more common diseases (caused by Rabies virus, HIV) (8).

It is likely that demand for manufacturing support will persist for years to come, especially with the immediate need for COVID-19 booster vaccinations. CDMOs will need to keep adapting to solve the challenges associated with the storage of mRNA technologies, as well as develop their services to provide end-to-end mRNA capabilities. Overcoming these issues may in turn position the manufacturers in a stronger position to support other therapeutic modalities such as C&GTs further on the horizon.

Lessons learned and moving forward
With an increased demand for drugs based on new technologies, CDMOs will need to consistently demonstrate their agility while ensuring quality and safety in all stages of a product cycle. This is essential to respond to other new technologies and shifting market dynamics. To achieve this, processes will need to be highly optimized to reduce timelines and provide speed to market.

The pandemic has highlighted that foresight, careful preparation, and agility continue to be essential traits for CDMOs and will prevent them from mismanaging their priorities. Client satisfaction and the lives of patients are, and always should remain, the highest priorities.

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Outsourcing Services —Contin. from page s17

Deorkar (Avantor): Listen to customers. Outsourcing companies need to spend more time listening to their customers rather than trying to make sales pitches. It’s critical to understand customers’ process/product requirements and application needs to deliver the service that would exceed customers’ expectations.

Capabilities and limitations should be laid out early in the project discussion. This would help avoid any promises that cannot be delivered.

Decide on a timeline. Companies should work with customers on a project timeline that can be delivered upon. Since outsourcing buffer management is a part of complex biopharma processes, it is essential that all outsourced services meet the customers’ critical timeline. If the project timeline cannot be met, always communicate early to find alternative solutions or paths.

Zehe (Sartorius): Be flexible and customer focused. In addition to good technologies, service providers also require a high level of flexibility and customer focus to overcome the manifold challenges related to biologics development. This includes tailor-made development approaches, short lead and response times, the possibility to stop or change work packages (also on short notice), clear and efficient communication (ideally single point of contact), and flexible business models.

Establish and apply platform technologies. Well-developed and efficient technologies are the basis to provide cost-effective services and fulfill the steadily increasing demands with respect to timelines, yields, scalability, and product quality. Furthermore, good platforms ensure regulatory compliance and a high project success rate.

Provide complete solutions. Single-vendor/one-stop-shop approaches comprising the full spectrum of cell-line development, cell-culture media, cell banking, analytical, and biosafety testing services provide big advantages, such as higher success rates, shorter timelines, and simplified project management and communication.

Fillosa (PerkinElmer): Know the client’s needs. Understand exactly what your client’s needs are so that you can meet them in the smartest ways.

Find solutions for multiple critical needs. Once needs are identified, create a solution that solves multiple critical needs (vs. only one or stove-piped issues). Creating an improved overall workflow will benefit both sides of the collaboration.

Think long-term. Good outsourcing is about creating optimal solutions and long-term, trusted relationships. Part of this can mean saying no sometimes and being flexible in creating new directions together. This really looks out for a client’s best interests. The partnership becomes stronger when you create opportunities for acceleration and improvement of the workflow.
Amorphous solid dispersions (ASDs) are increasingly used to address the need to enhance bioavailability of poorly soluble APIs. Contract development and manufacturing organizations (CDMOs) that have amassed knowledge and experience in this specialty area play a key role in the pharmaceutical industry by providing the capabilities of developing and manufacturing ASDs.

“The pipeline of poorly-soluble drugs continues to grow, and ASDs remain the best-in-class platform to address poorly-soluble drugs,” says Filipe Neves, strategic business senior director at Hovione. He says that spray drying has been proven as a technology for the current good manufacturing practice (CGMP) manufacture of ASDs and that pharmaceutical companies have gained confidence in the technology and its reliability. Spray drying is becoming widely accepted and is seeing a year-on-year increase in adoption, reports Neves.

“Today’s APIs are increasingly insoluble, and that can pose serious problems for formulators looking to manage the bioavailability of their formulations,” says Lieven Van Vooren, scientific director, Ardena, a Belgian-headquartered CDMO that acquired Spain-based Idifarma and its spray-drying capabilities in September 2021.

“The formulation of an ASD is increasingly being recognized as one of the more reliable and efficient strategies for optimizing the solubility and dissolution characteristics of low aqueous solubility compounds,” Van Vooren explains.

“The increased development of biologic-based drugs has also fueled demand for spray drying as an alternative for the manufacturing and processing of biologics, instead of the more traditional liquid or lyophilized solid forms,” adds William Wei Lim Chin, manager, global scientific affairs, Catalent. He says that additional growth in spray drying comes from the increased consideration of spray-dried intermediate powders for both local and systemic inhalation delivery of biologics.
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Spray-drying vs. HME
Spray drying and hot-melt extrusion (HME) are the two most widely used technologies for CGMP manufacturing of ASDs. In spray drying, the API and excipient are dissolved in a common solvent, which is then evaporated to form ASD particles. In HME, the API is dissolved and dispersed in the molten, polymeric excipient, which is then cooled to form ASDs. An advantage of HME is that it doesn’t require the use of solvents and the additional drying step. HME has some constraints, however, particularly for thermally sensitive APIs.

“The constraints of the HME process are that both the drug and the matrix must be miscible and compatible at the temperature at which the process takes place. In addition, the components must maintain this miscibility during the cooling stage,” says Van Vooren. “Another major limitation of HME is the stability of the drug at the high temperatures at which this process is performed. On the contrary, in the case of spray drying, the evaporation process is instantaneous and therefore suitable for thermosensitive products. In addition, the control of the physical properties of the spray-dried product allows manufacturers to obtain a particle size and morphology suitable not only to meet the dissolution goals, but also to obtain density and flow characteristics that facilitate the downstream processing.”

In HME, homogeneity may be more sensitive to process parameters (such as temperature) and equipment parameters, explains Neves. He adds that spray drying is, in general, more suitable for early clinical stages because formulations can be developed and produced with minimal amounts of API.

New tools, however, may be able to address the challenge of API volume at early stages. “There is currently a significant focus on creating advanced development tools for both spray drying and HME that allow for fast, de-risked development of ASDs using minimal quantities of API,” says Chin. “When the API is compatible with both the thermal and shear stresses of extrusion, HME offers a robust manufacturing process without the use of large volumes of solvents.”

Selecting HME or spray drying can depend on many factors, including the stage of drug development program, time, and cost, Chin concludes. Both HME and spray drying can be used in continuous solid dosage processing.

“Spray drying is a continuous manufacturing (CM) technology,” says Neves. “It offers a remarkable control over the properties of the manufactured powders, with significant downstream advantages. With adequate process development, spray drying can enable ASD formulations that are directly compressible, thus bypassing the need for granulation prior to tableting. When accomplished, this will enable much simpler CM equipment trains and processes, benefiting overall operational efficiency, speed, and conformity.”

Development and scale-up
Scaling up from development to commercial-scale spray drying present challenges related to the spray-dried bulk powder properties.

“Changes in process conditions, due to the different configuration and dimensions of the spray dryer from development to commercial scale, have a major impact on the critical quality attributes of the spray dried powder, especially on the particle size, its distribution, and residual solvent content,” says Chin. “To understand the impact of these process changes, thermodynamic and kinetic modeling techniques, supported by engineering modifications as well as exploratory laboratory work, have emerged to support a rapid and successful scale-up of spray drying processes.”

The downstream processing method should be considered in scale-up, says Neves. For example, directly compressible powders for tableting may require specific combinations of particle size and bulk density. Inhalation delivery would require different criteria, such as composite powders of small particle size, controlled within narrow ranges, explain Neves. He notes that streamlined scale-up relies on a thorough process understanding, which can be aided with advanced formulation and process modeling tools.

New tools may be able to address the challenge of API volume at early stages.

Formulation of ASDs involves screening APIs, excipients, and other ingredients to determine the optimal combination. The Hovione Intelligent PROprietary Screening methodology for ASDs (ASD-HIPROS) was launched in January 2021 and is offered from the company’s Lisbon, Portugal, R&D center (1).

“The service aims at developing ASDs formulations with maximum stability and performance by eliminating invisible candidates, thus saving the time and investment needed to bring the drug to the patient,” says Neves. He explains that this proprietary process can assess up to 24 formulation prototypes in six weeks, requiring as little as five grams of API.

“The three process steps are: in-silico computational screening based on the API properties (to determine most suited polymers, surfactants, and drug loads), spray drying experimental prototyping of the most promising formulations, and analytical testing and solid-state characterization (to confirm proper dissolution in bio-relevant media as well as stability under stress conditions),” says Neves.

Van Vooren adds that in scale-up, the large number of process parameters and product characteristics add to the complexity of the spray drying process. He explains that defining a design space where the process is controlled is key.

“Approaches such as quality by design, which employs tools such as design of experiments, allow us to identify from early stages the risks related to the formulation and manufacturing process that can potentially impact product quality and, consequently, to be able to guide studies to mitigate such risks,” says Van Vooren.

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Breaking through boundaries
To foster the development of treatments for under-treated and rare conditions, FDA grants orphan drug designation to drugs and biologics that treat, prevent, or diagnose diseases that affect fewer than 200,000 people in the United States or drugs that meet certain cost recovery provisions (1). This designation comes with incentives such as tax credits, user fee exemptions, and market exclusivity. To receive such designation, sponsors must submit requests and present data to support the request.

Pharmaceutical Technology asked Judith Jones, FRSC, Director Regulatory Affairs, Global Regulatory Affairs, Catalent, and Matthew Mollan, RPh, PhD, Regional Head of Operations, Early Phase Development North America, Catalent, about the specific ways contract development and manufacturing organizations (CDMOs) can assist sponsors in developing, applying for, and manufacturing orphan drugs.

**Regulatory requirements**

**PharmTech:** What are the criteria for receiving orphan drug designation in the US compared to the European Union?

**Jones:** In the US, to be designated as an orphan drug, sponsors need to show that the disease or condition that the drug is intended to treat has a prevalence of 7.5 or less for every 10,000 individuals, as opposed to five in every 10,000 individuals in the European Union. If this criterion is not met, orphan drug designation could still be granted in both the US and EU if sponsors can demonstrate that there would be insufficient return on investment to cover the cost of development when commercializing the drug in the respective markets. Another additional criterion in the EU is that there is no satisfactory method of diagnosis authorized in the EU for the prevention or treatment of the disease or condition in question.

**PharmTech:** How are the processes different in the US versus the EU to receive orphan drug designation?

**Jones:** While the process of orphan drug designation requirements for FDA and the EMA [European Medicines Agency] do not fundamentally differ, they do vary in terms...
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of the precision of evidence required. For example, in the US, sponsors need to provide scientific rationale and proof of efficacy for the use of an orphan drug. When clinical data or an applicable preclinical model is not available, sponsors may justify using data that include the pathogenesis of the disease, mechanism of action of the drug specific to the disease, and supporting in vitro data. Sponsors may also leverage data from published literature during the orphan designation application process. In the EU, justification using only in vitro studies and mechanism of action may not be enough to justify ‘medical plausibility’ and ‘significant benefit’, which is best supported by clinical or preclinical data.

PharmTech: Is it more difficult to gain orphan drug designation in the US versus the EU?

Jones: There seems to be an increasing trend for more drugs to be designated as orphan in the US than in the EU, as reported by the Regulatory Affairs Professional Society (RAPS) in March 2021. Between 2019 and 2020, there had been an increase of 41% in the number of requests for orphan drug designation in the US, bringing the total to 753 requests, whereas in the EU, the numbers remained steady, with 235 requests for orphan drug designation in 2020, compared with 233 requests in 2019. A recent commentary called for more alignment between the EU and other big markets’ regulatory practices to facilitate the submission package plausibility and significant benefit’, which is best supported by clinical or preclinical data.

PharmTech: What are some considerations when performing scale-up of orphan drugs?

Mollan: Most orphan drug product will not see the batch sizes or volumes associated with traditional commercial prescription products, meaning late-stage clinical-scale equipment can often be used for commercial manufacturing of orphan products. While the batch sizes may be smaller, regulatory agencies expect manufacturers to follow regulations and stay in compliance, ensure consistent product supply, and have the product stability data to support expiration dates. The manufacturing formulation and processes should be flexible to allow developers to respond to any changes in demand for the product, as well as being globally acceptable. Oncology orphan drug products can begin the commercial lifecycle as low volume products, but on occasion can experience increased demand as the treatments are studied in additional patient populations for different indications.

Orphan drug challenges

PharmTech: What are the challenges when developing an orphan drug? Are there different challenges for small-molecule versus large-molecule drugs?

Mollan: Clinical trial design is one of the biggest challenges in orphan drug development and can be driven by difficulties in setting the appropriate efficacy endpoints, as well as challenges in patient recruitment, and often, programs require a wider, global view, compared to more traditional drug development. The challenges in setting appropriate efficacy endpoints stem from the often-incomplete understanding of the disease pathophysiology and natural progression of the disease, which can lead to difficulties in identifying and validating surrogate biomarkers and critical clinical outcomes. By their nature, the relatively low incidence of orphan diseases makes patient recruitment for clinical trials more challenging. The heterogeneous nature of many genetic orphan diseases further diminishes the pool of patients that are likely to see benefits from a new treatment, with many potential patients being children.

PharmTech: What are the challenges when manufacturing an orphan drug? What types of manufacturing strategies work best?

Mollan: Because of the unmet medical needs, treatments for rare diseases often qualify for an expedited development program. With that in mind, a limited API supply, shortened timelines, and uncertain formulation requirements are some of the challenges in manufacturing orphan drugs. The limited API supply can impact the development activities that can be performed and places pressure to have Phase I formulations continue to late-phase development. Strategic investment in Phase I formulation development and de-risking the process, while adding a unit operation, such as roller compaction, can save time and reduce risks by ensuring the formulation is ready for scale-up to be processed on automated equipment. A risk-based CMC [chemistry, manufacturing, and controls] plan and communication of the plan with regulatory agencies can help ensure preparation for any unforeseen challenges.

PharmTech: How can a CDMO help a sponsor company develop an orphan drug? What specific services and/or facilities can a contractor provide?

Jones: Typically, the manufacturing of an orphan medicine is undertaken at a considerably smaller scale than traditional commercial manufacturing, because of the very limited patient population. When orphan designated drugs receive approval for expanded indications, this might affect the scale of commercial manufacturing. Therefore, a CDMO with the experience of manufacturing at customized scales, as well as the flexibility to respond to changes in the types of products being sold, the volume of sales, and the facilities and equipment needed for production, may be better able to help a sponsor company overcome barriers in terms of cost and timeline during an orphan drug development.

PharmTech: How can a CDMO help a sponsor obtain regulatory approval for an orphan drug? What specific services and/or facilities can a contractor provide?

Jones: When information is needed on specific technologies, or processes that require alteration, the CDMO’s regulatory team can respond quickly with minimal risk of error. A CDMO is also able to offer sponsors a global network of regulatory affairs experts that have local knowledge, to
facilitate successful agency interactions. In addition, CMC activities could be easily and quickly prioritized to ensure that they do not present as bottlenecks to the execution of the orphan development program and submission of application to regulatory agencies. A CDMO should already be intimately familiar with its dosage form(s), which can be customized to potentially address a specific orphan medicine’s need. They are then able to provide complete advice and provide support on the formulation, development, and manufacturing intricacies. Leveraging a CDMO to obtain regulatory approval for an orphan drug may also result in overall improvement of efficiency in orphan drug product development time and accelerate product approval.

PharmTech: How can a CDMO help a sponsor control the costs, specifically, of the development and manufacture of an orphan drug?

Mollan: A major global CDMO could provide access to an international network of technical expertise and state-of-the-art facilities. An integrated CDMO can save costs by accelerating timelines, reducing program risks, and ensuring a smooth transition between early and late-phase manufacturing sites. These benefits are achieved by harmonizing equipment, processes, pharmaceutical excipient vendors, collaboration tools, and project management structure between sites.

Manufacturing — 
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Van Vooren adds that differences between laboratory and industrial-scale equipment can cause variations in evaporation rate, particle trajectory, residence time, and other factors.

“It is highly recommended to also consider the finished dosage form manufacturing requirements and technologies, since integrating the spray drying process and the finished dosage manufacturing in a single facility reduces risks and timelines, and simplifies the supply chain for the product,” concludes Van Vooren.

Capacity expansions and collaborations

CDMOs have been adding capacity for both development and commercial scales to meet the expected demand for spray drying.

In November 2021, Hovione announced that the company would add commercial spray-drying capacity and equipment as part of its expansion at its facilities in the United States, Ireland, and Portugal (2). At the US facility in NJ, the company is constructing a new building and will have additional commercial spray drying capacity online by 2023. New commercial spray dryers are also slated for the Cork, Ireland and Lisbon, Portugal facilities.

Catalent acquired the manufacturing and packaging operations of Acorda Therapeutics, Inc. in January 2021, including a 90,000-ft² CGMP facility in Chelsea, Mass. with spray drying capacity that provides Catalent with significant commercial-scale capacity for new customer programs.

PharmTech: Can a CDMO help a sponsor company determine which medical needs might warrant the development of an orphan drug?

Mollan: For the most part, CDMOs do not determine which diseases to target, but can help refine the target product profile and ensure that the final product meets the needs of the target patient population. Developing a formulation and process that can accommodate a very wide range of potential drug loading is a key decision that can significantly de-risk changes in drug loading requirements as more information becomes known. Many factors drive the development of the target product profile, and these include the physicochemical and pharmacokinetic properties of the API, patient considerations such as age and co-morbidities, and manufacturability of the drug product used in the treatment.

References

Conclusion

Spray drying is suited to ASDs but is also finding use in other fields, such as microencapsulation, nanotechnology, and vaccines. “Spray-drying stands out as an accessible, repeatable, and scalable process that offers developers a cost-effective way to improve the solubility and bioavailability of their formulations,” Van Vooren concludes.

References
In pharmaceutical science several divergent paths typically exhibit clear validity. Decisions often boil down to embracing instead of eschewing risk, to accelerate as the only priority, or to trust a partner rather than emphasize self-reliance. Each molecule, each company or research group possessing that molecule, has an assortment of strengths and weakness to guard against or to leverage. Multiple factors weigh in the balance when deciding how best to move forward, and increasingly the route chosen is to outsource research, development, and manufacturing.

The global contract development and manufacturing organization (CDMO) industry, averaging across several market research firm estimates, is currently valued around $100 billion (1). In part, this growth is shaped through direct regulatory influences suggesting, if not demanding, that a drug have multiple sites of manufacture to spread the risk for supply chain planning. Above regulations, companies also seek to reduce the complexity of their operations internally, and to reallocate internal resources most effectively.

Rising demands
According to Hanns-Christian Mahler, CEO and board member of ten23 health—a new CDMO that offers development, manufacturing, and testing services for injectables—there are a variety of reasons as to why demand for outsourced services of technical R&D activities is increasing. “[Reasons] include a potential lack of internal asset(s) for a given technology and/or specific requirement,” he says. “For example, the building and operating costs of a sterile fill/finish facility are significant. If a pharma company would not have sufficient molecules in a portfolio that would benefit from being manufactured in that facility, the costs could be quite prohibitive, and outsourcing is surely much more cost efficient.”

There could also be instances where a pharma or biotech company has an asset but does not necessarily have the required technology or features, Mahler continues. For smaller companies, in particular, he adds, there may not be internal knowledge or industry and scientific expertise available. “Hence, specialized providers, such as ten23 health, may pro-
Outsourcing happens in many different shades,” notes Mahler. “Finally, even in existence of internal assets and internal experts, there may be insufficient capacity in house.”

Focusing somewhat on internal capacities and the fact that the outside economic environment is encouraging. Ramesh Subramanian, chief commercial officer, Aragen, believes it is a buoyant time for R&D outsourcing at the moment. He specifies that this buoyancy can be attributed primarily to three reasons, “increased fund flowing into [the R&D outsourcing] space, a high number of targets in the pipeline, and renewed interest in pharma R&D due to the COVID-19 pandemic.”

“In fact, as a direct consequence of this better funding environment, we are seeing increasing number of biotechs pursuing their research programs with renewed vigour,” Subramanian adds. “In the past, those companies that were quite conservative in advancing their discovery programs are now focusing on advancing their assets quickly through the development continuum to reach the proof-of-concept milestone. With this shift, we see more biotechs approaching us for more end-to-end integrated solution offerings, from discovery through to Phase IIB—where their assets get them better valuations. Venture capitalists are also open to a longer-term view on development and willing to take risks for such potential upsides from valuation of successful programs. For Big Pharma, outsourcing of all but core activity is the de rigour approach to achieve fastest development timelines.”

Sy Pretorius, MD, president, Clinical Development, and chief medical officer at Parexel, points to the need to focus on and build a lasting relationship when partnering. “To meet complex industry challenges, successful outsourcing partnerships are essential,” he asserts. “This is necessitated by increasing pressures to reduce the cost of drug development and to bring therapies to market sooner. Rather than purely transactional in nature, these partnerships should be truly collaborative. Strong relationships can foster innovation beyond contractual obligations and typically leads to higher levels of staff engagement and better quality. The reason for continued demand for outsourced services can be attributed to a variety of factors including a burgeoning drug pipeline, record levels of funding, lack of in-house resources or expertise, and increased operational complexities.”

Many different shades

“Outsourcing happens in many different shades,” notes Mahler. “Outsourcing can include full technical programs including drug substance and drug product, it can include only specific studies. It could be only for early-stages of a program or the opposite, just for the commercialization stage. In the end, the outsourcing model needs to fit to the needs of the pharma and biotech company, their own expertise and knowledge base and their preference on either working with the most qualified outsourcing partners for specific studies, versus the preference on working with just one partner.”

Subramanian reflects that the focus of Big Pharma has now shifted to ensure they can retain their core activities in-house. “[Big Pharma’s] definition of core has become a lot smaller as they look to CDMOs to be their R&D engines. We are seeing these emerging trends in R&D outsourcing,” he says. “Pharma/biotechs are looking for more integrated discovery service offerings to leverage on the efficiencies and synergies of chemistry and biology offerings from one service provider/co-location of these capabilities. In the outsourcing of development services, pharma/biotech companies still prefer to have the final drug substance being manufactured closer to their locations in the United States/European Union. Given the greater demand for access to capacities, a large number of these biotechs leverage the capacities/expertise available in Asia to execute the initial steps and the final steps in US/EU.”

The range of relationships is large, encompassing full-service outsourcing (FSO) to functional provider (FSP) type arrangements, Pretorius states. “Likewise, these [relationships] range from tactical/per study outsourcing to more strategic programmatic outsourcing,” he notes. “Landing on the right outsourcing model requires an assessment of each individual organization’s needs. Functional service provision continues to be a core outsourcing model allowing the vendor to provide embedded teams that support sponsors for specific services and work directly with their client’s systems and infrastructure. In other instances, a hybrid, more limited scope might work best.”

Decisions often boil down to embracing instead of eschewing risk...

COVID-19 impact

Pretorius observes that the pandemic forced industry to re-examine how research studies are designed and conducted, while also demanding record-breaking speed of innovation. “As a result, digital medicine was embraced in ways never seen previously. Decentralized clinical trials (DCTs) became embedded in the overall clinical development ecosystem and part of the new norm in how we operate,” he emphasizes. “At Parexel, DCTs are now being woven into 80% of Phase II/III trials and 100% of real-world evidence new trial proposals include DCT elements.”

However, Pretorius cautions this movement is not without obstacle. “A challenge is the lack of industry-wide data standards and how best to manage more and more data from disparate and diverse sources across multiple platforms while ensuring quality,” he says.

Mahler adds that downstream manufacturing and the supply chain were affected by the pandemic. “The significant demand in vaccine manufacture also led to significant demand in primary packaging and disposables,” he stresses.
“This has an impact on the globally available outsourcing capacity for any kind of (sterile) product development and manufacturing, which certainly has become smaller given the capacity need for vaccine manufacturing, and the shortage in supplies of raw materials poses some specific challenges and risks for supply chain planning and inventory.”

When contemplating the pandemic, Subramanian specifies that, on a global scale there has been an obvious impact on resources, with CDMOs required to prioritize COVID-19 targets and vaccines—an aspect that will continue onto the future as new variants of the virus continue to develop.

“Geo-diversity has also been on the rise, and if innovators are too reliant on China, Europe, or India, they will look to rebalancing their spread. However, the net result is that India has been the biggest beneficiary—as there was more reliance on China previously,” he says.

“The other interesting impact of COVID-19 has been the development further down the chain from the messenger RNA (mRNA) vaccines,” Subramanian continues. “So, there is much greater interest now in areas like oligonucleotide discovery and development, and even peptides—areas that Aragen is investing in due to increasing demand. In terms of mRNA vaccines, we are also seeing innovators look for smaller aspects of its production from lipids to linkers—basically they look for anything that can increase speed and deliver customer value.”

**Contract, Development, Action! Analyzing Recent Events in Outsourcing**

The actions taken by contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs), large or small, provide insight into the greater state of the biopharmaceutical industry. Recent news surrounding CDMOs prioritizing mRNA services and full-service integration may provide one such insight.

**Full-service integration**

Piramal Pharma Limited (PPL) increased its stake in Yapan Bio, an India-based biologics manufacturer, with an investment of approximately $13.7 million, which was announced in December of 2021. Yapan Bio works with various complex biologics, including current good manufacturing practice (CGMP)-compliant manufacturing of vaccines and biotherapeutics. This includes high-containment classes up to biosafety level-2, recombinant vaccines, both RNA and DNA vaccines, gene therapies, monoclonal antibodies, and therapeutic proteins.

According to a company press release, PPL made this move in an effort to augment their antibody-drug conjugation capabilities. Peter DeYoung, CEO of Pharma Solutions at PPL, noted in the press release that biologics (and their accompanying development services) are the fastest growing segments of the CDMO business. Integrating biologics into their offerings allows CDMOs to provide a full suite of services, including development, manufacturing, conjugation, and fill/finish (1).

**The shift toward mRNA**

Merck KGaA announced in January that they would spend $780 million to acquire Exelead, an Indianapolis-based CDMO specializing in complex injectable formulations. These include both lipid nanoparticle (LNP)-based drug delivery technology, as well as fill/finish capabilities.

According to Belén Garrio, CEO of Merck KGaA, Exelead was purchased because of the company’s complementary abilities as it concerns messenger RNA (mRNA) delivery services. mRNA therapies have received a well-documented boom in interest following the release of mRNA-based vaccines for the SARS-CoV-2 virus. In a press release detailing the acquisition, Garrio stated that Merck felt that the acquisition would allow the company to pounce on this fast-growing market for mRNA therapies (6).

Merck’s $780 million move may foreshadow an increased prominence on mRNA in the industry. In addition to Merck’s acquisition, industry powerhouses such as Lonza (7) and Samsung Biologics (8) have both ramped up their presence in mRNA over the course of the past year, suggesting a strong trend toward mRNA. CDMOs are being rewarded for putting significant sums of money into mRNA, an indication that mRNA delivery mechanisms will likely continue to grow in prominence in the biopharmaceutical space.

**References**

mAbxience, a global fully-fledged biotech company, with over a decade of experience in the development, manufacture and commercialization of biopharmaceuticals.

- Reliable, world-class biological Contract Development and Manufacturing Organization (CDMO).
- End to end solutions, latest state-of-the-art technology across multi product API and fill finish facilities.
- Committed to global quality standards to manufacture & supply our biosimilars worldwide.
Beyond the pandemic
Looking beyond the pandemic, Subramanian expects that industry will see a continuation in oncology as a leading therapeutic area of interest, although he adds that there has also been a rapid uptick in demand for central nervous system (CNS) targets. “Almost all Big Pharma is involved in oncology, so on the development side, we see a similar make up in CDMOs and of course in technologies like HP,” he says. “CNS is interesting, as there have been several high-profile failures. So, innovators are looking for partners to advance several candidates simultaneously to increase their chances of success.”

For Mahler, other potential trends that will likely impact outsourcing of R&D services are the diverse therapeutic modalities and APIs being investigated. “For example, in the category of therapeutic proteins, we see increasingly complex formats,” he says. “We also see a huge variety of indications and administration routes, including the challenging intravitreal and subcutaneously administered products.”

Additionally, the trend for self-administration is broadening out to areas such as oncology, where devices are typically required (i.e., an increasing trend towards drug/device combination products), Mahler notes. “Of course, these [trends] bring specific challenges related to the product design, manufacture, and testing,” he adds.

Pretorius returns focus to DCTs. “Given the rapid speed of adoption and the evolving vendor and regulatory landscape, [contract research organizations] CROs are particularly well-placed to deploy DCT strategies because of the breadth of experience obtained across multiple sponsors,” he empathizes. “Some CROs have been active in the space for more than a decade enabling them to leverage significant learnings and expertise.”

Looking toward another burgeoning area, cell and gene therapy, Pretorius lauds the availability of new technologies, which are allowing industry to see the potential of such innovative therapies. “For patients, [cell and gene therapy] provides promising options with potentially less toxicity,” he says. “We are seeing significant interest and investment in this area beyond treatment for oncology.”

Parting thoughts
As parting thoughts, Mahler expresses his belief that “outsourcing and the development and commercialization of medicines in general should be more a ‘system thinking’ approach. Companies or outsourcing services may be getting so specific about one given part of the product, that the interconnectivity and dependency of all the components of a drug product are being forgotten: a sterile product can only be reliably and reproducibly manufactured if the formulation, primary packaging, and processing parameters are wisely chosen in its entity.”

Furthermore, Mahler stresses the importance of focusing on ‘people’—patients and employees—as well as the planet. “We, at ten23 health, hence embed considerations of fairness and sustainability in all we do. There is only one Planet,” he adds.

Pretorius also points to the larger operating system, observing that outsourcing can also prove beneficial in the area of regulatory operations through aiding with submissions, product registration, tracking agency interactions, and so on. “This [service] requires working in tandem with partner internal regulatory teams and carefully defining roles and responsibilities to assure alignment,” he says. “At Parexel, our regulatory outsourcing teams consist of former regulators from FDA, European Medicines Agency, National Medical Products Administration, among others with specialized knowledge and first-hand experiences of regulatory expectations.”

While there is much to weigh and evaluate, the uptick in outsourcing appears well founded on benefits and advantages. This has led to what might be termed a ‘run’ on available scheduled slots within CMOs and CDMOs. Currently, not only must one place a large cash down payment but also the requesting company must now face wait times of around 12 months to get their place in the que. However, in this case good things take time, and time taken pays dividends at the (pun intended) finish line.

Reference
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