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The pharmaceutical outsourcing market has seen a growth in vaccine development and manufacturing activity in the past year, particularly due to the industry’s response to the COVID-19 pandemic. And this growth is likely to continue, according to Mike Kleppinger, chief commercial officer at Curia (formerly AMRI) (1). “If you look at the vaccine developers, much of that production was outsourced. And with its global impact, we would expect COVID to continue to drive growth because you’ll have more treatments, as well as vaccine boosters, different strains, etc.,” Kleppinger says.

Increased demand for new treatments, either for COVID-19 or other much-needed medicines, requires increased production. Many sponsors partner with contract development and manufacturing organizations (CDMOs) and contract manufacturing organizations (CMOs) to scale up and meet capacity demands for the commercial level in order to get treatments to patients quickly, according to Kleppinger. “Not only that, I believe they discovered that contract partners are particularly effective at the application of data, technology, and other innovations. CDMO partners have invested in greater capabilities and sponsors have realized that certain CDMOs have great innovation, great technology, and they have relevant subject-matter expertise. I think they’ve learned that partnering with a good CDMO enables agility, speed, efficiency, and quality,” Kleppinger says.

CDMOs have made investments in capacity and resources to address supply chain challenges, says James Choi, chief information and marketing officer at Samsung Biologics. “More modular construction and expansions, investments in the latest technologies, and process intensification strategies have all accelerated in the CDMO industry,” Choi says.
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Market growth
A continued increase in the need for new medicines is causing growth in the pharmaceutical industry, and sponsor companies will continue to use CDMOs as necessary, according to Andrew Henderson, chief commercial officer at Sterling Pharma Solutions. “Smaller or virtual biotechs rely almost entirely on outsourcing across all disciplines; mid-size pharma invests in core activities internally such as R&D and commercialization, but not manufacturing; and large pharma strategically outsources manufacturing in order to use assets efficiently,” says Henderson.

The industry has seen record highs in investment, according to Joe Sinclair, vice president, corporate strategy and business development at Vibalogics, which has created new companies and expanded pipeline assets. “In addition, requests for CDMO services are tracking in parallel fashion as service demand follows clinical and commercial industry progress. The industry has also seen a renewed focus and surge in demand in infectious disease R&D and cGMP [current good manufacturing practice] manufacturing, accordingly, fueled by the concerns of the COVID-19 pandemic,” Sinclair says.

Sinclair sees a potential for growth in the emerging oncolytic virus therapeutics market. “Much of the market is in preclinical or early-phase trials, but Amgen’s commercial approval of Imlygic here has created a regulatory pathway or template for others to follow in the future. As a result, we are seeing activity picking up due to improved confidence. I think we will continue to see more and more activity in the classes reviewed,” Sinclair says.

Gene Nakagawa, EVP business development at LGM Pharma, says his company has seen an increase in the outsourcing of analytical testing. “Our expectation is that the demand for analytical testing services will continue to be a strong area of growth as FDA elevates its testing requirements for products,” Nakagawa says.

According to Tom Wilson, contract manufacturing lead at Pfizer CentreOne, demand for mammalian drug substance has increased, but he has also seen growth in the outsourcing market in general. “[Sponsor companies] are looking for greater network efficiencies so they can share costs with other companies and ensure demand and supply protection without building redundant facilities. These partnerships benefit all parties involved but most importantly, the patients,” Wilson says. “While there hasn’t been a change in the quantity of business from sponsor companies, there has been a change in the type of business as requirements for outsourcing have changed,” he continues.

Biopharmaceutical development is expanding, according to Choi, and small and emerging biotechs are relying on CDMOs for their development and manufacturing expertise. “The bio/pharma outsourcing industry is actively revisiting its supply chain and investing more to offer the multi-scale capacity required to support increasing demand in the next five to 10 years. Moreover, many leading CDMOs are expanding their capabilities in new modalities such as [messenger RNA] mRNA and cell and gene therapy,” Choi says.

Matthew Barker, corporate strategy at Vectura, agrees that biologics and gene therapies have seen an increased focus recently, but other markets will also see growth in the future. “In addition to biologics, we expect other specialist market areas with a high degree of complexity and barriers to entry, such as inhaled drug delivery, to continue to grow. In contrast, we expect growth to slow in the more commoditized areas of the outsourcing market with lower barriers to entry, particularly for companies without the benefits of scale,” says Barker.

Partnerships, mergers, and acquisitions
The advancement of next-generation biopharmaceuticals will require consolidation of expertise, capacity, and know-how, according to Kleppinger. “It will be analogous to what we’ve seen in CROs [contract research organizations] buying up niche players to expand capabilities and deliver scale,” he says.

For example, the former AMRI announced several major developments in July 2021, changing the company name to Curia and entering into an agreement to acquire Integrity Bio, Inc., a formulation and fill/finish organization in Camarillo, Ca. (2). The company also agreed to acquire LakePharma, a biologics drug discovery, clinical research, development, and manufacturing company that has facilities in California, Massachusetts, and Texas (3). In April 2021, Thermo Fisher Scientific announced it had acquired PPD, a clinical research services provider, for $17.4 billion. The acquisition will give Thermo Fisher access to PPD’s drug development platform, patient recruitment capabilities, and laboratory services, Thermo Fisher said in a company press release (4). The collaboration is expected to offer new solutions for customers, while reducing the time and cost of the drug development process.

“M&A in the CMO/CDMO space is definitely ‘hot’ right now,” says Nakagawa. “Valuations are high for both manufacturers and for lab-services companies that are US-based. The partnership model is expected to continue to be strong as companies try and save on development costs. In the pure generic space though, the trend for partnership is decreasing, primarily due to the downward pricing pressure we are seeing in the generic drug space,” he says.

According to Henderson, consolidation in the small-molecule CDMO market is “inevitable” as outsourcing companies invest and expand. “This industry consolidation will include M&A to broaden capacities and capabilities and expanding service offerings within the value chain. It will be driven by the needs of customers and their strategies for partnering with companies; either...
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through integrated service providers, or by using multiple specialized suppliers to meet their developmental milestones,” Henderson says.

Bill Vincent, chairman and CEO at Genezen agrees that consolidation in the CMO/CMO market will continue during the next five years. “Companies that were in one segment are now looking to expand into other segments and there is continued interest in expanding into other geographic regions as well. I also believe we will also see further development of niche or boutique CDMOs that specialize in unique services or cater to special needs,” he says.

Bio/pharmaceutical companies will be looking to partner with CMOs and CDMOs for technology innovations, risk mitigation, and overflow management, according to Choi. “We’re also going to see more M&A as more CMO/CMO companies look for opportunities to expand their portfolio of services,” Choi says. “The great thing about strategic CDMO partners is that they can buffer the supply chain. The right ones have higher buying power and supply reliability built in that partners can leverage when trying to secure scarce or high demand raw materials and components. Strong CDMO partners can also help implement more effective supply chain strategies. Samsung Biologics establishing itself regionally in the bio cluster hub in South Korea is a good example of the added value CDMOs are capable of delivering post pandemic,” adds Choi.

“Compared with other sub-sectors in the healthcare industry, the CMO/CMO competitive landscape remains highly fragmented, with the top 10 companies accounting for around 20% of the $90–100 billion market. This proportion has increased over the past decade and will continue to do so for the foreseeable future,” says Barker. “However, we expect M&A to be more targeted in coming years. Acquiring companies should have a clear rationale if entering an adjacency, with a high value placed on specialist areas of expertise that help customers overcome complex formulation and development challenges,” he adds.

“Acquisitions have been following a trend as CDMOs look to build platform service and end-to-end capabilities. Companies and CDMOs will focus more on platform development, acquiring companies and technologies that will give them advantages across cell line, media, and formulations, upstream and downstream operations and intellectual property. They will be seeking to drive customer benefit by offering both technologically advanced, and diversified services, ultimately saving customers time and money,” says Sinclair.

Future trends

In addition to market consolidation, Vincent sees capacity as an ongoing challenge for the pharmaceutical industry. “We will see continued physical and technological expansion as a result so capacity will increase through investment in new facilities as well as new technologies that increase throughput and yields on each production batch. These technologies will also lower the overheads and material costs for each batch,” says Vincent.

Assistance with regulatory matters is an area Nakagawa sees potential in. He also believes the need for sterile fill will continue to remain high. “Novel technologies with new delivery systems, sterile fill and high potency products, have been areas of rising demand and growth for CDMOs,” says Nakagawa. “We expect this trend to continue.”

Technology will also be a trend for the pharmaceutical outsourcing market in the future. “For CDMOs, there is a push towards digitization, and exploring the potential value of technologies such as artificial intelligence and machine learning in a way that can improve manufacturing by reducing project timelines, while at the same time enhancing process efficiency and minimizing costs, as well as ensuring product quality,” says Henderson.

As a result of the quick development and production of COVID-19 vaccines, Britton Jimenez, vice president, business development at Metrics Contract Services, anticipates that sponsor companies will be looking at what lessons can be learned from the pandemic to increase speed to market. “Sponsors are going to be much more selective in choosing their partners as they are going to want to ensure risk mitigation plans are in place as well as truly evaluate the region in which they should perform their development work,” Jimenez says. “One thing many companies learned is having a risk mitigation plan is critical to ensure that supply of their therapies does not get interrupted. Many organizations were exposed during this time due to not having risk mitigation plans in place or redundancies built in to ensure continuity of supply. Some sponsors were also put in a very tough place as they had chosen to go into low-cost markets for services, which made it very difficult to get their products out of these markets into primary markets where clinical trials are run due to COVID,” says Jimenez.

Wilson believes outsourcing partnerships will continue to grow in the future. “CMDOs offer a range of expertise and capabilities that are in high demand from sponsor companies to help them meet their goals and ensure that medicines reach the patients who need them. The past year has demonstrated the power of collaboration in the industry and these partnerships are here to stay,” Wilson says.

References

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The COVID-19 pandemic has shined a light on the healthcare industry, particularly biopharmaceuticals, which has created strong tailwinds for the pharma services industry. As money continues to flow into the biopharma sector and industry players look to outsource more of its value chain, both contract research organizations (CROs) and contract development and manufacturing organizations (CDMOs) will continue to benefit. Additionally, the advent of personalized medicine and the development of complex gene therapies have led to greater specialization by smaller CROs, signaling a persistence in market fragmentation—a consistent theme seen over the past decade.

Outcome Capital, a Boston-based life sciences advisory and investment banking group, has been following the pharma services market dynamics for the past five years. The authors believe this fragmented market will give way to greater consolidation by both financial buyers looking to consolidate smaller players and larger CRO players wanting to expand into value-added specialty service areas. To secure future business, larger CROs will move toward long-term alliances with major pharmaceutical and biotech companies, which will put greater pressure on further market consolidation. Adding to this consolidation is a tepid fundraising environment, opening the door for financial buyers to play a more active role in consolidating many of the niche players. The increased presence of financial buyers will also likely lead to greater initial public offering (IPO) activity in the next three to five years, reversing a long industry trend.

Software and analytics will continue to have a greater influence in pharma services as more players look to leverage population data to help in enrollment and management of clinical trials. Acquires have already moved upstream to clinical trial management and analysis to complement traditional research and manufacturing capabilities. While the authors see the growth of the clinical segment outpacing that of preclinical services, highly specialized players with expertise across the development value chain offer a more well-rounded value proposition to potential clients, enabling them to lock in long-term alliances and capture more mar-

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market share. However, with a surge of investigational new drug (IND) filings in 2020 (more than 3800 in 2020 vs. approximately 3600 from 2012–2019)\(^1\), the discovery/preclinical segment will remain very active in the years to come.

Pharma services continue to see growth

Prior to COVID-19, investments in the biopharmaceuticals industry increased consistently year-over-year for the past five years on the heels of technological advancements and attractive returns for investors. The authors see a more robust investment landscape post-COVID as the pandemic has increased awareness of the healthcare sector. With more scrutiny on pharma R&D pipelines, the CRO and contract manufacturing organization (CMO) industry will continue to see growth. The clinical research segment will see a higher growth rate (8.1% 2018–2024 compound annual growth rate [CAGR]) \(^2\), while the discovery and preclinical segment maintaining strong growth (7% 2018–2024 CAGR) \(^2\) as biopharma players broaden their clinical pipelines.

The CRO market remains highly fragmented (Figure 1), with approximately 52% of the market captured by smaller or niche service providers. Large players such as IQVIA, LabCorp, PRA, PPD, and Charles River Labs will continue to command significant market share, but this fragmented market points toward consolidation from both the large strategic and financial buyers. The authors expect to see the trend of both vertical and horizontal expansion to persist for the foreseeable future. The majority of strategic acquisitions have been to capture specific niche or specialty services in a specific vertical. We have not seen any major CRO looking to move from the discovery/preclinical space to the clinical space or vice versa.

In 2020, the Outcome Capital’s CRO Index (see Figure 2), comprised of large, public CRO players, who often command market share due to size, scope, and scale, vastly outperformed the broader market as its performance was buoyed by COVID-19 testing, research, and therapeutic development. Interestingly, the public markets have rewarded different strategies over the past year. Charles River Labs (+65%) has been rewarded for its aggressive growth by acquisition strategy, while Medpace (+67%) has seen success by capturing the market share from smaller and medium-sized biopharma players.

Conversely, the smaller pharma services players still face intense competition in this fragmented industry, which will put downward pressure on valuation and may keep value suppressed without increased scale or scope. As larger players offer more diverse skillsets, smaller CROs will need to compete on more than just price. Increased specialization, faster turnaround times, and enhanced customer focus may continue to allow smaller CROs to capture customers, increasing their value and helping to improve the probability of a transaction.
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InVentiv (now Syneos) and the $5B buyout of PAREXEL by Pamplona Capital. The wave of large transactions looks to be picking back up in 2021 as ICON announced its $12 billion acquisition of PRA Health Sciences, and Thermo Fisher announced their acquisition of pharma services giant PPD for $17.4 billion. An area of consolidation has been around software solutions and analytical technologies used in the pharma services space. ICON noted PRA’s mobile clinical trial management software as a primary catalyst for the acquisition, continuing the trend of technology acquisitions seen in 2019 and 2020. Both the IQVIA and Syneos mergers were driven by the need to deliver greater value through data and clinical trial analytics. Additionally, the largest deal by a financial buyer (Astorg’s $1.8 billion buyout of eResearch Technology) also focused on clinical analytics.

While clinical trial software and analytics will continue to drive value, traditional services companies still saw healthy activity over the past five years; however, both strategic and financial buyers sought to acquire CROs and CDMOs with differentiated offerings either through specialized indications or breadth of services. Curiously, CMOs have not been able to take advantage of advanced analytics or specialization, and as a result, their overall deal numbers and values have lagged. In the past five years, only 23 CMO acquisitions have taken place for a total of approximately $1.3 billion (compared to 25 deals totaling >$5.8 billion for CDMOs and 70 deals totaling >$21.8 billion for CROs).

Over the past five years, the number of CRO transactions remained relatively stable (see Figure 3), but the number of transactions seen in either the discovery/preclinical space or clinical space fluctuated widely from year-to-year, along with the deal values (see Figure 4). The overall difference between discovery/preclinical (31 transactions) and clinical (34 transactions) were even, despite each year having its own unique profile. Generally, the clinical segment draws larger transaction sizes, with >$18.3 billion in deal value (including 4 deals >$1 billion each) over the past five years. Companies with clinical trial management tools or analytical software drove most of the transaction volume with more than $14.7 billion across 23 deals. The discovery/preclinical segment had a total deal value of only approximately $2.1 billion (0 deals >$1 billion) over the same time period.

Many of the large industry players were active in the M&A markets from 2016–2020 with Charles River Laboratories (nine deals), LabCorp (five deals), ICON (four deals), Syn- eos (four deals), and Cambrex (three deals) leading the pack in deal counts. As previously noted, clinical trial management, enrollment, and analytics were of particular interest as buyers looked to expand capabilities in the value chain. In addition to clinical trial management, LabCorp used its acquisitions to expand its focus into medical technology and diagnostics services to diversify its biopharma offerings. Conversely, the most active buyer, Charles River Labs, has continued to focus on a vertical acquisition strategy and has focused its efforts on broadening its capabilities in the bio-

A strong appetite for M&A and consolidation

Over the past five years, the number of M&A transactions has remained steady (see Figure 3); a few large mergers have skewed the total dollar value—2016 saw the $8.8 billion merger between Quintiles and IMS Health (now IQVIA), while 2017 saw the $4.6 billion merger of INC Research and
While strategic buyers placed significant interest in data management and clinical trial software, financial buyers focused on traditional CRO services to roll-up the offerings into a larger and more diversified company.

Financial buyers active and hungry
The COVID-19 pandemic has also created a tailwind for financial buyer activity in pharma services especially as biopharma players of all sizes have gained more attention from investors and the public at large. There were several large buyouts in 2020 including Astorg’s $1.8 billion transaction for eResearch Technology, KKR’s $1.0 billion buyout of PCI Pharma, and Ares’ $500 million buyout of ArchiMed. There were 10 buyouts in 2020, and it became the most active year for buyouts since 2017 (10 deals) when the industry saw a flurry of large deals from both strategic and financial buyers, including Pamplona Capital’s $5 billion acquisition of PAREXEL. In total, financial sponsors accounted for 34 deals from 2016–2020.

While strategic buyers placed significant interest in data management and clinical trial software, financial buyers focused on traditional CRO services to roll-up the offerings into a larger and more diversified company. However, increased financial buyer activity will likely be seen in analytics offerings as data management’s importance in the value chain continues to grow. The trend is starting to emerge with three of the four analytics buyouts completed in 2020. Compared to strategic buyers, financial buyers also put more emphasis on expanding manufacturing capabilities, as 14 of the 34 deals were buyouts of manufacturing companies. Of the 14 manufacturing deals, eight had a primary focus on medical technology, signaling a potential diversification strategy to capture another market segment. With the rise of robotics in medical technology, this trend will likely continue in the near-term.

Of the approximately 50 financial sponsors participating in deals from in the past five years, no other firm has been more active than London-based GHO Capital, which completed four deals over the period. GHO has been in the process of building a comprehensive biopharma services platform as its deals spanned most of the value chain from discovery/preclinical to clinical services and manufacturing. As the industry continues to garner attention, the authors expect to see more financial buyers following GHO’s strategy, which will lead to a larger IPO pipeline in the next three to five years.

Capital markets are waiting on the sidelines
Given the lack of intellectual property in the pharma services space, along with the consultative nature of the businesses, growth capital is typically unavailable to the sector. As a result, the financing landscape has remained tepid, with only eight companies raising a combined $270 million over 12 rounds of equity. Of the eight companies, five were developers of clinical trial software tools, while the other three focused on scaling manufacturing capacity. The authors expect to see more clinical trial analytics companies accessing more traditional venture capital, but a vast majority of pharma services companies will need to rely on organic growth over a long period of time to achieve scale; in fact, CROs and CDMOs had an average time to exit of 22 years and 27 years, respectively.

Additionally, the public markets have not been a viable path for traditional pharma services either. The only companies that have successfully completed an IPO were large, diversified companies with geographic scope and economies of scale. Notable IPOs during the authors’ analysis include large players, Medpace (2016) and PPD (2020). With the continued interest of financial buyers consolidating the CRO and CMO market, it seems likely that an IPO exit strategy could be a target for the financial buyers for their aggregated companies.

Conclusion
Both the CRO and CDMO segments will continue to see long-term sustainable growth and will remain an active area for consolidation. The larger strategic players will need to continue to grow by acquiring specialized services and technologies to improve efficiency. Outcome Capital believes the market may start to see larger strategic CROs engage in a bolt-on acquisition strategy and will also look to move from strictly focusing on either the discovery/preclinical or clinical space to becoming highly integrated to capture large long-term pharma and biotech partnerships. This integrated strategy will allow the service provider to capture more value. Financial buyers will continue to look to consolidate specialty research and clinical services to build out a larger offering to either make those companies attractive for a future IPO or acquisition by the larger strategic players. This market will remain frothy with activity over the next three to five years, and we will continue to see consolidation and growth.

References
This article summarizes a pharmaceutical industry consensus viewpoint of the current regulations regarding data integrity as applied to analytical test data generated to support regulatory activities. In particular, the focus will be on data generated by external personnel (e.g., a third-party laboratory or instrument service technician), hereafter referred to as a vendor.

There are considerations for data integrity (1–4) when data are generated by a vendor. For example, analytical instrumentation (e.g., chromatographic, spectroscopic, spectrophotometric, thermogravimetric, electrochemical, or microscopy instrumentation) utilized in the pharmaceutical industry generates data not only during analytical sample analysis but also during routine or preventive maintenance, such as instrument calibration or qualification, and during troubleshooting associated with repairs. For preventive maintenance or repairs, data may be generated by company personnel, hereafter referred to as the sponsor, or by vendors. The authors will refer to vendor-generated data, whether generated using the sponsor’s instrumentation or the vendor’s own instrumentation, as “outsourced data”.

Although data generated during routine testing may employ well-established processes that ensure data integrity, because pharmaceutical companies deal with many vendors as well as in-house support for instrument support, the maintenance/calibration/qualification process may be fully paper based, fully paperless, or a combination of both (i.e., hybrid documentation). As such, the approaches taken to ensure data integrity during these activities may vary and should be assessed on a case-by-case basis. In addition, the possible modes of remediation may evolve as instrument manufacturers and testing/maintenance vendors evolve their approaches and capabilities.

Within this article, data are defined as electronic and/or paper records generated during GxP testing (e.g., release or stability testing) as well during analytical instrument calibration and/or qualification activities. Outsourced (or third-party) data are data generated on qualified/validated instruments by outside personnel. These include:

- Data generated by vendors when visiting a sponsor site and generating electronic and/or paper records
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that are created and saved outside of the sponsor’s network and support regulated activities (e.g., lot release, clinical stability, etc.)

- Data that support regulated activities generated by a vendor other than at the sponsor site; these data include electronic and/or paper records
- Data generated by secondary vendors contracted by a primary vendor, which may include electronic and/or paper records (e.g., in the case of hybrid systems).

All expectations should be clearly described in the written agreement (e.g., maintenance contract, quality agreement) in any of these situations.

Data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA). Data management, retention, and archiving should be managed based on documented risk, including the format of the data. If electronic, dynamic data are available, these data or a complete, certified true copy thereof should be maintained.

Dynamic data are formatted to allow for interaction between the user and the record content. With dynamic data, a user may be able to reprocess using different parameters or modify formulas/entries that will alter a calculation result. If it is not possible to maintain the electronic, dynamic data record, a complete static representation of all data including metadata, audit trails, etc., must be maintained. Static data (that are fixed and allow little or no interaction between the user and the record content) may allow for a more streamlined approach than that required for dynamic data. For instance, because there is no need to monitor changes in data processing or in reported results, in many cases it may be appropriate for the third-party to supply only a printed or static electronic report (e.g., a PDF file) of the reported data for archive and retention. For data that were generated in static format, a static archived representation is appropriate if it is a true copy (including all relevant metadata) of the data. In all cases, the original data must be completely reconstructable.

The various scenarios under which outsourced data may be generated and managed are summarized in Table I and are further discussed in the following scenarios. In each case, key requirements and points to be considered are given. For all three scenarios, the vendor should be approved by the sponsor and there should be an agreement in place for services provided. The necessary details of the agreement vary depending on the service provided and the scenario.

### Table I. Scenarios under which outsourced data may be generated and managed. ALCOA is attributable, legible, contemporaneously recorded, original or a true copy, and accurate

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Location of data generation</th>
<th>Data storage/archival</th>
<th>Data review</th>
<th>System level review</th>
<th>Audit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario A</td>
<td>At sponsor site</td>
<td>Follows sponsor’s standard IT process</td>
<td>Follows sponsor’s standard process</td>
<td>Follows sponsor’s company procedure.</td>
<td>In scope for audit of equipment/work process/data generated using equipment</td>
</tr>
<tr>
<td>Scenario B</td>
<td>At sponsor site</td>
<td>Follows potentially non-standard process. Controls needed for ALCOA need to be managed by written agreement (including IT controls such as retention, review, archival and other data integrity concerns)</td>
<td>Follows potentially non-standard process</td>
<td>Follows sponsor’s or vendor’s company procedure. ALCOA controls (including who retains, reviews and archives) should be managed by written agreement</td>
<td>In scope for audit of equipment/work process/data generated using equipment. Should be in-scope for sponsor and vendor.</td>
</tr>
<tr>
<td>Scenario C</td>
<td>At vendor site (should limit ability to subcontract without sponsor preapproval in the written agreement)</td>
<td>Follows vendor’s standard process. Controls are needed for ALCOA which need to be managed by written agreement including IT controls such as retention, review, archival and other data integrity concerns</td>
<td>Follows vendor’s standard process</td>
<td>Follows vendor’s company procedure. ALCOA controls (including who retains, reviews and archives) should be managed by written agreement</td>
<td>In scope for audit of equipment/work process/data generated using equipment. Should be in-scope for sponsor and vendor.</td>
</tr>
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### Outsourced data scenarios

**Scenario A: Vendor-generated data on sponsor instruments using the information technology (IT) infrastructure of the sponsor.** In cases where data are acquired and stored by the vendor through the sponsor’s standard workflows and on the sponsor’s technology infrastructure, the sponsor’s standard data integrity policies and procedures should apply. The accounts and roles utilized by the vendor should be unique and configured to ensure attributability and be specific to the work being performed. The sponsor should ensure that the vendor possesses the appropriate training required for access per sponsor’s applicable standards and retain documentation of this assurance.

**Scenario B: Vendor-generated data on sponsor instruments using the IT infrastructure of the sponsor and non-standard processes.** This scenario pertains to situations where the instrument hardware, firmware, or software is being accessed or utilized in a non-routine manner (different than it would typically be used to collect or process data). Examples could include using diagnostic mode or calibration mode, accessing the software outside of the network, saving in a different file
location, or using a hybrid paper/electronic process. A risk assessment and mitigation strategy should be considered to ensure compliance with ALCOA principles.

It is recognized that some of the previously mentioned examples may require non-standard access. The accounts and roles utilized by the vendor should be unique and configured to ensure attributability and be specific to the work being performed. The sponsor should ensure (through a written agreement, direct training, or other written process) that the vendor has appropriate technical and good documentation training per sponsor’s applicable standards and retain this documentation. Data review should follow the sponsor’s standard practices and may include a defined, documented risk-based approach for reviews of vendor-generated data. System level reviews should include reviews of vendor account access. Vendor-generated data on sponsor instruments should be in alignment with the sponsor’s standards for segregation of duties. Controls should be in place to ensure data integrity is appropriately managed. In particular:

- Access needs to be traceable.
- Specific and unique user roles, permissions, and passwords for access are required.
- Where appropriate, access should be provided on a temporary basis and subsequently rescinded after a defined period.
- Controls for remote access, especially by vendors, should be evaluated to determine the effectiveness of physical controls and to ensure appropriate data and system protection.
- Data security (including the ability to delete/modify data) should be subject to appropriate controls (technical, administrative, or procedural); consider accidental loss or corruption of sponsor data.
- Changes in the data retention path (relative to that in the qualified configuration) should be subject to change management.
- Reviews of vendor data (including the audit trail, if applicable) should be defined based on documented risk.
- Vendors should be granted access at the lowest level that allows the performance of necessary duties.
- In cases where administrative access is required for the vendor to perform their duties, their ability to make critical changes (such as deleting, editing, or modifying data without detection) should be controlled through technical, administrative, or procedural means.
- Hybrid paper/electronic processes may be captured in the vendor agreement, but in any case, should be documented and assessed for data integrity risks.
- Deletions or modifications of data or metadata (e.g., dates) should not obscure previously recorded information and should be attributable.

**Scenario C: Vendor-generated data stored on the IT infrastructure of the vendor.** One of the critical elements of data integrity for data generated by a third-party is where the raw and reported data are stored and to whom the data are accessible. Regardless, data should be retained and archived in accordance with a quality agreement (or equivalent) and in compliance with regulatory requirements. These written agreements should establish sponsor expectations and vendor responsibilities related to data integrity controls for good manufacturing practice (GMP) or good laboratory practice (GLP) records, as well as how communication and auditing of such records should take place. The agreement should ensure the following, for the vendor:

- Vendor procedures are in place to ensure that for all data, whether paper or electronic, at a minimum the ALCOA requirements are met.
- Vendor testing records are reviewed by the vendor to ensure compliance with all procedures, specifications, and regulatory requirements.
- Vendor investigations and vendor internal auditing include data integrity (e.g., calculations, quality of procedures/processes to uncover data integrity issues, documented training with a focus on data integrity and responsibilities for the vendor).
- The sponsor should agree to regularly update, review, and communicate the following to the vendor:
  - Any updates to procedures reflecting data integrity practices providing a quality environment between sponsor and vendor.
  - Audit/investigation results and reviews of vendor data integrity quality metrics.

The sponsor should clearly communicate that sponsor audits of the vendor will include a focus on data integrity elements and practices, and the sponsor should ensure that audits include assessment and evaluation of data integrity controls in place.

The written agreement should additionally delineate the record retention responsibilities of the two parties and any hand-offs between vendor and sponsor at specific milestones. In cases where data are collected using software that the sponsor does not have, the vendor should retain e-records and the software necessary to make them human-readable (including metadata).

A primary concern is that of security of the raw data. Data stored on the IT infrastructure of a third party are inherently less under the control and protection of the sponsor. In cases where the third party retains the original data, it is critical that appropriate expectations and responsibilities are clearly defined in a quality agreement (or equivalent). These agreements should include the following considerations:

- Because the sponsor may, in some cases, receive only reports of final data (e.g., from sample analysis or from calibration, maintenance, and qualification), an audit for selecting an external vendor should challenge the process from raw data generation through to distribution of final reports to ensure the accuracy and reliability of raw data generated by the vendor. This audit should include a review of the mechanisms used to generate and distribute data summaries and reports.
- Transparency around the vendor’s IT infrastructure (including the subcontracting of IT infrastructure to cloud-based providers) should be defined in a written
agreement. This agreement should include notification of the unauthorized accessing of sponsor data (e.g., through a hacking attack).

- Responsibilities, including clearly defined ownership and retention requirements/schedules, should be clearly described in the written agreement.
- Where data are transferred between the sponsor and their vendor site, the written agreement should specify how this is done to ensure adherence to ALCOA + principles, including management of true copies.
- All electronic data (or certified true copy thereof) should be retained and include a means to retrieve/read these data (including metadata such as audit trails, etc.). In particular, the vendor must retain the ability to read data from retired instruments through the retention period of the data (as defined by the sponsor).
- Electronic data should be maintained in its original format unless otherwise defined/agreed upon with the sponsor.
- Timing expectations for data retrievability should be clearly described in the written agreement.
- The written agreement should define who is responsible for backup and archiving features. Any incidents with or changes to data archival, backup, or restoration should be clearly documented in accordance with appropriate procedures and reported to the sponsor within an agreed time period.
- The written agreement should include expectations on confidentiality of all disclosed information. The written agreement should define who in the vendor organization has access to sponsor data.
- The written agreement should define the requirements for data review. This should include review against ALCOA + principles (e.g., metadata such as audit trails, where applicable) and system-level reviews.
- Any vendors using cloud service providers should be assessed to ensure infrastructure controls are in place, including infrastructure and services for change control, system backup/restore, and data archiving processes.

Additional considerations for data generated during instrument calibration, qualification, repair, and troubleshooting (can be Scenario A, B or C). Data integrity controls for analytical instruments and equipment may be challenged during internal or regulatory authority audits and inspections. It is a regulatory expectation (1–4) that the integrity of supporting instrument data is robust and that risks to these data have been adequately mitigated. Some examples where data integrity controls (including appropriate change control) are needed include calibration and qualification of raw data, control of standards (e.g., reference standards, external calibrated test probes, etc.) used during calibration, and management of internal and vendor documentation.

There are several aspects of the data lifecycle needed to underwrite the accuracy of analytical data. Requirements include demonstration that an instrument can produce accurate results and is under adequate system controls. Adequate system controls relate to documented procedures that support initial qualification, periodic calibration and maintenance, instrument repair and troubleshooting (including change control), and periodic review of the calibration/qualification status of the instrument.

Analytical instrument qualification and/or initial calibration is critical to ensure data generated on an instrument is accurate (ALCOA). Data generated using systems other than the one under qualification or calibration (e.g., a thermocouple used to calibrate a chromatography column heater) should be subject to the same controls as other data. In a scenario where initial validation/qualification is performed prior to mitigation of data integrity concerns, consideration should be given to potential data integrity concerns of the qualification testing. In general, data generated during calibration, qualification/validation, or maintenance activities should comply with all the foregoing requirements. However, there may be scenarios where data are generated outside of the normal workflow. In these cases, deviations from the normal workflow should be evaluated for risk and documented appropriately, particularly for risks that may impact the attributability or accuracy of the resultant data.

Conclusion

While all three scenarios, as well as many permutations of them, are possible and may be managed, Scenarios A (vendor-generated data on sponsor instruments using IT infrastructure of the sponsor) and C (vendor-generated data stored on the IT infrastructure of the vendor) are strongly preferred from a compliance and risk perspective. If Scenario B (vendor-generated data on sponsor instruments using the IT infrastructure of the sponsor and non-standard processes) is employed, a risk assessment and mitigation strategy should be considered to ensure compliance with ALCOA principles. In any case, the considerations described in this article should be evaluated to achieve compliance.

Acknowledgements

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Preventing for the Unexpected: E&L Studies in Biopharma

Mark Rogers

Extractable and leachable (E&L) studies have become an integral part of any drug development program and serve to ensure compatibility between the product and its packaging. While such studies are now generally well defined in terms of experimental design and data evaluation, these have had to adapt to the ever-increasing diversity of therapeutic products. There are, for example, some unique challenges in the analysis of biopharmaceutical products as a result of certain formulation components, as well as the complexity of the therapeutic itself. This article describes a number of challenges and solutions in the E&L evaluation of biopharmaceuticals, and highlights a selection of those encountered with emerging cell and gene therapy (CGT) products.

Ongoing E&L challenges

The risks posed by leachables on product quality and patient safety are an ongoing challenge for the pharmaceutical and biopharmaceutical industries. Continued investigational development in this area is primarily driven by a number of factors, including: the increased adoption of single-use technologies; progress in the medical device field, particularly combinational devices; expanded directives from industry regulators; and advances in analytical technologies.

Extractables (I) are defined as compounds that migrate from any product-contact material (including elastomeric, plastic, glass, stainless steel, or coating components) when exposed to an appropriate solvent, under exaggerated conditions of time and temperature. To study materials at risk of potential leachable components, extractions of the contact material are performed, generally using aggressive conditions including acidic, basic, organic, and aqueous solvents. These conditions are not intended to distort the material under investigation but do attempt to mimic the drug formulation. The resulting extracts are usually analyzed using a combination of analytical techniques such as liquid chromatography–mass spectrometry (LC–MS), gas chromatography–mass spectrometry (GC–MS), and inductively coupled plasma–mass spectrometry (ICP–MS) that can qualitatively and quantitatively evaluate both the organic and inorganic components, or “extractables”. Such studies are

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well established and may be undertaken with a certain predict -
ability in experimental design and even outcome. In contrast,
however, certain excipients used in the formulation of some bi-
otherapeutics present unique analytical challenges for leachable
determination. Among these excipients are the commonly used
nonionic surfactants, such as polysorbate 80 (Tween 80), which
constitute a mixture of fatty acid esters of polyoxyethylene sorbi-
tan. These have an extremely low ultraviolet (UV) response but
are highly responsive to ionization methods commonly used in
LC–MS (2). This often leads to significant interference, either by
coe- lution and/or suppression during analysis, raising the real
possibility of contaminants remaining undetected. Extraction
of these surfactants prior to analysis is a possible means of mit-
gation but is often not highly effective due to the surfactant’s
inherent heterogeneity and limited extraction efficiency. Care
must also be taken in the application of such an approach since
the leachable may be co-extracted with the surfactant.

In the growing area of CGT, there are currently no spe-
cific guidelines for E&L studies. However, such products
have some unique challenges, such as the use of “ancillary
materials”. These materials are used during manufacturing
but are not intended to be present in the final product. They
are often themselves complex biological materials, such as re-
combinant insulin and human serum albumin, used as media
supplements, and collagen, used as a scaffold in implantable
devices (3). Since these materials can potentially interact with
and be affected by leachables, in the same manner as the bio-
therapeutic itself, the choice of materials and controls must
be carefully considered to avoid adverse consequences for the
manufacturing process.

The evaluation of biotherapeutics for leachables presents
many challenges, some of which are somewhat unique to this
type of product. For example, the biopharmaceutical itself may
interfere in the testing regimen due to its high concentration,
heterogeneity, and/or high detector response. A potential solu-
tion is to remove the biotherapeutic prior to analysis, but the
procedure must be very carefully considered because associated
leachables may be unknowingly removed and/or additional ex-
traneous components may be introduced.

The major concern of leachables in pharmaceutical products
is their specific toxicity and/or genotoxicity. The additional issue
with biotherapeutics is the potential for interaction between the
structurally complex biopharmaceutical itself and any leachable
components. Compared to traditional pharmaceuticals, pro-
teins and other biotherapeutics are often significantly less stable,
due to their strong dependence on physico-chemical and con-
formational structural properties. These larger molecules often
have both hydrophilic and hydrophobic regions, with many re-
active sites for possible leachable binding, potentially resulting
in the loss of activity via mechanisms such as unfolding, trunca-
tion, aggregation, and precipitation. Consequently, the adverse
effects of extractables and leachables can be more significant
and more difficult to assess on biopharmaceutical products than
small molecules. Acrylic acid, for example, a leachable from sy-
ringes, has been shown to react at three different sites within a
protein structure, resulting in potential changes in charge and
hydrophobicity with consequential effects on the therapeutic
properties of the protein-based drug (4).

As the manufacture of many biotherapeutics involves
cellular-based processes, the presence of certain leachable
components can have unfavorable consequences not only on
the final drug product but also on the production process it-
self. Productivity can certainly be adversely affected by
leachables that result in cellular toxicity, leading to signifi-
cant loss in manufacturing yield.

During the past decade, many biotherapeutic manufacturer-
ners have migrated to the use of disposable, single-use systems (SUS)
for production, and this has now become commonplace in the
emerging CGT field. Every operational phase of a biomanufac-
turing process that uses SUS technology is at risk of leachable
contamination. This contamination can be introduced as a re-
sult of contact and interaction with different materials, such as
polymers, metals, and additives used to construct holding
tanks, films, bags, tubing, and filters. This concern extends to
containers for buffers, media, water for injection, and other liq-
uids required for manufacturing. The possibility of leachable ac-
cumulation may also arise since concentration stages are often
used in the manufacturing process.

The majority of biopharmaceuticals are injectable products
and, therefore, contaminants enter the bloodstream directly,
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Biologic E&L studies: the difficulties

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These drugs can be stored for long periods of time, providing higher risk of leachable adulteration of the product than the solid dose forms common with traditional pharmaceuticals.

Certain products developed in the CGT area can present further challenges for E&L evaluation. Since the quantities of product can be relatively low, the ratio of contact material surface to the drug volume is very high, increasing the potential for leachable contamination. This may be further exacerbated in those treatments that are essentially customized, with each patient receiving the entire product dose.

**Product development strategy**

Risk assessment in terms of E&L is now an integral part of any product development strategy. This is of particular importance for CGTs, which should not only evaluate the likely compatibility of contact materials used in manufacturing, but also include an experimental study designed to provide an accurate assessment of the extractable and leachable profiles.

While many biotherapeutics are produced as liquid formulations, lyophilized forms of drug product are also commonplace, as part of efforts to improve stability during storage. Interestingly, the FDA Center for Drug Evaluation & Research, the FDA Center for Biologics Evaluation & Research, and the United States Pharmacopeial Convention (in United States Pharmacopeia <1664> [5]), describe sterile powders for injection as being “low risk” for leaching, despite some evidence to the contrary. It has been demonstrated, for example, that several semi-volatile organic compounds originating from butyl rubber stoppers—part of the primary packaging system—may leach into a lyophilized product but not a liquid formulation stored in the same packaging (6). The explanation for this finding lies in the hydrophobicity of the leachables, rendering them very poorly soluble in aqueous media but able to diffuse from the stopper. This is perhaps facilitated by their volatility and the nature of the drug product.

There are multiple types of material used in the manufacture and storage of biopharmaceuticals, and most may be classified as either glass, metal, or synthetic polymer/elastomer. The latter are recognized as the most significant sources of leachables, often resulting from monomers/oligomers of the polymer itself, as well as catalysts, initiators, additives (e.g., lubricants, antioxidants, antitack, and antistatic agents), adhesives, anchoring agents, adhesive resins, colors, fillers, and degradation products of almost all these components. The diversity and nature of these potential contaminants and their often-unpredictable interactions with formulated biopharmaceuticals pose significant challenges to analytical assessment of the drug products and process materials. There are now significant guidance documents available from regulatory authorities, industry organizations, and researchers providing at least some support in the design and rationale for suitable experimental approaches.

For biopharmaceuticals, inorganic leachables (generally associated with glass and metal) are of particular concern because of their potential impact on the stability and efficacy of the drug itself. A metal commonly used is stainless steel, which has found applications in manufacturing, shipping, and storage, and is known to leach iron, chromium, and nickel, particularly if the steel is unpassivated (7). Trace levels of metal ions can potentially cause protein degradation by mechanisms such as protein oxidation and fragmentation. The latter occurs because of the metal-binding propensity of aromatic amino acids such as tryptophan, tyrosine, and histidine. Certain metal–protein binding is also known to induce secondary and tertiary structure changes resulting in the formation of insoluble protein aggregates (8).

Glass has also been demonstrated to be a source of certain metal leachables. For example, manganese and iron oxide—used as coloring agents—are present in Type I amber vials as are zinc and barium oxides. Higher levels of manganese and iron have been shown to leach from amber glass compared to clear glass. Meanwhile, sterilization techniques, such as steam autoclaving and gamma irradiation, may also lead to the presence of metal ion contamination (9).

Some biotherapeutic excipients, and the drug itself, may also play a significant role in facilitating the extraction of metals from contact surfaces. Certain proteins and chelating agents, such as ethylenediaminetetraacetic acid, have been shown to increase the quantity of metals such as aluminum, calcium, and iron from plastic container systems. Similarly, buffers such as phosphate and lactate can also increase the metal leaching from both metal and glass surfaces.

The area of E&L investigation has developed rapidly over the past decade, resulting in technological and regulatory advancement. Ultimately, this has led to safer medications. However, developments in biopharmaceuticals and specifically in CGT are likely to present further demands on expertise in areas of manufacturing and analytics.

It is clear that a single, common strategy, for monitoring and/or eliminating leachable contaminants will never be sufficient to address all situations. Instead, engineers and investigators must be always prepared for the unexpected.

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Picking the Perfect Method Development Partner

Felicity Thomas

Outsourcing time-consuming and costly services is becoming increasingly popular within the bio/pharma industry. The right contract development and manufacturing organization (CDMO) can not only provide the best equipment for certain tasks but can also provide a wealth of expertise to provide the best possible chance of success.

To learn more about best practices for selecting an outsourcing partner and the questions that should be posed to a sponsor company when approaching a method development project, Pharmaceutical Technology spoke with a panel of experts. The panel included Emma Leishman, manager, Advanced Analytics, Avomeen; Alex Wheeler, senior technician, and Louise Rigden, technical documentation officer, both from Wickham Laboratories; Rebecca Coutts, general manager, and Amanda Curson, head of Analytical Development, both at PCI Pharma Services; Vincent Thibon, technical development lead, RSSL; Jerry Mizell, senior director, Analytical Services, Metrics Contract Services; and Anders Mörtberg, analytical chemist, Recipharm.

Selecting an outsourcing partner

PharmTech: Could you provide some best practices for selecting the optimal outsourcing partner for method development?

Leishman (Avomeen): Finding an outsourcing partner can be tough—nobody wants to be left hanging on a critical project due to outsourcing delays. A good outsourcing partner will understand this and will do their best to meet your needs. Communication is key. You should be able to talk directly to the scientists and technical directors who will be overseeing the project. That way, the project can get started correctly with everyone on the same page.

When selecting an outsourcing partner, the experience, expertise, and equipment capabilities of the outsourcing lab should be assessed. If the method is for filing with a regulatory authority, then quality systems should be part of the initial assessment. It is especially promising when a partner has prior experience with similar methodology or even recommendations from previous clients.

There are some key questions that should be asked by both the sponsor company and the outsourcing partner before undertaking a method development project.
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With these practices, a strong relationship can be built as would ensure that there is good, clear communication and the required timeframes for any given project. A good collaboration, and good planning to meet agreed timelines.

Also, and possibly most importantly, expectations around timelines should always be discussed before engaging in testing as just because a company can offer the testing does not always mean their availability will match the required timeframes for any given project. A good recommendation is to establish expectations early, communicate clearly, and ensure there is contingency built into your project timeline to deal with any issues that may arise.

Moreover, the experts in a CRO can advise on regulatory requirements and therefore assist in advising on the testing required as it can sometimes be difficult to interpret the guidelines. Consultancy services can be invaluable to a smaller drug development organization, or to clients such as student researchers who may not have experience of the industry.

Best practices for selecting the best outsourcing partner for method development include picking a partner who has the following: previous practical experience in developing methods for particular dosage forms; a number of successful validations as a result of initial method development over the past five years; available equipment with multiple models, capacity, and resources that will be allocated; the ability to deliver within required timelines; the ability to provide summary development reports or copies of data required to support regulatory submissions; a good history with the regulatory authorities; and lastly, the ability to safely handle certain compounds, for example, potent molecules.

In addition to the outsourcing partner complying with regulatory standards (e.g., company standards, GMP approvals, quality compliance procedures, and auditing systems), we think that the correct outsourcing partner would ensure that there is good, clear communication and collaboration, and good planning to meet agreed timelines. With these practices, a strong relationship can be built as trust is key.

Key questions to consider when selecting a potential outsourcing partner include: Are the labs approved by the relevant regulatory body (e.g., FDA or Medicines and Healthcare products Regulatory Agency)? What technical knowledge and instrument capabilities are available at the CRO? Can they assist developing the methods within the required deadlines?

A company should ask for examples of previous development projects and what led to success. Detail should be given regarding the types of samples in which methodology was developed. For example, asking whether a company specializes in method development for inhalation, ointments, creams, liquids, or solid oral dosage formulations is an essential first question. Detail should also be given describing development experience with challenging molecules or formulations and how those challenges were overcome. For the initial meeting with the prospective CDMO, sponsors should interview chemists and ask for the strategies that would be employed when developing methodologies. This could include asking what strategy they use to develop a tablet dissolution procedure where the API is practically water insoluble.

There are a few key questions that a drug developer should ask of a potential partner before entering a working relationship with them. These questions include do you have experience in similar projects to mine? Do you know what to do, and will your solutions work effectively? What is your track record in successful method development in my particular field or category, such as small molecules, or biopharma? What are your team’s qualifications? How many members of your team have in-depth expertise in my field? Do you have the necessary instrumentation and infrastructure to support me and my project? Do you have a GMP-certified laboratory? When can the work be finished? It is often the case that developers ask when the work can be started, but delivery is the key issue to consider. Are you a reliable and well-established partner that will still be around to be able to deliver the project? How will the method development work be documented? It is important to understand how and why specific method parameter choices were made by a partner. When the new International Council for Harmonisation guideline Q14 on method development will become effective, it is important the outsourcing partner is well versed with its implications for method development practices.

Establishing service requirements

Are there specific questions the outsourcing partner should ask too, before undertaking a potential method development project?

Before undertaking a potential method development project, outsourcing partners may want to ask what data are available for review on the physical and chemical properties of the drug substance, also whether there is information on potential dosage form, strength, formulation information, and the phase of drug development. Additionally, they may want to ask if there is any previous an-
Any method development project needs to address the actual needs of the project. What deliverables do you want to specify? What protocols, reports, or method descriptions do you want to receive on completion of the project? The intended use of the method to be successful. When does the project need to be delivered in full? Answering ‘as soon as possible’ should be avoided as it will necessarily lead to higher costs. 

Müller (RSSL): First, the potential partner should ask is there a technical package for the API or drug product that describes the chemical and physical properties of both? Properties such as morphology, solubility (organic, aqueous, and pH range solvents), stability, and any forced degradation data should be requested along with methodology, and any associated validation reports. Having a solid technical package available when beginning development typically accelerates the development process.

Thibon (RSSL): Questions we try to ask before undertaking potential method development projects include: What are the purposes of the method? How many formulations and are there any plans to extend formulations? When the method is used routinely, will it be used for quality control testing or investigation only? When is the method needed by and have other alternative techniques been considered? Is the method development project to improve an existing method or develop something from scratch?

Mortberg (Recipharm): There are several questions that a drug developer can expect to hear from a potential partner. Answering these questions as comprehensively as possible is key to help the partner provide a realistic timeframe for delivery and deliver the best possible service. The key questions a drug developer should answer include what is the ‘pre-history’ of the project? Could you provide any background information and context to help understanding of the project’s needs? How do you intend to use the method once it is developed? Any method development project needs to address the actual use of the method to be successful. When does the project need to be delivered in full? Answering ‘as soon as possible’ should be avoided as it will necessarily lead to higher costs. What deliverables do you want to specify? What protocols, reports, or method descriptions do you want to receive on completion of the project?

Wheeler (Wickham Labs): Potential partners should establish the intended use of the product. Knowing this can not only help the potential partner establish testing but could also help deliver valuable insight regarding how the product should be tested, specific quantities to test, and any regulatory specifications. If the CRO has tested similar products before, they may also be aware of additional requirements which had not already been considered, and capturing these issues early on could save time later.

The CRO should be asking questions specifically relating to the product. For instance, if the testing required is microbial limits testing, then it should be established if the product contains properties or constituents which might inhibit microbial growth during the product’s validation.

A timeframe should also be established early on, with the CRO confirming they have the capacity to perform exactly what the client has requested. If those targets cannot be met, it should be considered whether there is room to compromise on the timeline or alternatively, whether new methods or systems could be considered for validation to facilitate the project.

Rigden (Wickham Labs): It is also critical that confidentiality and technical agreements are in place to provide guidelines for the relationship between the parties before any testing commences as this protects the customer and the CRO by establishing responsibilities and ensuring they are meeting regulatory and legal requirements.

Leishman (Avomeen): The purpose of the method must be established to guide the work. A method development scientist will ask questions to figure out the purpose. For example, who will be using this method? What sort of conclusions will be made based on data obtained from the method? Where is the method going to be used? At a single lab or transferred between sites? When will this method need to be implemented? Why is this method required? How has this testing been performed in the past? Does the method need updating to keep up with current standards?

The regulatory requirements and the timeline should be established to scope the work. Timelines to reach the end goal of the method need to be realistic—it is not possible to develop a method from scratch and validate it within a week. Obtaining detailed information on the analyte, the matrix, and the final purpose of the method assists with devising a customized and purpose-driven scope of work.

Three steps to success in outsourced method development

If optimized, method development can ensure a drug product successfully progresses through to commercialization. Outsourced partners that specialize in method development services can help companies through the three main stages of method development, leading to success.

The first step, feasibility, is to collect sufficient background information on the API, determine the objective of the method development, see if there are established pharmacopeial methods, and define the phase of the development work. Secondly—development—it is important to minimize the complexity of the methods and prepare the sample suitably. The last step, involves optimization or validation of the methods—a transferable method is a robust one that will find future application.

To learn more about the steps involved in method development, read “Outlining the Key Steps to Method Development” on PharmTech.com.

—Felicity Thomas
For inhaled products, dry-powder inhaler (DPI), pressurized metered-dose inhaler (pMDI), and nebulizer devices are the most commonly used delivery platforms, with others that have less common, niche applications. The choice of delivery platform may be driven by different factors at different points in the development cycle; one device may be used up to proof-of-concept and an alternative chosen for commercialization.

Each drug program has unique drivers; factors related to the device platform, in combination with the drug’s needs, should be evaluated for each new product concept and development program. A device-agnostic development approach is best to avoid being swayed by previous programs or a technology bias towards a single platform.

Considerations are both technical—the API and its associated physical properties and dosage requirements—and also practical—the target patients’ needs, such as age, usability, lifestyle, and expectations based on other available devices. Additionally, there are therapeutic target considerations and strategic and commercial ramifications of a program, depending on the innovators’ goals and lifecycle plans. Making informed choices at a given stage of development can save time and money while maximizing the probability of a project’s success.

The use of dry powder formulations originally focused on respiratory diseases such as asthma and chronic obstructive pulmonary disease. Pulmonary administration of an API provides direct, rapid action when treating these diseases, and a DPI allows patients to breathe medicine into their lungs quickly, while being breath-activated, meaning that the act of breathing through the inhaler releases the drug into the lungs. There are a variety of DPIs, some with a supply of the drug inside, and some where the drug needs to be added to the device before use.

Dry powder formulations delivered to the lungs offer numerous advantages. In the deep lung, the tissue wall is only one cell thick, allowing rapid, systemic delivery to the bloodstream. This approach affords lower doses, eliminates the risk of first-pass metabolism, and reduces the chance and severity of potential
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Development

side effects. DPIs are generally small and portable, do not require use of expensive propellants, and can be relatively simple devices, which can result in lower manufacturing costs.

The development and manufacturing of DPI products is complex, and close integration between formulation, device development, analytical, and manufacturing teams can help overcome challenges and shorten timelines, reducing the risk of expensive and time-consuming changes later in development.

Device selection factors
There are a number of DPI device options open to innovators, and selection is important both for the drug and the phase of development. For accelerated development to achieve clinical milestones, a capsule device may be appropriate. For commercial purposes, blister-based, multi-dose, commercially validated devices may be more suitable.

Choosing a DPI starts with the defined target product profile (TPP) and matching it to the user requirements. Ultimately, the device must deliver the required payload of drug to the desired site in the patient’s lungs; and the patient must be able to use the device easily.

DPIs are not generally used for pediatric purposes; patients who have arthritis, have low strength, or are unable to inhale as intended, ensuring both patient compliance and effective delivery. Market intelligence and vigilance of similar products is necessary to understand likely problems in the commercial environment.

Bespoke DPIs offer advantages for potentially non-standard formulations and where intellectual property must be protected. This option, however, must factor in the device’s functional attributes and physical characteristics, as well as formulation needs, safety, reliability, and standards and regulations. Practical aspects of construction and use, including cleaning, maintenance, and lifespan must also be evaluated, and balanced against potential impact on the supply chain, prescriber, and payer.

Designers and innovators must ensure the compliance of the patient is still at the core of product design, but factors including cost of goods, safety, and effectiveness are crucial in the operational success of any device and creating solutions to real problems by designing the right medical device.

Particle engineering and formulation
The combination of formulation and the device used to deliver it is integral to an effective drug product, and the key areas to consider when developing a DPI formulation are the drug substance, excipients, and the processing method.

Most dry powder formulations are a blend of a micronized drug substance with lactose monohydrate and other excipients. The forces of particle cohesion and adhesion in the dry powder formulation are key; to manipulate these to the optimal parameters, additives, excipients, or particle engineering measures are used. When designed properly, these factors enable the patient to successfully empty the dose receptacle and achieve reproducible dose delivery during inhalation. The drug product must also be uniform, a common challenge in carrier-based formulations.

Drug formulation stability is also crucial, both from a physical and chemical perspective. The API’s properties must be understood to evaluate the risk of particle-particle, moisture, and excipient interactions, and the appropriate processing method and excipient choice, as well as potentially incorporating moisture protection in the dose packaging, can be used to minimize stability issues. Biologics molecules are particularly prone to instability, as formulations with reducing sugars such as lactose can react with functional terminal amines of peptides or proteins.

A design-of-experiments approach is often used to understand the interactions between the drug’s characteristics, excipients, and processing conditions. For drug substances that are physically or chemically degraded by micronization, spray drying is an alternative.

Whatever device delivers the drug formulation, flowability of the powder is paramount, and excipient choice is a major factor in maximizing this. During development, consideration must be given to the filling technology, whether into blisters or reservoirs; drum filling, capsule filling, and fill-to-weight technologies are commonly used.

Spray-dried powders tend to be hygroscopic, so performance can be quickly compromised by moisture absorption, whereas this is less common for lactose blends. Preventing segregation is critical for reservoir devices to ensure consistent metering and dosing; however, for blister formats, segregation does not impact the dose unless it reaches a point where the powder cannot readily be aerosolized, and the dose evacuated is impacted.

Analyzing attributes
For spray-dried powders, techniques such as modulated differential scanning calorimetry and dynamic vapor absorption give information on the amount and stability of the amorphous content, moisture uptake, sensitivity, and phase transitions. This analysis can be used to modify manufacturing conditions to ensure a more stable formulation and provide a rapid screen of formulations without the need for extensive stability testing.

The complexity of large-molecule drugs presents additional challenges to DPI development. Small molecules can undergo chemical degradation, and the degradation products can generally be detected by a single method such as reverse phase-high performance liquid chromatography. Large molecules have multiple degradation mechanisms, and so a more orthogonal
A key challenge in manufacturing inhaler devices is evaluating the molecule's degradation. Assessment of potential degradation mechanisms for each molecule will inform the critical quality attributes (CQAs), which drive the selection of appropriate analytical methods.

For a generic drug DPI program development, where the test product must match the reference, experience in formulation development can significantly speed the development process. Testing is vital to understand aerodynamic particle size distribution of the drug using more anatomically relevant mouth/throat models coupled with actual or simulated breathing profiles, as well as getting further insight into where the drug deposits in the lungs. Morphology-directed Raman spectrometry and United States Pharmacopeia dissolution apparatus also gives insights into the fate of the aerosolized formulation at the local site of action by assessment of its structural composition and dissolution of the drug.

Deposition of the carrier in the formulation can also provide useful information, and experience in method development in similar models and instruments reduces method development time. This information can guide further refinement of manufacturing process parameters, the particle size distribution of lactose and the drug, or device design to enhance delivery. Performing these tests early on helps target formulation and reduces the need for multiple screening studies, giving greater confidence of clinical success.

Advanced analytical tests can be used to characterize the powder within the reference DPI, and where a successful pharmacokinetic (PK) match is required between test and reference, use of more advanced characterization tests that have greater clinical relevance can be a powerful tool to help drive product development before embarking on costly PK studies. European and US regulatory authorities are keen to see greater generic-drug competition and are supportive of efforts to reduce the time and cost of development, while maintaining product safety and efficacy. This generic-drug competition can only be achieved by greater use and understanding of these advanced analytical methods. While standard methods still have uses in formulation development, advanced methods are beneficial, and developers of DPIs should not be constrained by standard pharmacopeial tests.

Sizing up scale up
A key challenge in manufacturing inhaler devices is evaluating what constitutes an appropriate scale at each development stage. In early development, when materials are often in limited supply, there is an inevitable conflict and balance between the scale of manufacture and the number of batches needed to build scientific understanding.

Depending on whether a DPI device uses a capsule or a blister-based platform for commercial purposes in early development, capsule-based technology is seen as preferable as it offers flexible dosing and a relatively quick pathway to clinical phases.

However, capsule development brings different considerations and complexities as dry powder blends can interact with the capsule material. Capsule composition (typically gelatin or hydroxypropyl methylcellulose), water content, lubricant level, and surface quality can result in changes in performance, chemical stability, physical sticking, and agglomeration. The characteristics of formulation and device must be understood so that the most appropriate capsule type can be matched. Effective control of manufacturing environmental conditions and long-term packaging considerations are necessary to maintain stability and performance of capsule-based DPIs.

Developing validated models in the early phases that establish robust processes can mitigate the risks associated with scale up. If comparable drug product performance from batches made at laboratory-scale and commercial-scale can be established, a significant amount of the development work can be conducted at a smaller scale, reducing material costs and enabling faster execution of experiments, while giving confidence in future scale up. It also allows capital investment in commercial manufacturing to be made on a risk-based approach, once milestones have been reached.

For these models to be effective, early-phase development equipment and processes should be synergistic with that at the scale-up phase, reducing the required data capture for critical process parameters (CPPs) and CQAs. Involving late-phase manufacturing teams early in development can reduce the risk of issues later in the product lifecycle. Using cross-functional teams and streamlined protocols to ensure all CQAs and CPPs are captured can simplify the process and reduce delays in later development.

Lean manufacturing techniques can ensure optimal resource and equipment utilization and future-proofing capacity can be done by sourcing equipment that is directly scalable from that used during early-phase development. Effective and timely sourcing of device components, as well as excipients and APIs for manufacturing campaigns, can mitigate against drug shortages. Forward-looking allocation of resource, as well as the ability to repurpose or procure additional equipment and resource with speed, is also key to maintain delivery supply chains.

An integrated approach
From all the options open to developers of inhaled drugs, DPIs have many advantages, but the development and manufacturing of devices is complex, and respiratory formulations are a balance between formulation considerations, delivery device, and patient population.

Device and formulation development are symbiotic, and each must take into account the effects and interactions on the other, and overlooking issues of scalability at an early stage can avoid changes in later development phases, which can be especially time-consuming and costly. Using a development partner with experience in both device and drug development, and the regulatory and manufacturing needs for commercialization, allows program teams to integrate the formulation, device development, analytical, and manufacturing development to avoid potential challenges and shorten timelines.
Manufacturing

Packaging for Stability Studies: to Outsource or Not?

Scott Kenny

The average cost of bringing a new drug to market is estimated at $1.3 billion (1), and the average timescale from initial discovery to market often spans 10 years or more. It is well documented that the investment and time involved in developing new drugs has resulted in big pharma organizations choosing to outsource some or all of their R&D operations to academia, contract research organizations (CROs), or contract development and manufacturing organizations (CDMOs). CROs and CDMOs are facing increasing competition, cost pressure, technological innovation, and consolidation activities (2), meaning that they, in turn, might outsource specific activities, such as stability studies and the associated requirements, to smaller specialists.

Many big pharma organizations instead choose to acquire or buy formulations from small-cap developers once they have been proven. A report in 2020 found that large and mega-cap companies were the most likely group to source new molecular entities (NMEs) through company acquisitions (3). For example, in October 2020, Gilead purchased US biotech Immunomedics and its potential cancer blockbuster Trodelvy (sacituzumab govitcan-hziy), and Sanofi added a potential multiple sclerosis drug to its pipeline when it bought Principia Biopharma in August 2020. These smaller players are likely to be dependent on outsourcing, with key partners already firmly in place when they are acquired.

As of Feb. 1, 2021, there were 365,829 clinical studies registered globally, which is a monumental increase since 2000, when there were just 2119 (4). In that time, the focus has also shifted to rare disease and personalized medicine, with orphan drugs, biotechnology, and gene therapies attracting significant investment. Because of this, packaging requirements are becoming more complex, to accommodate sensitive formulations and APIs, as well as the small-scale nature of personalized medicines. The more sensitive or potent a drug is, the higher the barrier properties are, therefore, the more emphasis placed on the packaging.

Developers might invest in small-scale equipment to produce packaging for stability studies in-house, or they might outsource production. Manufacturers should consider the benefits and risks to both approaches.

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With discovery work of these kinds of drugs being done more often by smaller players, the scale, size, and resources of these smaller players dictate their dependence on outsourcing of key activities, such as stability testing, to specialists. These activities often require small batches of packaging to be produced. Developers might invest in small-scale equipment to produce the packaging in-house, or they might outsource production; there are benefits and possible risks to both approaches that need to be weighed.

**For individualized production, small-batch packaging is a key requirement.**

**Personalized medicine and Industry 4.0**
The shift towards personalized medicine sees therapies targeted to particular groups of patients (stratified) or individuals (personalized), such as the case of patient-specific autologous cell and gene therapies (5). These therapies will require a shift in manufacturing to agile, small-scale individualized production, in which the patient quickly receives individualized drugs, suited to their specific needs. This new reality is to be facilitated by Industry 4.0—which includes connectivity, advanced analytics, automation, and advanced-manufacturing technologies (6)—and is expected to better enable quality by design. In this new paradigm, outsourcing becomes even more important, with fast, efficient, small-batch packaging a key requirement.

**Enabling fast, effective stability studies**
Each new drug application requires a stability study, as regulation requires expiration dates to be indicated on all pharmaceutical products, and stability is a critical quality attribute.

In a stability study, the effects of variations in temperature, time, humidity, light intensity, and partial vapor pressure on the pharmaceutical product are investigated (7). Accelerated stability studies are common for process validation and material selection pre-commercialization. In accelerated studies, developers imitate a two-year shelf life in the space of around three months, usually at 45 °C and 75% humidity.

Multiple accelerated stability studies might be required to test different packaging materials pre-production. Some stability studies may require one to 200 packs, while others may require up to 2000, depending on the amount of pull points in the stability study. Developers need flexibility and speed from their packaging department or supplier to accommodate increasingly complex and varied stability studies.

**The role of material selection**
Stability studies are not only critical for regulatory approval, they prove key for the newer types of drugs when material selection can be challenging. When it comes to material selection, it is common that developers will over-specify their blister-pack material. They might know from past experience that aluminum gives close to the best barrier possible, so without always knowing exactly how sensitive their material is, might request it regardless of need.

Contract packaging suppliers can provide advice on material selection and, for example, recommend testing the originally requested high-spec packaging alongside alternatives, such as high barrier thermoform materials, which might be half the price and also faster to form, easier to fill, and smaller. Stability studies will then establish what barrier is actually required, for example, whether thermoform is suitable, or whether cold form is necessary. The small investment in running stability trials with different blister packaging materials could save a significant amount of time and money when the product is scaled up.

**Running stability trials with different blister packaging materials can save time and money at product scale up.**

Stability studies are required for material selection or shelf-life validation, process validation, and through the lifecycle of the drug. While post-commercialization studies will use the final product and packaging, for the accelerated studies, it is important to have ready access to quick turnaround, small-batch packaging to achieve compliant, effective stability studies.

**Considerations for outsourcing**
Whether drugs are developed by CDMOs or by small cap players, careful consideration would need to be made as to whether to outsource the packaging for stability studies. In both cases, a hesitation not to do this might be to protect intellectual property (especially with experimental, high-value drugs); the benefits of outsourcing, however, might outweigh that risk.

In the case of CDMOs, some key benefits of outsourcing packaging for stability studies might include:
- Reducing the risk of cross-contamination if developing a potent or experimental drug
- No need to change lines over for small batch runs
- No additional tooling required
- No delays due to availability of stability chambers. For smaller developers, the benefits might include:
- No need to invest in equipment/facilities
- No requirement for auditors, licensing, etc.
- Achieve milestones in a shorter timeframe
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- Provide technical expertise, because many employees in smaller developers have biological, chemical, or medical backgrounds, but may not always have detailed knowledge of packaging operations.

If the decision is made to outsource packaging for stability studies, there are some key questions to ask of a potential supplier. These questions might include:

- What turnaround times can you guarantee?
- Cost? Note that there may be additional cost to the packaging, such as design services and tooling manufacture.
- Minimum quantity? This question should be asked early in supplier qualification as they may not have the capacity or motivation for small-batch packaging.
- Material availability? Some materials have relatively long lead times, so it is worth looking for a supplier with a large selection of material grades in stock.
- Material selection expertise? Working with a supplier who can help give guidance through the available material grades can be beneficial.
- Design expertise/experience? A good supplier will be able to understand your requirements immediately and may be able to meet them with an existing toolset, reducing the overall cost of your project. Experience in larger production environments can be beneficial to help you design a package that is scalable with common packaging processes.
- Cleanroom capabilities? Understanding the options for environmental conditions will help to determine which type of drug the supplier can handle.
- Leak testing? Non-destructive leak detection can be beneficial for stability trials, as it ensures all packs are leak-tight prior to stability so package integrity can be immediately ruled out as a risk/concern if outliers are found in the stability data.

Conclusion

In the case of stability studies, experts in packaging can deliver small batches quickly and cost-effectively for accelerated stability studies that are crucial to the future success of a new drug.

References

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