OUTSOURCING TRENDS IN BIOPHARMACEUTICALS AND CELL/GENE THERAPY

Institutional Industry Report

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Introduction
The cell and gene therapy community gathered recently in La Jolla at the annual “Meeting on the Mesa” of the Alliance for Regenerative Medicine to review the state of the industry. The mood was ebullient as attendees celebrated the emergence of the industry from “R&D/developmental puberty” into commercial adulthood. The clear consensus was that cell/gene therapy, benefiting from substantial R&D and development efforts over the last two decades, has come of age in its ability to provide transformative new treatments for patients. At the same time, the generational change wrought by these treatments, compared to traditional standard-of-care medicines, will require significant adjustments in the behavior of all industry participants, including developers, outsourcing providers, caregivers and payers.

In her opening remarks, ARM CEO Janet Joyce Lambert provided some instructive data, noting that there were 892 active cell/gene therapy clinical trials currently underway globally (including 466 in the U.S.), and that capital investment in cell/gene therapy companies had skyrocketed since 2010, as shown in the following table:

<table>
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<tr>
<th>Year</th>
<th>Grand Total</th>
<th>Private Equity</th>
<th>Venture Capital</th>
<th>IPO</th>
<th>Public Secondary</th>
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<tr>
<td>2010</td>
<td>$1.5Bn</td>
<td>$46M</td>
<td>$235M</td>
<td>$31M</td>
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<tr>
<td>YTD 2018</td>
<td>$10.3Bn</td>
<td>$690M</td>
<td>$2.6Bn</td>
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Heard throughout the meeting was a consistent refrain: the industry was approaching an inflection point in which “commercialization needed to catch up with R&D and development” and enable the manufacturing and distribution of therapies “at scale, in a sustainable way.” To this end, participants repeatedly emphasized three key industry priorities:

- Significantly increasing manufacturing capacity to sustain the pressures of producing new cell/gene therapies at commercial volumes.
- Addressing the perceived resistance to the high initial cost of these therapies, with a focus on the education of patients, caregivers, and payers.
- Achieving general acceptance of a deferred payment system in which payer/patient disbursements would match the long-term therapeutic effect of the new products.

Manufacturing is a significant hurdle to commercialization. Given the multiple steps in the removal, modification and administration of a patient’s cells or genetic material, the processes and controls for the creation of cell and gene therapies are geometrically more complex than they are for traditional medicines. As such, the commercialization of these therapies will clearly require substantially more manufacturing capacity than is currently available. The message is clearly articulated and axiomatic: much of that expanded capacity will come from outsourcing suppliers.

In this report, we examine recent outsourcing trends and performance in discrete portions of the prescription (non-OTC) drug market: biotherapeutics and cell/gene therapies. Biotherapeutics are “large-molecule drugs” or “biologics,” that is, biologically derived drugs developed through biotechnology research. Cell and gene therapies are the newest class of drugs and are widely viewed as “the next pillar of medicine.” These treatments use the body’s own physiology — with discrete human interventions at the cellular or genetic level (or both) — to alter what are typically inherited dysfunctions. In contrast with traditional therapies, they target the permanent, or at least very long term, reversal of the conditions they address, and seek to cure disease rather than merely manage its symptoms. They also eliminate or greatly reduce the need for long-term maintenance therapy. As such, the cost of a cell/gene therapy is “amortized” over a lengthy — perhaps lifelong — period of freedom from therapeutic intervention. Nonetheless, the high initial cost of cell/gene therapies, reflecting the high cost of the goods and services needed to produce them, is likely to result in “sticker shock” for caregivers, patients, and payers unfamiliar with the transformative nature of these therapies.

As discussed below, we expect this combination of high costs, manufacturing complexity, and insufficient industry capacity to provide significant opportunities for outsourcing providers in the years ahead.

Outsourcing of Cell/Gene Therapies
Global biopharmaceutical revenues are growing at a 12%-14% annual rate and account for more than 40% of current drugs in development; outsourced R&D and manufacturing services provided to the developers of these therapies have grown, and are expected to grow, at a similar rate. The outsourcing of R&D and manufacturing functions for cell and gene therapies, and the intensity of outsourcing activity, may grow at an even faster rate.

Outsourcing intensity in cell and gene therapies, though likely to grow rapidly in the coming years, has yet to reach the levels regularly seen in the small-molecule drug space. We believe that the current low intensity reflects a range of factors, as listed below:

- the relative complexity of R&D and bespoke manufacturing processes for cell and gene therapies compared to those for small-molecule drugs.
- the fact that very few biopharmaceuticals have reached the end of their protected sales cycles, which has thus far limited opportunities for outsourcing-intensive biosimilars, biobetters and biogenerics.
- the relatively low margin pressures for developers of cell and gene therapies, who typically face less competition than their small-molecule brethren, as well as less public investor-driven scrutiny of their financial performance.
- the shortage of suitable manufacturing facilities and qualified outsourcing staff.
• the relatively early stage of industry development, reflected in the fact that simply “getting products to market” has thus far taken precedence over cost concerns.

As these factors suggest, the economic benefits of outsourcing (i.e., productivity, efficiency, time-to-market and quality gains) have yet to be fully realized in this industry segment. The providers of outsourcing services to this segment thus appear poised for extended growth as biopharma companies take advantage of the demonstrated economies and expertise of outsourcing. Among the drivers of this growth:
• Strong growth in underlying biopharmaceutical and cell/gene therapy markets.
• Increasingly expensive drug discovery is forcing developers to focus on core competencies, i.e., target finding, drug discovery and global marketing and sales rollout, rather than on nonproprietary, outsourcable functions.
• Development and manufacturing will increasingly be outsourced as a noncore activity, especially during the highly volatile clinical development phase.
• Large pharmaceutical companies are focusing on fewer therapeutic specialties, which may nonetheless be targeted by a wide range of technologies; this will require new development and manufacturing platforms, which cannot all be run in-house and will require at least some outsourcing.
• Pharma companies increasingly view the use of CMO/CDMOs not only as a means of lowering costs, but as a strategic priority, providing benefits that include flexibility, speed and lower capital investment.

**Cell and Gene Therapies Require Outsourcing Increases**

The manufacturing needs and current manufacturing capacity for cellular/gene therapies point to a worsening “capacity crunch.” [See Endnote 1 on page 12] BioPlan has estimated that the current capacity shortfall in the cellular/gene therapy space is 5x or 500%, i.e., five times the current capacity would be in use if this capacity were available. It also expects the shortfall to increase to 50x or 5,000% in five years, implying that 50x current capacity would then be needed. [See Endnote 2 on page 12] BioPlan’s 2017 annual survey data also shows that biopharmaceutical industry outsourcing is becoming more strategic and long-term.

**Increased Competition in Maturing Biopharmaceutical Markets**

As biopharmaceutical markets become increasingly competitive, it has become more and more critical to lower costs, including manufacturing costs, and time to market through productivity and efficiency improvements. In making these improvements, biopharma firms have benefited from the experience of their small-molecule peers, e.g., in developing sophisticated production management systems to provide real-time monitoring/optimization. Nevertheless, in comparison to their small-molecule counterparts, they still have substantial room for improvement in efficiency, quality and cost, especially with respect to material increases in the level of outsourcing.

**Emerging Market Opportunity**

Cell/gene therapies may be a way to leapfrog the delivery of traditional “maintenance-based” medical services to underserved patients in the developing world. Developing countries often face challenges in providing these services due to a lack of financial resources, suitable infrastructure, and experienced caregivers. However, cell and gene therapies largely eliminate the need for periodic maintenance administration. For example, 75% of global hemophiliacs are under- or untreated because the administration of Factor X is a complex, infrastructure-intensive event that must be undertaken frequently. The cell and gene therapies for hemophilia currently in late-stage development could provide a one-time, permanent cure for these patients that would no longer depend on an existing infrastructure to deliver. The high initial cost of such therapies would likely be more than offset by the lack of ongoing costs for traditional Factor X treatment (the advantages are analogous to those provided by the arrival of cellular telephone networks in the developing world, where telecommunications had previously been hampered by a lack of telephone landlines and hard networks).

**Summary of Market Volumes**

BioPlan estimates that more than 10,000 therapeutics in R&D, both biopharmaceuticals (including cell and gene therapies) and drugs (chemical substance pharmaceuticals or “small molecules”), are under development, with nearly 40,000 ongoing (or recently reported) clinical trials. [See Endnote 3 on page 12] Among these, ≥40% (or likely soon approaching 5,000 therapeutic candidates in R&D) are biopharmaceuticals. A significant portion, >1,400, of these products are “follow-on biopharmaceuticals,” mostly biosimilars and biobetters (in major markets) as well as a large number of biogenerics (in developing countries and international commerce). These “follow-on biopharmaceuticals” are the biologic analog of generic drugs. This data also indicates that there are more than 650 developers of cell and gene therapies, each with multiple candidates in development.
Recent Developments
Much is happening, and rapidly, in the biotherapeutics and cell and gene therapy space. A sampling:

- The continuing maturity of the biotherapeutics space is demonstrated by the FDA approval of biosimilars for such prominent biologics as AbbVie’s Humira, J&J’s Remicade, Amgen/Pfizer’s Enbrel, Amgen’s Epogen, and oncology products Genentech/Biogen’s Rituxan and Genentech’s Herceptin, and Amgen’s Neulasta. In some cases, the actual marketing of these products has been delayed because of patent litigation and other IP disputes.

- Major integrated pharmaceutical companies (Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Sandoz, Biogen, AstraZeneca, Pfizer, Genzyme, Eli Lilly, Amgen, Baxter, Roche, Regeneron, Alexion Pharmaceuticals, Allergan, Grifols and ShangPharma have each made major additions to their biologic manufacturing capacity, primarily through the construction of new facilities.

- The cell and gene therapy space has been led by products such as CAR-T drugs. Two of these have been approved to great fanfare, though distribution has been limited due to caregiver unfamiliarity with the new paradigm of medicine that they represent (cure rates of 80-91% not withstanding), high costs and toxicity concerns; however, future volumes in this class of therapies are likely to be significant, as more than fifty of these highly specialized treatments, both allogeneic and autologous, are in development.

- The FDA has created a qualification regimen for Regenerative Medicine Advanced Therapy (RMAT) status, for which 21 therapies have already qualified; the designation is for cell therapy-derived drug candidates that address serious or life-threatening conditions, for which there is no other therapy and for which there is preliminary clinical evidence of efficacy. RMAT is analogous to the FDA’s designation for breakthrough therapies.

New Cell and Gene Therapies
Conditions for which new cell and/or gene-based therapies are in development include:

- Amyotrophic lateral sclerosis (ALS) – Dr. Clive Svendsen and his colleagues at Cedars-Sinai Hospital in Los Angeles have achieved success in the clinic using a combination of astrocytes and glial cell line-derived neurotrophic factor (GDNF) derived from neural progenitor cells (a/k/a human brain stem cells). The combination is administered to ALS patients to encourage the regeneration of motor neurons while simultaneously neutralizing the dysfunctional environment for neural growth.

- Blindness – gene therapies are being developed to address multiple previously untreatable congenital causes of blindness, including retinitis pigmentosa (RP), Leber congenital amaurosis (LCA) and choroideremia (CHM); ocular diseases are especially suited for cell therapy applications because the retina does not fully share in the body’s circulatory system. As a result, the therapy can be targeted to a specific location and is largely protected from attack by the body’s immune system – other bodily regions with similarly isolated circulatory subsystems will likely be targeted in a similar way:
  - iCyte has developed its jCell therapy using retinal progenitor cells to perform ex vivo manipulation of therapeutic stem cells prior to re-introduction into the retina; this therapy is one of 21 that has been granted RMAT status.
  - Nightstar Therapeutics has initiated a Phase III study of its NSR-REPI gene therapy, which uses an adeno-associated virus (AAV) to introduce recombinant human complementary DNA (cDNA) that is designed to produce Rab escort protein -1 (REP-1) in the eye.
  - Spark Therapeutics has received approval for LUXTURNA as a treatment for retinosa pigmentosa and other eye diseases. This is the first FDA-approved gene therapy for a genetic disease.

- Multiple Sclerosis (MS) – several developers are generating positive clinical data from trials of allogeneic therapies based on the transplantation of haematopoietic stem cells (HSCs) harvested from bone marrow; such therapies are showing success in restoring myelin to nerve axons that have suffered from the demyelination of multiple components of the central nervous system (CNS) — the mechanism of action of MS.

- Adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID) or “baby bubble disease” – these patients have an inherited gene mutation that deactivates the adenosine deaminase gene, blocking the development of a functioning immune system, and must live in ultra-clean, isolated environments, i.e., “bubbles”; Dr. Don Kohn at the Eli & Edythe Broad Center of Regenerative Medicine & Stem
Cell Research at UCLA and others have pioneered allogeneic adenosine deaminase gene replacement into HSCs, which are administered after a potent regimen of chemotherapy has severely degraded the patient’s immune system, allowing the therapy to essentially create a new, healthy immune system.

• **Spinal cord injury** – traumatic spinal cord injury can reduce or block the transmission of neural signals from the brain to other regions of the body, resulting in the reduction or elimination of sensation and motor control.
  — *Asterias Biotherapeutics* has developed a treatment (AST-OPC1) utilizing oligodendrocyte progenitor cells derived from embryonic stem cells in the brain/spinal cord for direct application to affected locations; these progenitor cells assist in the regeneration of nerve cells
  — *The Gladstone Institute* has used human pluripotent stem cells (HPSCs) to derive V2a spinal nerve cells to regenerate spinal interneurons. The latter facilitate transmissions between sensory neurons in the brain and the motor neurons that control muscle movement; multiple clinical trials in these and other similar therapies are showing significant improvement in neural function in patients with spinal cord injuries.

• **Diabetes** – *ViaCyte* has made significant progress developing stem cell-based therapies to replace pancreatic beta islet cells that have been attacked by Type 1 diabetes. Its VC-01 [PEC-Encap] therapy uses an implanted device to store and administer differentiated embryonic stem cells that develop into pancreatic progenitor cells upon release. These cells are, in turn, expected to develop into mature, insulin-secreting cells; the VC-02 [PEC-Direct] device is similar, but uses direct vascular contact to administer the therapy.

• **Hemophilia** – Factor IX is a naturally produced protein that helps blood to clot; any failure to produce this protein results in hemophilia B. *Spark Therapeutics* has initiated a Phase III trial for a gene therapy that uses an adeno-associated viral vector (AAV vector), coupled with a high-activity factor IX transgene, to mediate a mutation in Factor IX.

• **beta-Thalassemia** – Patients have reduced oxygen-carrying ability because of a defect in the beta-globin gene, which codes for oxygen-carrying protein in blood; the therapy involves ex vivo treatment with a retro-virus to add a working copy of the beta-globin gene; *bluebirdbio* is developing a therapy that works by inserting a functional human beta-globin gene into a patient’s own hematopoietic stem cells outside the body (ex vivo) and then transplanting those modified cells into the patient’s blood stream through infusion, also known as autologous stem cell transplantation.

• **Sickle-cell** – *bluebirdbio* has administered an autologous gene therapy for sickle-cell disease, an inherited blood disorder that is caused by a single genetic mutation. The therapy introduces copies of a gene into HSCs to prevent red blood cells from becoming “sickled.” The modified cells, when re-introduced into the patient, enable the production of normal blood cells that eventually dominate in the blood stream.

• **CAR-T immunotherapy** - Chimeric antigen receptors (CARs) are genetically engineered allogeneic cells that are developed in the laboratory and infused into a patient to help in detecting and fighting cancer cells. The protein constructs stimulate anti-cancer T-cells, which in turn boost a patient’s immune system. A T-cell is a subtype of white blood cell that plays a central role in immunity. T-cells are distinguished from other white blood cells, such as natural killer cells, by the presence of a T-cell receptor on the cell surface. In CAR-T immunotherapy, T-cells are extracted from a patient, modified in the laboratory to add CARs, and reintroduced into the patient to stimulate an immune response to the cancer. Two companies have received FDA approval for CAR-T therapies, *Gilead Sciences/Kite Pharma* (for *Yescarta*, for relapsed or refractory large B-cell lymphoma), and *Novartis* (for *Kymriah*, a treatment for B-cell acute lymphoblastic leukemia using autologous T Cells), and more than 40 are proceeding with well-capitalized programs based on CAR and related science.

**Cell and Gene Therapy Are A Unique Subset of Biopharmaceuticals, With Many of the Same Issues, Only Magnified.**

The cell/gene therapy segment has recently benefited from positive clinical results, including the emergence of powerful immunotherapy therapies such as CAR-T, with two market approvals in the U.S., a first for the industry. The cell/gene therapy subset is characterized by an enormous mismatch between demand and R&D and manufacturing capacity. As noted above, BioPlan has identified a worsening “capacity crunch.” [See Endnote 5 on page 12] It estimates that the current capacity shortfall in the cellular/gene therapy segment will rise from the current 5x (meaning that five times current capacity would be in use if it were available) to 50x in five years.

Cell and gene therapy technology falls into three distinct types: cell therapy, gene therapy, and gene-modified cell therapy:

• Cell therapies are the use of cells as therapeutic agents; these have been largely allogeneic endeavors in the past – success has been somewhat sluggish in this category as stem cells have not gained the expected traction.

• Gene therapies focus on modifying the expression of a patient’s genes through the use of DNA/RNA; these agents
are typically enabled by viral vectors and have begun to gain traction, particularly in targeting monogenic diseases in specific organs.

• Gene-modified cell therapy, which involves the genetic modification of cells prior to their use in cell therapy, has had significant clinical and commercial success — as exemplified by the new CAR-T drugs. However, the need for cell modification exacerbates the manufacturing challenges seen in both gene and cell therapy. Gene-modified cell therapies usually require the supply of viral vectors along with the processing of patient cells. The supply chain is currently long, complex, and inefficient.

The recent success of the first of these therapies, after a protracted history of failure, has resulted in a significant lag in the manufacturing process. The processes used were designed primarily to provide sufficient material to establish safety and efficacy in clinical quantities, and are only now being optimized for commercial production. The recent demand for viral vectors for gene therapy and as a key raw material for gene-modified cell therapies has far exceeded the supply of cGMP manufactured product. The current system is unsustainable and requires greater scale, more platform-based processes, and improved vector system productivity.

Drug developers and tool providers (i.e., outsourcing providers) of cell therapy, gene therapy and gene-modified cell therapy will need to work in harmony to ensure efficacy, safety, and commercial readiness as they bring new therapies to market. The early history of cell and gene therapies has convincingly demonstrated that CMO/CDMOs can help to accelerate the development of new drugs, speeding the time-to-market, and that such early entry can be invaluable. The new therapies have a bright future, but will require significant industrialization of existing processes and dramatic expansion of outsourced capacity. CDMOs are well-positioned to lead the industrialization effort.

While gene therapies are still quite far from the mainstream, there are many clinical trials in progress and therapies in use. However, to become a sustainable business for CMO/CDMOs, there must be more FDA approvals and, importantly, general acceptance of mainstream development platforms. CMO/CDMOs would then have a greater incentive to invest in these platforms, which may then be used to develop similar products for different customers at multiproduct facilities.

As processing methods move from experimentation to commercial production, the cell therapy market faces challenges that both resemble and differ from those seen in viral vector manufacturing. The need for improved methods is now largely centered on autologous applications. The high-profile successes of CAR-T therapies have brought significant attention to the use of these technologies to develop personalized, autologous treatments. The success of the resulting therapeutics has in turn pushed the industry to begin to squeeze out inefficiencies, develop processes that work at both intermediate and large scale, and automate the laborious processing of autologous cells.

Several autologous, patient-specific therapeutics are in development, most involving patient-specific cell culture. The increased commercialization of stem cell therapies, gene therapies, therapeutic cancer vaccines and other patient-specific therapies will present its own capacity issues. Most of these products involve the small-scale culture of cells that are taken from patients, modified externally, and then returned to patients, or that otherwise involve the transplantation/implantation of specialized cells from other sources. This means that each patient’s therapeutic requires its own culture and purification process, generally using single-use systems. Production costs on a per-patient or per-treatment basis can thus be very high depending on the product and technology involved. The individualized culture, along with the associated testing requirements for “lot release” of each patient’s treatment, will ensure that prices for these treatments remain relatively high.

As they focus on more narrowly targeted and even individualized therapies, biopharmaceutical cell and gene therapy developers will need to produce a larger number of products in the same facilities, with many more changeovers. New facilities will also tend to have a smaller physical footprint than existing facilities, in line with higher titers and lower volumes. Disposables allow for a significantly reduced capital outlay, lowering the risk associated with facility construction. While this may not always increase productivity outright, it typically reduces overall manufacturing costs and lowers manufacturing footprints per kilogram of product produced. These developments will only exacerbate the capacity shortfalls referenced above and increase the need for outsourcing providers to meet demand.

We expect the cell therapy manufacturing space to evolve rapidly in the coming years as the continued success of new therapies is threatened by high manufacturing costs, particularly for autologous processes. At the same time, we expect to see:

• increased use of automation to reduce process time and labor costs
• streamlining of unit operations, e.g., reduction or elimination of cell expansion
• increases in scale to enhance efficiency
• supply-chain improvements, particularly in logistics and the tracking of patient tissues
• movement of manufacturing processes closer to the point-of-care (i.e., the patient’s bedside)
• a growing preference for allogeneic processes over autologous ones where possible
Biopharmaceuticals in the Clinic and the Market

Fact: biopharmaceuticals are growing as a segment of the overall drug market – the portion of new drugs represented by large-molecule biologics, particularly those of the greatest value, has risen steadily. These products also continue to dominate new drug approvals and drugs in research & development. The “perfect storm” of higher per dose costs and smaller markets has driven the prices of biopharmaceuticals well above those of small-molecule drugs. Outsourcing remains much more prevalent in small-molecule drugs than in large-molecule biopharmaceuticals because the latter have competed on the basis of new, previously unaddressed, indications and dramatic increases in efficacy rather than on cost. This has made the pursuit of lower discovery, development, and manufacturing costs less important in the case of large-molecule drugs. These factors, in the aggregate, are increasingly compelling developers to accelerate their utilization of outsourcing for multiple R&D and manufacturing functions.

Further, outsourcing is being used not only to fill temporary gaps in capacity or to control costs or to reduce process time, but also to help companies focus on their core competencies. Nearly all biopharmaceutical developers use outsourcing services of some description, whether this involves the manufacturing of clinical or commercial supplies, process development, R&D, assay and testing services, toxicology testing, regulatory affairs, the design and management of clinical trials, validation, bioprocessing design, media optimization, bioprocessing waste removal/recycling, fill-finish, custodial services, or other activities. As a result, activities that were previously considered essential to retain in-house have become, and will continue to become, options for outsourcing. For example, outsourcing allows developers to partner with CMO/CMOs that have adopted new technologies and platforms or that possess sophisticated know-how and specialized resources. Specialized outsourcing providers can create production units that focus on specific product types for multiple customers and thereby achieve even greater process efficiencies.

Developers of biopharmaceuticals facing pressure to enhance efficiency and lower pricing must make a difficult “make-or-buy” decision with respect to outsourcing. They have two main options:

- retain all or most R&D and manufacturing functions in-house to protect the scientific integrity and confidentiality of company processes while incurring high costs for reduced efficiency (due to less well-qualified, more error-prone staff or underutilized operating facilities), or
- outsource noncore aspects of R&D and manufacturing to reduce costs and enhance efficiency, thus gaining the ability to lower product pricing.

Biopharmaceuticals, including cell and gene therapies, are scientifically distinct from chemically derived small-molecule drugs. Indeed, they are the tangible products of biotechnology and have their origins in living, biological organisms rather than in the historical chemistry of traditional pharmaceuticals. Most importantly, they are the result of discoveries based on a heightened understanding of disease pathways/mechanisms made possible by groundbreaking discoveries in biotechnology and associated sciences. Over the past four decades, academic, government and industry researchers have developed instruments of drug discovery (e.g., the Human Genome Project, molecular and cellular biology, massive data compilation and analysis tools, etc.) that were unimagined only a generation ago. These new tools have enabled researchers to go beyond the mere compiling of empirical evidence obtained from testing different treatments against groups of symptoms, using rudimentary concepts of human physiology, as has been the case in traditional drug development.

Change in Addressable Market Sizes

These biotechnology-derived tools have enabled researchers to rapidly expand their understanding of the fundamental mechanisms and pathways of disease at the cellular and molecular level, and of the complex biology, chemistry and physiology that underlie dysfunctions in the human body. With this knowledge have come resets of fundamental principles guiding the development of all new therapies, including small molecules: (i) a patient presenting with a familiar set of symptoms may suffer from one of many diseases rather than from the condition that the prior standard of care might have assigned to that symptom set, and (ii) armed with such particular knowledge, researchers and caregivers can seek therapies that attack the specific mechanism of action of the disease, providing far greater treatment efficacy. The research tools and biopharmaceutical therapies stemming from these discoveries are transforming the delivery of medicine to patients and unlocking radically new possibilities for the diagnosis, treatment and cure of diseases. They are also, importantly, providing opportunities for strong growth in the CMO/CMO space.

Biotherapeutics have certain unique characteristics compared to small-molecule drugs. Traditionally, each small-molecule drug was developed to treat a discrete patient population presenting with a loosely defined set of symptoms, resulting in a massive patient population for each drug. To succeed in this environment, small-molecule drugs needed to be “blockbusters” with multibillion-dollar annual revenue. The huge addressable markets for these drugs enabled developers to amortize discovery, R&D and manufacturing costs (including the costs of other, failed drugs) across enormous patent-protected revenue streams. This business model prioritized scale and marketing and distribution skills, and placed less emphasis on productivity, efficiency and prudent resource deployment.
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By contrast, the new biotherapeutic model allows patients who may present with similar symptoms to be segregated into multiple discrete disease states based on the underlying pathway/mode of disease. The resulting subdivision of similarly presenting patient populations creates many smaller target markets. As a result, going forward, all drugs will address ever-smaller market niches without a corresponding reduction in cost-to-market. Biopharmaceuticals also require greater sophistication to discover, develop and manufacture than small-molecule drugs, resulting in higher costs per dose.

These more narrowly defined disease states enable more precise and effective treatment of each patient subgroup, improving treatment efficacy across the entire, formerly integrated patient population. However, this also results in higher unit prices, as separate and no less costly research and clinical development programs must be undertaken for each new drug candidate, even though the typical addressable market size is significantly smaller. In contrast to the blockbuster approvals of the early 2000s, the largest portion of current and upcoming biopharmaceutical approvals are for smaller niche-market products, additional indications for existing products, extensions into new international markets, and biosimilars/biogenerics.

Going forward, the diagnosis of diseases will continue to become more precise, which will result in more and smaller subgroups of treatments. As an example, breast cancer can now be classified into several subgroups, e.g., ER+ or HER2a positive, that are suited to different treatments. As a result, the treatment of broad indications with blockbuster drugs will give way to smaller stratified treatment regimes. Similarly, the addressable market for each new drug will decrease even as the overall pharmaceutical market continues to grow. These factors, along with the fact that R&D and manufacturing for biopharmaceuticals is at an earlier stage on the outsourcing curve established by small-molecule drugs, should accelerate the movement of many R&D and manufacturing activities to outsourced providers.

In addition, as biopharmaceuticals become an ever-larger portion of the therapeutic arsenal and their efficacy and costs increase, developers will need to drive down manufacturing costs to compete with suppliers of other reference therapies and multiple follow-on biotherapeutics. As such, we expect them to increase their use of outsourcing to lower manufacturing costs — leading to strong growth for CMO/CDMOs. Based on analyses of industry growth over the past 28 years, the market for bioprocessing tools, materials and services continues to grow at a 12%-14% annual rate. [See Endnotes 6 and 7 on page 12]

Financial markets still drive the foundation of many of these new companies, which tend to invest more in the drug discovery pipeline than in development and manufacturing platforms. In all, we expect biopharmaceutical companies to retain core competencies but to steadily reduce in-house R&D and manufacturing by outsourcing these functions to CMO/CDMOs. [See Endnote 8 on page 12]

Outsourcing on the Ground

Developers of small-molecule drugs have aggressively outsourced services to increase efficiency/productivity and reduce unit costs and process time to remain competitive. As addressable patient populations get smaller, the number of distinct therapies increases, and the match between disease and therapy becomes more exact, the effectiveness of treatments per patient has also improved significantly. Smaller patient populations also mean smaller batch sizes. These changes have increased the need for efficiency in R&D and manufacturing, particularly for large-molecule therapeutics, but also for cell and gene therapies.

To remain competitive, the outsourcing provider must be able to deliver lower costs per unit of output, reduced changeover times, and fewer errors. To achieve this result, outsourced providers must
- achieve high levels of productivity/efficiency through high capacity utilization
- consistently perform quick and error-free changeovers
- develop the ability to hire, train and keep high quality staff
- deliver error-free execution of protocols; and
- make prudent investments in the most efficient equipment and processes.

Moreover, unlike their biopharmaceutical developer clients, outsourcing vendors cannot offset unnecessarily high operating costs against high-margin activities such as discovery value, IP leverage, marketing and sales success, or a low cost of capital due to public company status.

Parallels in Outsourcing Market Development

As noted above, the market for outsourced services for biopharmaceuticals and cell and gene therapy is at a much earlier stage of development than the comparable market for small-molecule drugs. Many developers continue to maintain multiple development/manufacturing capabilities in-house, operating at much lower rates of efficiency and productivity in order to protect their IP and process integrity. In so doing, developers sacrifice opportunities for improved productivity/efficiency and assume risks related to the R&D and manufacturing functions they retain in-house. Outsourcing providers are able to leverage their expertise in one or more of these functions and thus generate cost and process time savings and efficiency improvements for their developer customers. At the same time, they take on the risk of investing in, and achieving optimal utilization of, special-
ized facilities, and of hiring, training and retaining experienced staff — which are in critically short supply in both technical and regulatory areas. They manage these risks, in part, by taking on multiple projects from different customers and carefully scheduling them to optimize utilization rates. For example, CMO/CDMOs can establish multiproduct production units to implement like technologies for multiple client projects.

Going forward, we expect biopharmaceutical outsourcing to mimic the historical dynamics of small-molecule outsourcing, with growth driven both by increased outsourcing intensity and the expansion of clients’ markets. As biopharmaceutical developers climb the development curve first traced by their small-molecule brethren, they typically perceive a smaller number of “core competencies” and greater value in outsourcing additional functions.

That said, the R&D and manufacturing processes for biotherapeutics and cell/gene therapies are highly complex, and therefore require choices regarding speed to completion, quality, and price, each of which is a critical parameter. Developers can generally emphasize two of these factors, but cannot maximize all three. However, given their specialized resources CMO/CDMOs are able to optimize R&D and manufacturing processes for speed, quality, and price to a much greater degree than developers can typically do on their own.

The Perception of “Core Competencies” Drives Outsourcing Decisions; Function-Driven Shifts From Core to Non-Core and Increased Specialization Drive Intensified Outsourcing

Large biopharmaceutical companies are also focusing on fewer fields, which can be targeted by a multitude of technologies. These require new development and manufacturing platforms, which cannot all be run in-house and require at least some outsourcing. Most biopharmaceutical companies now at least periodically re-evaluate their core competencies and decide how they will direct their resources for R&D, manufacturing, and related outsourcing. This promotes the reclassification of functions within the R&D and manufacturing continuum from “core” to “noncore” as developers recognize that outsourcing suppliers are able to supplement their internal resources at a lower cost and with higher rates of quality, efficiency and productivity. This trend has accelerated as developers increasingly redeploys capital away from development and manufacturing activities to research and IP acquisition.

Mandatory CMO/CDMO Outsourcing

More and more biopharmaceutical companies now use CMO/CDMOs as their only source of development and manufacturing; consequently, they must outsource large parts of the value chain. The same is true for “virtual” drug companies and firms specializing in orphan drugs. These companies normally do not install R&D or manufacturing technology given their low production volumes, or, in the case of virtual firms, have no intention of ever manufacturing in-house. In the end, they are not unlike large pharmaceutical companies that invest primarily in target finding and drug discovery.

Personalized Medicine

The ultimate expression of this phenomenon is personalized medicine, in which individual patient profiling enables autologous treatment regimens derived from a patient’s genetic and physiological characteristics. The recent growth of CAR-T therapies, in which a patient’s own T-cells are boosted and proliferated outside the body and then readministered to the patient, and other autologous gene and cellular therapies, is early evidence that personalized medicine, while complex and eye-wateringly expensive, will continue to be pursued aggressively. Personalized medicine implies the ultimate granularization of patient populations (n=1), and by definition makes the “manufacturer” an outsourcing provider. The growth of personalized therapies will inevitably require the increased use of outsourcing as developers cannot profitably manage such a low-volume process on their own. Ultimately, the production of these therapies may be decentralized to the point-of-care, i.e., the hospital bedside, and may no longer take place in CMO/CDMO factories at all. However, the obstacles to such a development are many and extend well beyond any foreseeable investment horizon.

The Biosimilar/Biobetter Phenomenon

As biopharmaceutical technology becomes more well-known, and, to an extent, commoditized, attempts to “clone” successful biopharmaceuticals have proliferated. The origin of these products as living organisms makes achieving identical duplication of the reference biologic literally impossible; however, achieving nearly the same therapeutic result (through a biosimilar) or improving on that result (through a biobetter), is not. The rapid growth of biosimilars is also being driven by the expiration of patents on both individual antibodies and entire therapies. According to one estimate, biologics worth up to $100 billion will lose exclusivity by 2020. [See Endnote 9 on page 12]

The traditional (i.e., small-molecule) route of optimizing costs for drugs coming off patent was to file an ANDA or an NDA under §505(b)(2) to obtain approval for chemically identical “generic” (perhaps reformulated) versions of reference drugs. By contrast, biosimilars are product copies of already authorized large-molecule products that are as similar to the reference drug as possible, and are widely accepted by regulatory authorities worldwide. Their great success in the last decade has been driven mainly by price pressure from reimbursement agencies and by increased demand for modern drugs in developing countries. However, it is significantly more difficult to replicate a large-
molecule drug (in a way that will satisfy the FDA) than to clone a small-molecule drug, where bioequivalence and stability studies can be done relatively quickly and with little risk of failure. The equivalent process for a biosimilar more closely resembles a full clinical development program for a new drug. It thus requires commensurately increased time, resources, and facility capacity, as well as different skillsets, and entails greater risk.

Typically, biosimilar developers specialize in the complex analysis and initial process development needed to develop these biopharmaceutical follow-on products; however, they lack most of the development capability and the manufacturing facilities necessary to create an approvable and marketable product. Such developers can be matched with appropriate CMO/CDMOs that have the ability to complete the scale-up and manufacture of biosimilar drugs.

The large number of biosimilars and biobetters under development reflects the maturation of the biopharmaceutical industry, as earlier blockbuster products start to go off-patent and an increasing number of new biopharmaceuticals reach the market.

The large proportion of industry R&D and manufacturing resources being allocated to biopharmaceutical follow-ons also reflects a basic shift in the pharmaceutical industry from small-molecule drugs to biopharmaceuticals. In our view, any overall decrease in small-molecule R&D is likely being more than offset by the shift of both established and entrepreneurial pharma companies into biopharmaceuticals. This increasingly includes a large number of new entrants specializing in biosimilar/biobetters/biogenerics, as well as cell and gene therapies.

The market dynamic for biosimilars closely resembles the early stages of the generic pharmaceutical market; as the first biopharmaceuticals (including Humira, Enbrel, and Entyvio) approach patent expiration, new biosimilar versions of these products are reaching the market. We note that there are likely to be 10 or more biosimilar or biogeneric products under development for every successful biopharmaceutical reference product, and that some outsourcing providers have reported a 15% increase in revenue attributable to biosimilar development. Indeed, there is no lack of attractive opportunities for developers as well as for outsourcing providers with the appropriate resources and capabilities.
## APPENDIX

### Capstone Headwaters Life Sciences Global BPOS Transaction Summary

**June 1, 2018, to date**

<table>
<thead>
<tr>
<th>Transaction Date</th>
<th>Acquired/Investee</th>
<th>Acquiror/Investor</th>
<th>Transaction Value ($ in 000s)</th>
<th>Acquired Industry Space</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/13/18</td>
<td>Sanoplasma</td>
<td>Shire</td>
<td>Not Disclosed</td>
<td>Plasma Collection</td>
</tr>
<tr>
<td>09/12/18</td>
<td>DXS Clinical</td>
<td>WDB Medical Data</td>
<td>Not Disclosed</td>
<td>Provider of clinical development and data analytics services</td>
</tr>
<tr>
<td>09/04/18</td>
<td>Suono Bio</td>
<td>FujiFilm</td>
<td>Not Disclosed</td>
<td>Drug development technology</td>
</tr>
<tr>
<td>08/29/18</td>
<td>AdaptPharma</td>
<td>Emergent BioSolutions</td>
<td>$735,000</td>
<td>Clinical trial benchmarking and intelligence</td>
</tr>
<tr>
<td>08/29/18</td>
<td>KGK</td>
<td>Auxley Cannabis</td>
<td>$12,300</td>
<td>CMO</td>
</tr>
<tr>
<td>08/23/18</td>
<td>Trillium Health Care Products</td>
<td>New Water Capital L.P.</td>
<td>Not Disclosed</td>
<td>CMO</td>
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<tr>
<td>08/21/18</td>
<td>RDMD</td>
<td>Lux Capital, Village Global, etc.</td>
<td>$3,000</td>
<td>Rare disease data compilation</td>
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<tr>
<td>08/21/18</td>
<td>TraceLink</td>
<td>Georgian Partners</td>
<td>$93,000</td>
<td>Supply chain information</td>
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<tr>
<td>08/20/18</td>
<td>Kinapse</td>
<td>Syneos Health</td>
<td>Not Disclosed</td>
<td>Consulting</td>
</tr>
<tr>
<td>08/15/18</td>
<td>SNBL Preclinical Testing Business</td>
<td>Altasciences</td>
<td>Not Disclosed</td>
<td>Pre-clinical CRO</td>
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<tr>
<td>08/15/18</td>
<td>Florida Pharmaceutical Products, Inc.</td>
<td>Woodfield Distribution, LLC</td>
<td>Not Disclosed</td>
<td>Supply chain and CMO</td>
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<tr>
<td>08/13/18</td>
<td>Modulus Discovery</td>
<td>Fast Track Initiative, DBJ Capital, PeptiDream</td>
<td>$7,200</td>
<td>Drug discovery company</td>
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<tr>
<td>08/09/18</td>
<td>PaxVax</td>
<td>Emergent BioSolutions</td>
<td>Not Disclosed</td>
<td>CRO</td>
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<tr>
<td>08/08/18</td>
<td>WellSpring Pharmaceuticals, Inc.</td>
<td>ANI Pharmaceuticals, Inc.</td>
<td>$18,000</td>
<td>CDMO</td>
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<tr>
<td>08/08/18</td>
<td>Gibraltar Laboratories</td>
<td>Sotera Health</td>
<td>Not Disclosed</td>
<td>Analytical testing</td>
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<tr>
<td>08/07/18</td>
<td>Syneos Health</td>
<td>NA</td>
<td>$300,900</td>
<td>Combo CRO/CCO</td>
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<tr>
<td>08/06/18</td>
<td>Regulatory Professionals, Inc.</td>
<td>Premier Research</td>
<td>Not Disclosed</td>
<td>Consulting</td>
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<td>07/31/18</td>
<td>Metrics Champion Consortium</td>
<td>WIRB-Copernicus Group</td>
<td>Not Disclosed</td>
<td>Clinical trial benchmarking and intelligence</td>
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<tr>
<td>07/23/18</td>
<td>Halo Pharma</td>
<td>Cambrex</td>
<td>$425,000</td>
<td>Dosage-form CDMO</td>
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<tr>
<td>07/18/18</td>
<td>Asian Eye Institute</td>
<td>Novotech</td>
<td>Not Disclosed</td>
<td>Ophthalmic drug/device CRO</td>
</tr>
<tr>
<td>07/18/18</td>
<td>Univercells</td>
<td>NA</td>
<td>$18,800</td>
<td>Vaccine CMO</td>
</tr>
<tr>
<td>07/13/18</td>
<td>SK Holdings</td>
<td>AMPAC Fine Chemicals</td>
<td>Not Disclosed</td>
<td>CMO</td>
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<tr>
<td>07/11/18</td>
<td>Cu-Tech</td>
<td>SynteractHCR</td>
<td>Not Disclosed</td>
<td>Dermatological CRO</td>
</tr>
<tr>
<td>07/10/18</td>
<td>Juniper Pharmaceuticals</td>
<td>Catalent</td>
<td>$133,000</td>
<td>CDMO</td>
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<tr>
<td>07/09/18</td>
<td>Optivia Biotechnology</td>
<td>BioIVT</td>
<td>Not Disclosed</td>
<td>Transporter assays, models, systems biology and research solutions</td>
</tr>
<tr>
<td>06/29/18</td>
<td>Helomics</td>
<td>Precision Therapeutics</td>
<td>Not Disclosed</td>
<td>AI, diagnostics labs, CRO</td>
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<tr>
<td>06/28/18</td>
<td>Gatan, wholly-owned subsidiary of Roper Technologies</td>
<td>Thermo Fisher</td>
<td>$925,000</td>
<td>Electron microscope instrumentation and software manufacturer</td>
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<td>06/20/18</td>
<td>PCI Synthesis</td>
<td>Novacap</td>
<td>Not Disclosed</td>
<td>CDMO</td>
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<tr>
<td>06/18/18</td>
<td>Sanofi infections disease unit</td>
<td>Evotec</td>
<td>$69,810</td>
<td>R&amp;D CRO</td>
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<tr>
<td>06/13/18</td>
<td>Sanofi contract inhalation drug business and manufacturing center</td>
<td>Recipharm</td>
<td>$72,200</td>
<td>CMO</td>
</tr>
<tr>
<td>06/13/18</td>
<td>MetaSafe AB</td>
<td>Admescope</td>
<td>Not Disclosed</td>
<td>CRO</td>
</tr>
<tr>
<td>06/12/18</td>
<td>SHYFT</td>
<td>Medidata</td>
<td>$195,000</td>
<td>Drug development and approval research IT</td>
</tr>
<tr>
<td>06/11/18</td>
<td>Sciformix</td>
<td>Labcorp/Covance</td>
<td>Not Disclosed</td>
<td>CRO</td>
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<tr>
<td>06/04/18</td>
<td>Alcami</td>
<td>Madison Dearborn Partners</td>
<td>Not Disclosed</td>
<td>CDMO</td>
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<tr>
<td>06/03/18</td>
<td>Science 37</td>
<td>Softbank</td>
<td>$150,000</td>
<td>Clinical trial telemedicine</td>
</tr>
</tbody>
</table>

Please see Transaction Attributions on Page 12
ENDNOTES

Endnote 1

Endnote 2

Endnote 3

Endnote 4

Endnote 5

Endnote 6

Endnote 7

Endnote 8

Endnote 9

TRANSACTION ATTRIBUTIONS

HIGHLIGHTS FROM RECENT RESULTS
COMPILED BY ARGUS RESEARCH

BIO TECHNE (TECH)
Quarterly Results Summary
Bio Techne recently reported above-consensus results for fiscal 4Q18. For the quarter, sales grew 15% on a GAAP basis and 9% on an organic basis, to $180 million. The adjusted operating margin expanded by 80 basis points to 39.5%. Adjusted EPS increased 23% to $1.34, above the consensus forecast of $1.29. For all of FY18, sales grew 14% to $643 million, and adjusted EPS rose 22% to $4.54.

The company does not provide earnings guidance.

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>4Q Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotechnology</td>
<td>64%</td>
<td>18%</td>
</tr>
<tr>
<td>Protein Platforms</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>18%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Business & Customers-4Q18 Transcript
• FY18 was the first year in which the company benefited from a unified selling model across all three divisions.
• Europe was the first region to benefit from the unified selling model, bringing together reagents and instruments.
• The company is hiring in India to capitalize on new business opportunities.

Capital Strategy and M&A
• Two recent acquisitions (Quad Technologies and Exosome Diagnostics) are helping the company move further into clinical markets and diagnostic and therapeutic tools.
• Quad Technologies provides biocompatible dissolvable polymer (QuickGel) that captures and activates T-cells.
• Exosome Diagnostics has developed and commercialized an exosome-derived diagnostic test based on the expression signature of three specific genes.

CAMBREX (CBM)
Quarterly Results Summary
Cambrex recently reported above-consensus results for 2Q18. For the quarter, sales grew 13%, to $152 million; revenue declined 1% on an organic basis. Adjusted EBITDA fell 13% to $37.2 million; the adjusted EBITDA margin declined 230 basis points to 24.5%. Excluding the impact of adopting ASC 606, adjusted EPS rose 18% to $0.87.

Along with the results, the company reaffirmed its 2018 revenue and adjusted EBITDA guidance. The company expects full-year adjusted net revenue, excluding the impact of foreign currency and the change in accounting principles, to be down 2% to up 2% from 2017, and looks for adjusted EBITDA of $150-$160 million. This guidance does not include any impact from the Halo Pharma acquisition.

On 9/12/18, Cambrex completed the acquisition of Halo Pharma, a dosage form CDMO with locations in New Jersey and Quebec, Canada. Cambrex paid $425 million for Halo. Based on the timing of the deal, Halo will contribute for slightly more than one full quarter in 2018.

Business & Customers- 2Q18 Transcript
• Reflecting strong demand for highly potent compounds for oncologic and other therapeutic classes, Cambrex is investing for growth.
• Cambrex’s goal is to continue growing its Innovator business even as it navigates an expected decline in sales of its major product, an API in the innovator category.
• With large pharma companies looking to reduce their small-molecule footprint, Cambrex has a robust and growing small-molecule clinical development pipeline.

CATALENT INC. (CTLT)
Quarterly Results Summary
Catalent recently reported above-consensus results for fiscal 4Q18. For the quarter, sales grew 11% — 9% on an organic basis — to $685 million. Adjusted EBITDA increased 14%, as the adjusted EBITDA margin rose 90 basis points to 26.6%. Adjusted EPS rose 3% to $0.67, above the consensus forecast of $0.61.

For all of FY18, revenue of $2.46 billion rose 19% as reported and 16% organically. Adjusted EBITDA rose 22% to $454 million.

For FY19, management projects revenue of $2.50-$2.59 billion and adjusted EBITDA of $597-$622 million.

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>4Q Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Softgel Technologies</td>
<td>35%</td>
<td>-6%</td>
</tr>
<tr>
<td>Biologics &amp; Specialty Drug Delivery</td>
<td>29%</td>
<td>100%</td>
</tr>
<tr>
<td>Oral Drug Delivery Solutions</td>
<td>22%</td>
<td>-11%</td>
</tr>
<tr>
<td>Clinical Supply Services</td>
<td>16%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Business & Customers – 4Q18 Transcript
• The integration of the Bloomington business acquired in fiscal 2Q18 is progressing ahead of schedule.
• The company’s third manufacturing train at its Madison facility is up and running and contributing to revenue; management is considering further additions at the Madison site.
• Catalent is overcoming headwinds in the Softgel business by optimizing capacity across the network.

Capital Strategy and M&A
• In July, the company announced the acquisition of Juniper Pharmaceuticals, which provides dose-form development and early-stage manufacturing services.
• Juniper builds on the company’s 2017 Pharmatek acquisition and strengthens its offerings in formulations, bioavailability solutions, and oral dose manufacturing.

CHARLES RIVER LABS (CRL)
Quarterly Results Summary
Charles River Labs recently reported above-consensus results for 2Q18. For the quarter, sales grew 25% to $585 million; excluding acquisitions and currency effects, organic sales grew 7%. The adjusted operating margin declined 130 basis points to 18.7%. Adjusted EPS increased 26% to $1.62, above the consensus forecast of $1.46. For all of FY17, sales grew 10.5% to $1.86 billion and adjusted EPS rose 16% to $5.27.

Along with the 2Q results, the company updated its outlook for 2018. It expects organic revenue growth of 7%-8%, up from its prior estimate of 5.7%-6.7%; GAAP revenue growth of 19%-21%, raised from 18%-20%; and adjusted EPS of $5.85-$6.00, raised from $5.77-$5.92.

Segment % of Sales 2Q Segment Growth Rate
Research Models & Services 22% -5%
Discovery & Safety Assessment 59% 37%
Manufacturing Support 19% 17%

Business & Customers - 2Q18 Transcript:
• The company is showing strong growth, reflecting an extremely healthy market environment and its position as a premier early-stage CRO.
• Clients are stepping up product development spending, leading Charles River to invest further in its pipeline.
• To enhance speed and responsiveness, both internally and with clients, CRL has adopted a new operating model that creates a more agile organization, accelerates decision-making, and empowers unit leaders.

Capital Strategy and M&A:
• The acquisitions of MPI Research, Brains On-Line, and KWS BioTest helped to drive double-digit top-line growth in 2Q18.
• The pipeline of acquisition candidates remains robust, and M&A is Charles River’s preferred use of capital.

ICON PLC (ICLR)
Quarterly Results Summary
Icon recently reported above-consensus results for 2Q18. For the quarter, and excluding the impact of adopting ASC 606, sales grew 10% to $474 million. GAAP revenue (including ASC 606) was $642 million. The adjusted operating margin expanded 30 basis points to 20.2%. Adjusted EPS rose 17.6% to $1.54, above the consensus forecast of $1.48. For all of 2017, sales grew 5.5% to $1.76 billion and adjusted EPS rose 13% to $5.39.

Along with the 2Q results, the company raised its full-year outlook. Icon expects revenue of $2.56-$2.64 billion, up from a prior forecast of $2.52-$2.64 billion, and adjusted EPS of $5.98-$6.12, up from $5.91-$6.11.

Business & Customers - 2Q18 Transcript:
• Excellent order trends resulted in a 2Q18 book-to-bill ratio of 1.27 and a ratio of 1.29 on a trailing 12-month basis.
• Favorable trends for Icon include a growing backlog of $5.2 billion and reduced customer concentration.
• Icon’s ability to successfully manage projects under a range of outsourcing models is leading to new business opportunities.

Capital Strategy and M&A:
• Innovative partnerships with Intel and Saama, and collaborations with TriNeX, EHR4CR, and Practice Fusion, are helping to enhance the company’s engagement with sites, patients and healthcare providers.
• Icon is managing rapid employee growth (up 10% year-over-year) with careful recruiting, a disciplined on-boarding program, and programs to help employees map individual career paths.

ILLUMINA INC (ILMN)
Quarterly Results Summary
Illumina recently reported above-consensus results for 2Q18. Second-quarter revenue rose 25.4% from the prior year to $830 million. The non-GAAP operating margin rose 630 basis points to 28.4%. Adjusted net income rose to $1.43 per share from $0.82 a year earlier and beat the consensus by $0.32. For all of 2017, revenue rose 14.8% to $2.75 billion and adjusted EPS rose 20.1% to $4.00.

Along with the 2Q results, management provided revised guidance for 2018. The company expects 20% revenue growth, up from a prior estimate of 15%-16%, and non-GAAP EPS of $5.35-$5.45, up from a prior $4.75-$4.85.

Segment % of Sales 2Q Segment Growth Rate
Product/Consumable 65% 34%
Product/Instrument 15% 7%
Service & Other 19% 32%

Business & Customers - 2Q18 Transcript:
• Although 225 petabytes of sequence data have been generated on Illumina platforms, less than 1% of the human genome has been mapped, signaling a vast opportunity ahead.
• Illumina saw higher sales of consumables across all three of its sequencing system categories — high, mid and low throughput — in 2Q18.
• In the high-throughput category, Hiseq sequencer customers continue to transition to the newer NovaSeq model.

Capital Strategy and M&A
• The May acquisition of Edico Genome is expected to accelerate genomic data analysis at Illumina.
• The “All of Us” program from the U.S. National Institutes of Health and genomic programs in the UK, Australia and other nations represent multiyear opportunities.

IQVIA (IQV)
Quarterly Results Summary
IQVIA recently reported above-consensus results for 2Q18. Second-quarter revenue of $2.57 billion rose 9% on a reported basis and 8% in constant currency. Adjusted EBITDA rose 14% in constant currency, and the adjusted EBITDA margin expanded by 90 basis points to 20.8%. Adjusted EPS rose 25% from the prior year to $1.29 and beat the consensus by $0.06. For all of 2017, revenue (adjusted to take account of the IQV-Quintiles combination on 1/1/16) rose 4.3% to $8.06 billion, and adjusted EPS rose 20.1% to $4.67.

Along with its 2Q results, management provided revised guidance for 2018. With 2017 results recast to reflect impact of accounting standard ASC 606, the company expects revenue growth of 10.5%-11.5%, tightened from a prior forecast of 10.0%-12.0%, and non-GAAP EPS of $11.35-$11.65, tightened from $11.30-$11.70. The non-GAAP EPS guidance assumes growth of 22.7%-25.9% this year.

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>2Q Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology &amp; Analytics</td>
<td>39%</td>
<td>14%</td>
</tr>
<tr>
<td>R&amp;D Solutions</td>
<td>53%</td>
<td>10%</td>
</tr>
<tr>
<td>Contract Sales &amp; Medical</td>
<td>8%</td>
<td>-13%</td>
</tr>
</tbody>
</table>

Business & Customers - 2Q18 Transcript:
• The company posted stronger-than-forecast 2Q revenue, driven by organic growth, higher pass-through revenue in R&D Solutions, and contributions from tuck-in acquisitions.
• The IQVIA Technology & Analytics unit is benefiting from two significant contract wins with top-five pharma companies.
• IQVIA is also seeing strong trends in bookings and as-contracted book-to-bill.

Capital Strategy and M&A:
• IQVIA recently launched its Orchestrated Customer Engagement (OCE) SaaS offering.
• OCE SaaS uses artificial intelligence and machine learning to integrate functions in clients’ commercial operations.

LABORATORY CORP. OF AMERICAN HOLDINGS (LH)
Quarterly Results Summary
Laboratory Corp. of America Holdings (LabCorp) recently reported above-consensus results for 2Q18. Second-quarter revenue of $2.87 billion rose 13% from the prior year. Adjusted operating income rose 8% to $465 million, though the adjusted operating margin narrowed by 50 basis points to 16.2%. Adjusted net income rose 23% to $2.98 per share and topped the consensus by $0.05. For all of 2017, revenue rose 8.2% to $10.21 billion, and adjusted EPS rose 8.7% to $9.60.

Along with its 2Q results, management provided guidance for 2018. With 2017 results recast to reflect the impact of accounting standard ASC 606, the company expects revenue growth of 10.5%-11.5%, tightened from a prior forecast of 10.0%-12.0%, and non-GAAP EPS of $11.35-$11.65, tightened from $11.30-$11.70. The non-GAAP EPS guidance assumes growth of 22.7%-25.9% this year.

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>2Q Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>LabCorp Diagnostics</td>
<td>63%</td>
<td>5%</td>
</tr>
<tr>
<td>Covance Drug Development</td>
<td>37%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Business & Customers - 2Q18 Transcript:
• Strong organic growth, contributions from acquisitions, the LaunchPad initiative, and a lower tax rate powered mid-teens revenue growth in 2Q18.
• LabCorp is executing on strategic initiatives that include supporting customers’ transitions to value-based care, enhancing drug development processes, and creating a leading consumer engagement platform.

Capital Strategy and M&A:
• The June 2018 Sciformix acquisition has enhanced and expanded Covance’s solution set.
• Covance LaunchPad uses automation and new IT platforms to help align people and capabilities with client demand.
• The company’s strategic partnership with Walgreen has now expanded to 16 stores, including sites in Florida.

LONZA GROUP (LONN)
Quarterly Results Summary
Switzerland-based Lonza Group reports semi-annually in Swiss Francs (CHF). On January 31, Lonza reported 1H18 revenue of CHF 3.08 billion, up 33% from the prior year. Excluding Capsugel, revenue rose 8% in constant currency. Core (non-IFRS) EBIT grew 42.3% (12.4% in constant currency and ex-Capsugel). Core net income of CHF 6.56 per diluted share rose 33% from the prior year. For all of 2017, revenue for standalone Lonza rose 10.4% to CHF 4.56 billion. Including results from the acquired...
Capsugel business, revenue of CHF 5.11 billion rose 23.5%; core (non-IFRS) EBITDA of CHF 1.27 billion rose 37.8%, and core basic EPS of CHF 11.84 rose 51.6%.

Along with the 1H18 results, management provided guidance for 2018. The company expects mid- to high single-digit growth, raised from earlier guidance of mid-single-digit growth. Management expects the full-year core EBITDA margin to be in line with the 1H18 margin of 26%.

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>1H Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharma &amp; Biotech</td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td>Specialty Ingredients</td>
<td>49%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**MEDPACe HOLDINGS INC. (MEDP)**

**Quarterly Results Summary**

Medpace Holdings (Medpace) recently reported above-consensus results for 2Q18. Second-quarter revenue of $170 million under ASC 606 rose 60% from the prior year; under the prior standard of ASC 605, revenue of $118 million increased 25%.

The adjusted EBITDA margin under ASC 606 was 19.4%; under the prior ASC 605 standard, the adjusted EBITDA margin of 30.4% expanded by 190 basis points. Adjusted net income was $0.61 per share under ASC 606 ($0.67 under ASC 605) versus $0.38 a year earlier; earnings beat the consensus estimate by $0.19. For all of 2017, service revenue rose 4.3% to $387 million and adjusted EPS declined 0.7% to $1.52.

Along with the 2Q results, management issued revised guidance for 2018 under the prior accounting standard ASC 605 in order to provide comparability. Medpace expects 19.3%-22.4% net service revenue growth, to $461-$473 million, and non-GAAP EPS of $4.13-$4.23.

**PRA HEALTH SCIENCES INC. (PRAH)**

**Quarterly Results Summary**

PRA Health Sciences recently reported above-consensus results for 2Q18. Second-quarter revenue of $723 million under ASC 606 rose 35% (34% in constant currency); under the prior ASC 605 standard, revenue of $575 million rose 24% in constant currency and 12% organically. Adjusted EBITDA grew 28%, while the adjusted EBITDA margin (under ASC 606) narrowed to 15.2% from 16.0% a year earlier. Adjusted net income of $1.00 per share rose 27% from the prior year and topped the consensus by $0.04. For all of 2017, service revenue rose 23.3% to $1.95 billion and adjusted EPS advanced 32.1% to $3.33.

Along with the 2Q results, management provided revised guidance for 2018. The company expects revenue of $2.87-$2.95 billion, representing growth under accounting standard ASC 606 of 47%-50%; organic growth in constant currency is forecast at 10%-12%. Management also guided for full-year non-GAAP EPS of $4.13-$4.23.

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>2Q Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Service Revenue, Net</td>
<td>87%</td>
<td>26%</td>
</tr>
<tr>
<td>Reimbursement Revenue</td>
<td>13%</td>
<td>13%</td>
</tr>
</tbody>
</table>

**Business & Customers - 2Q18 Transcript:**

- Net new business wins rose 11% in 2Q18, reflecting strong order trends with a net book-to-bill ratio of 1.3.
- The integration of the Symphony Health acquisition, which closed in September 2017, is progressing as planned.

**Capital Strategy and M&A:**

- The company’s 2Q18 capital spending of $12.7 million supported investment in information technology and infrastructure expansion.
- In 2Q18, PRA amended its A/R financing agreement, which increased borrowing capacity and extended the maturity date.

**SYNEOS HEALTH INC. (SYNH)**

**Quarterly Results Summary**

Syneos Health recently reported slightly above-consensus results for 2Q18. Second-quarter revenue under ASC 606 was $1.07 billion; under ASC 605, revenue of $796 million more than tripled from $258 million a year earlier, reflecting strong gains from the former InVentiv Health business. The adjusted EBITDA margin under ASC 605 rose 190 basis points to 19.7%. Adjusted EPS under ASC 606 rose 24% to $0.62, above the consensus of $0.61. For all of 2017, sales declined 6% to $3.06 billion on an organic basis, while adjusted EPS rose 33% to $2.27.

Along with the results, the company provided an updated outlook for 2018. It expects revenue of $4.40-$4.55 billion and adjusted EPS of $2.55-$2.83.

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>2Q Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Service Revenue, Net</td>
<td>86%</td>
<td>25%</td>
</tr>
<tr>
<td>Reimbursed Out-of-Pocket Revenue</td>
<td>14%</td>
<td>63%</td>
</tr>
</tbody>
</table>
HIGHLIGHTS FROM RECENT RESULTS (CONTINUED)
COMPILED BY ARGUS RESEARCH

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>2Q Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Clinical Solutions</td>
<td>70%</td>
<td>6%</td>
</tr>
<tr>
<td>Combined Commercial Solutions</td>
<td>30%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Business & Customers - 2Q18 Transcript:**
- Syneos, formed in August 2017 from the merger of InVentiv and INC Research, is seeing strong customer engagement based on the breadth of its biopharmaceutical outsourcing offerings.
- In the Commercial Solutions unit, Strong customer wins in 2Q resulted in sequential growth in this business for the first time since the merger.

**Capital Strategy and M&A**
- Syneos is carefully managing its capital structure while taking a balanced approach to capital deployment.
- The company is on track to achieve its 2018 merger synergy target of $65-$70 million.
- In August 2018, Syneos acquired Kinapse, which delivers services across the clinical and commercial lifecycle.

**THERMO FISHER SCIENTIFIC (TMO)**
Quarterly Results Summary
Thermo Fisher recently reported above-consensus results for 2Q18. Second-quarter revenue of $6.1 billion grew 22% on a GAAP basis and 8% on an organic basis. Adjusted operating income grew 21% to $1.40 billion, while the adjusted operating margin fell 20 basis points to 23.1%. Adjusted EPS increased 20% to $2.75 and topped the consensus forecast by $0.13. For all of 2017, sales grew 14% — or 5% on an organic basis — to $20.9 billion, and adjusted EPS rose 15% to $9.49.

Management provided guidance for 2018. It projects revenue of $23.7-$23.9 billion, implying growth of 13%-14%. It also raised its full-year non-GAAP EPS guidance to $10.89-$11.01 from $10.80-$10.96, representing 15%-16% growth.

<table>
<thead>
<tr>
<th>Segment</th>
<th>% of Sales</th>
<th>2Q Segment Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Sciences</td>
<td>26%</td>
<td>12%</td>
</tr>
<tr>
<td>Analytical Instruments</td>
<td>22%</td>
<td>12%</td>
</tr>
<tr>
<td>Specialty Diagnostics</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Laboratory Products</td>
<td>42%</td>
<td>42%</td>
</tr>
</tbody>
</table>

**Business & Customers - 2Q18 Transcript:**
- The company’s 2Q results were strong across end markets, regions and products.
- Customer feedback on new products remains very positive.
- New products include sequencers, oncomine panels, and autoimmune assays.
- During the quarter, the company opened a Precision Medicine Science Center, which will help U.S. customers to improve genomic, proteomic and metabolomic analysis.

**Capital Strategy and M&A:**
- In September 2018, the board authorized the repurchase of up to $2 billion in TMO common stock. There is no expiration date for this authorization.
- Thermo Fisher has reached an agreement to acquire Becton Dickinson’s Advanced Bioprocessing business. The acquisition, announced in September 2018, is expected to close early in calendar 2019.
### BPOS VALUATION TABLE

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Ticker</th>
<th>Mkt. Cap ($BIL)</th>
<th>Revenue ($BIL)</th>
<th>Op Mgn (%)</th>
<th>D/E (%)</th>
<th>Growth Rates</th>
<th>1-Yr Return (%)</th>
<th>5-Yr Return (%)</th>
<th>EV/EBITDA (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio-Techne Corp.</td>
<td>TECH</td>
<td>7.7</td>
<td>0.6</td>
<td>25.4</td>
<td>31</td>
<td>11</td>
<td>12</td>
<td>69</td>
<td>153</td>
<td>12.0</td>
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<tr>
<td>Cambrex Corp.</td>
<td>CBM</td>
<td>2.2</td>
<td>0.6</td>
<td>26.3</td>
<td>NA</td>
<td>7</td>
<td>6</td>
<td>20</td>
<td>392</td>
<td>3.7</td>
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<tr>
<td>Catalent Inc.</td>
<td>CTLT</td>
<td>6.6</td>
<td>2.6</td>
<td>12.2</td>
<td>250</td>
<td>5</td>
<td>12</td>
<td>14</td>
<td>128</td>
<td>2.7</td>
</tr>
<tr>
<td>Charles River Laboratories Intl, Inc.</td>
<td>CRL</td>
<td>6.4</td>
<td>2.2</td>
<td>17.0</td>
<td>108</td>
<td>15</td>
<td>9</td>
<td>24</td>
<td>183</td>
<td>3.2</td>
</tr>
<tr>
<td>ICON Public Limited Company</td>
<td>ICLR</td>
<td>8.3</td>
<td>2.6</td>
<td>26.0</td>
<td>28</td>
<td>8</td>
<td>15</td>
<td>34</td>
<td>272</td>
<td>3.8</td>
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<tr>
<td>Illumina Inc.</td>
<td>ILMN</td>
<td>53.8</td>
<td>3.3</td>
<td>27.5</td>
<td>38</td>
<td>14</td>
<td>12</td>
<td>84</td>
<td>352</td>
<td>17.4</td>
</tr>
<tr>
<td>Syneos Health Inc.</td>
<td>SYNH</td>
<td>5.2</td>
<td>4.4</td>
<td>4.5</td>
<td>103</td>
<td>7</td>
<td>18</td>
<td>-2</td>
<td>129</td>
<td>1.5</td>
</tr>
<tr>
<td>Iqvia Holdings Inc.</td>
<td>IQV</td>
<td>26.3</td>
<td>8.5</td>
<td>9.7</td>
<td>141</td>
<td>6</td>
<td>15</td>
<td>36</td>
<td>195</td>
<td>3.1</td>
</tr>
<tr>
<td>Laboratory Corp. of America Holdings</td>
<td>LH</td>
<td>17.7</td>
<td>10.9</td>
<td>14.6</td>
<td>92</td>
<td>7</td>
<td>12</td>
<td>15</td>
<td>73</td>
<td>1.6</td>
</tr>
<tr>
<td>Medpace Holdings Inc.</td>
<td>MEDP</td>
<td>2.3</td>
<td>0.5</td>
<td>14.3</td>
<td>35</td>
<td>13</td>
<td>16</td>
<td>87</td>
<td>120</td>
<td>4.3</td>
</tr>
<tr>
<td>PRA Health Sciences Inc.</td>
<td>PRAH</td>
<td>7.1</td>
<td>2.4</td>
<td>11.9</td>
<td>136</td>
<td>12</td>
<td>17</td>
<td>45</td>
<td>447</td>
<td>3.0</td>
</tr>
<tr>
<td>Thermo Fisher Scientific Inc.</td>
<td>TMO</td>
<td>100.0</td>
<td>23.1</td>
<td>15.4</td>
<td>74</td>
<td>8</td>
<td>11</td>
<td>31</td>
<td>106</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Averages</strong></td>
<td></td>
<td><strong>20.3</strong></td>
<td><strong>5.1</strong></td>
<td><strong>17.1</strong></td>
<td><strong>94.2</strong></td>
<td><strong>9</strong></td>
<td><strong>13</strong></td>
<td><strong>38</strong></td>
<td><strong>213</strong></td>
<td><strong>5.1</strong></td>
</tr>
</tbody>
</table>

**Sources:** Argus Research, Bloomberg Inc. Data as of 10/3/2018

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**HIGHLIGHTS FROM RECENT RESULTS (CONTINUED)**

**COMPILED BY ARGUS RESEARCH**
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