Pharmaceutical Outsourcing Monitor

17 QUESTIONS FOR 2017

March 7, 2017

Postponing this annual “Questions” edition of our Monitor enables us to not only pose some questions for the pharmaceutical and outsourcing industries, but also comment on both President Trump’s initial activities and some fourth quarter earnings releases. We must begin by acknowledging that the November 2016 election of Donald Trump as President of the United States may make 2017 a year of substantial changes to the domestic healthcare industry.

In that broad arena, the new president has announced his intention to lower the prices Americans pay for prescriptions drugs, repeal and replace the Affordable Care Act (ACA), reduce the regulatory requirements for the approval of new drugs, accelerate the approval of generic drugs (including biosimilars), and extend “compassionate use” to virtually everyone who seeks it. We believe such an ambitious agenda will be difficult to achieve since even his fellow Republicans who control the Senate and the House of Representatives disagree with some of these proposals.

Putting aside these concerns about potential changes in the regulatory and legislative landscapes, it seems to us that the outlook for the pharmaceutical outsourcing industry is still very positive. Drug and biotech companies may still not view CROs as true strategic collaborators. But they continue to regard them as effective transactional partners in bringing new products to the marketplace.

Michael A. Martorelli, CFA
michael.martorelli@fairmountpartners.com
610.260.6232
How Will The Trump Administration Affect the Drug Industry and Its Product Development Efforts?

President Trump wants Medicare to have the authority to directly negotiate drug prices.

Giving the Centers for Medicare and Medicaid (CMS) that authority will require a change in the law. The 2003 law that created the Medicare Part D prescription drug program specifically prohibited Medicare from negotiating prices directly with drug companies. Instead, it authorized the insurance companies that administer that program to use pharmacy benefits managers (PBMs) to negotiate selective price discounts with those manufacturers. Other government payers such as Medicaid, the Veterans Administration, and the Children’s Health Insurance Program do have the authority to negotiate prices directly with drug companies.

Both the drug industry and the PBMs that negotiate on behalf of Medicare assert that they have been able to restrain the rate of increase in the prices that covered individuals have had to pay for prescription drugs.

It's unclear how much savings the Medicare Part D program could achieve if CMS was to be granted the authority to negotiate prices directly for some or all the drugs it purchases for its 41 million enrolled members. But making that change could be a major blow to those pharmaceutical manufacturers’ sales and profits - and possibly to their future R&D expenditures.

- As a businessman not involved in or particularly knowledgeable about the clinical research enterprise, we suspect Mr. Trump had not given much thought to the challenges of developing new drugs. However, in addition to stating his intention to bring down drug prices for every American, the president and/or his advisers have floated the following ideas for radically altering the drug development and approval landscape.

  o Authorize the Food and Drug Administration (FDA) to consider pricing in its evaluation of new products, particularly those aimed at relatively small patient populations.

  o Permit manufacturers of biosimilars to launch their products immediately upon FDA approval, rather than waiting an extra six months as is now the case.

  o Permit the re-importation of drugs from Canada and elsewhere.

  o Revise the legislation allowing drug companies to grant exclusive rights to a firm producing an Authorized Generic before other generic versions are approved.
The informed reader may recognize many of these and/or similar ideas as elements of Democratic lawmakers’ and candidates’ plans to address the issue of rising drug prices.

- As noted on page 1, President Trump has also recently voiced his support for granting the “compassionate use” of an unapproved drug to virtually anyone who requests it. Granting the right to use any compound that has cleared its Phase I safety hurdle but that has not yet been tested for clinical efficacy would seem to fly in the face of the long-established procedure of conducting rigorous and limited testing of such a compound before authorizing its widespread use.

- Finally, we should note that some of the President’s initial actions may be having unintended consequences for the drug development enterprise.
  - Putting a hiring freeze on government may hurt the FDA’s efforts to begin implementing provisions of the recently passed 21st Century Cures Act.
  - Putting a freeze on new regulations may also delay other government activities aimed at implementing that law.

With little consensus on most elements of Mr. Trump’s healthcare policy, we find ourselves channeling Betty Davis’ famous line from the 1950 movie All About Eve:

“Fasten your seatbelts, it’s going to be a bumpy ride.”
What Do Investors Think About Some Recent Outsourcing Firms’ Earnings Reports?

Investors seemed very pleased at CRL’s results, merely satisfied with most other companies’, and less enthusiastic about the reports from INCR, MEDP, and PRXL. We note only the highlights of those addressed below.

**Catalent**

CTLT reported its second solid quarter following some unusual hiccups in the middle of 2016. As management predicted in April 2016, the softgel facility in France remains on track to generate about half the annual revenue level it was generating before the company was forced to close it in November 2015 due to quality control issues. A revamped segment breakdown is giving investors a new look at CTLT’s $300 Clinical Supply Services business. Management is continuing to add to CTLT’s capabilities via acquisitions. Buying Accucaps moved it into the consumer products arena; buying Pharmatek added both formulation and drug delivery know-how. Unlike some peers, the company is still not a particularly large factor in the biologics business. But it is building more capacity and making a stronger effort to boost its participation in cell line development, analytical services and biomanufacturing. Investors remain wary of potential one-time problems that caused some variability in CTLT’s 2016 results.

**Charles River**

CRL turned in the best performance of the companies that have reported their December 2016 results, posting better-than-expected revenue and earnings. This broad-based provider of early-stage contract research services worked on 70% of the drugs approved by the FDA last year. The company again expanded its portfolio of services with the acquisitions of WIL Research, Blue Stream Laboratories, and Agilux Laboratories. (A few weeks ago it divested QS Pharma, the CDMO portion of WIL Research.) CRL’s Research Models and Services, Discovery/Safety Assessment, and Manufacturing Support segments each recorded solid organic revenue growth. Only the D/SA segment experienced a (slight) decline in its operating margin. CRL benefitted strongly from the robust financing environment for the biotechnology industry; it generated a record $500 million in revenue from that portion of its client base, including about $90 million from portfolio companies of the venture capital firms in which it has invested. Both figures are much higher than in the previous two years. We can best summarize investors’ expectations regarding revenue, profits, acquisitions, and stock market performances in 2017 with the hopeful phrase “more of the same”.

The December quarter included the impact from Pfizer’s cancellation in November of further development work on its anti-cholesterol drug bococizumab. Revenue in the quarter was only minimally affected. But the estimated $100 million hit to backlog caused the reported net book-to-bill ratio to fall from 1.8 in September to 1.0 at the end of the year. As anticipated, full-year revenue from Pfizer fell just a bit from almost $490 million in 2015 to about $465 million in 2016. Management estimates revenue from that large client will approximate $275 million in 2017. In reporting the December results they reiterated the guidance given in early January for total revenue growth this year of about 4%. Given the anticipated decline in business from Pfizer, that forecast suggests growth of about 17% from non-Pfizer clients; it does not assume any additional acquisitions. As far as profitability is concerned, management expressed confidence in their ability to maintain a full-year operating margin in excess of 19%, aided by solid contributions from businesses in the commercialization, government research, and laboratory sectors.

Management was disappointed in having to announce lower-than-expected results for revenue, earnings, and net new bookings in the December quarter. As is usually the case, investors on management’s quarterly conference call did not appear particularly concerned about the negative effect of cancellations on the financial results. They were much more concerned about the relatively low level of new business awards. Clients’ delays in awarding new business, and competitive losses of potential new business, particularly in the Large Pharma segment of INCR’s client base, proved problematic. Management suggested that none of the cancellations or project re-prioritizations were particularly related to INCR’s work product. They did acknowledge, however, that the company was not gaining as much traction with its largest clients as management had suggested at an investor meeting last August. They also reiterated the need for INCR to broaden its range of services and to become more competitive in providing single point FSP type services. In 2017, the need to make investments in potential FSP acquisitions, as well personnel hires in both business development and operations, could cause the operating and EBITDA margins to come in at lower levels than in 2016. Analysts will be closely watching INCR’s revenue and new business progress through the next couple of quarters.
In an unusual coincidence of timing, the management of LH held their conference call discussing December 2016 financial results against a strong backdrop of M&A speculation. They did not address reports from Reuters and the Lund Group about the potential acquisitions of PPD Inc. or Pathology Associates Medical Lab. But they did remind investors of the major criteria they use in their continuous search for acquisitions. Those criteria involve “fit”, internal rate of return, growth prospects, and earnings accretion. Management also emphasized a desire to begin returning capital to shareholders in 2017, probably by share buy-backs, and to reduce LH’s long-term debt. Other major goals are completing the integration of Covance, and continuing to generate moderate increases in revenue, earnings and cash flow. In a move that is a bit confusing to analysts largely interested in the CRO portion of the company, the Covance unit is now including in its reported backlog only net orders under contract; it will no longer include work that has been won but that is not yet under contract. Management will also begin estimating the amount of contracted backlog that is expected to convert into revenue during the next twelve months. The Covance segment contributes about 30% of LH’s net revenue and 25% of its operating income. Management’s financial guidance for LH in 2017 envisions growth in net revenue and adjusted EPS of about 5.5% and 8.0%, respectively.

Like INCR, MEDP was negatively affected by clients’ delays in awarding new projects in the fourth quarter of 2016. Management attributes much of this difficulty to the relatively uncertain funding environment for clients with a revenue base of less than $250 million. MEDP is more heavily dependent on such clients than other CROs; they accounted for 65% of its revenue in 2016. One client’s bankruptcy cost the company $4.3 in lost revenue in the fourth quarter. Another client’s financial difficulties will expose MEDP to the loss of an additional $4.5 million in revenue in 2017. Unlike its largest competitors, this company generates virtually all its CRO business from full service contracts; many Big Pharma companies prefer to limit their outsourcing work to either strategic partners or providers of specific functional service capabilities. Those actions could limit MEDP’s potential revenue from the largest drug companies. Management anticipates tailoring the company’s expense levels to the anticipated (i.e. relatively low) level of revenue growth in 2017. They are guiding analysts to expect full-year revenue growth of only about 7% but an adjusted EBITDA increase closer to 9%. Thus, it should continue to be one of the most profitable CROs in the industry.
Investors were concerned about the implications of PRXL’s disappointing revenue results in the second fiscal quarter ended December 31. A slow backlog-to-revenue conversion rate and a high cancellation rate caused unanticipated weakness in the Clinical Research Services (CRS) segment. Those same issues prompted management to lower their revenue and earnings guidance for the March and June quarters. In further explaining the situation management told of their plans to not only continue the restructuring and expense modification initiatives previously announced but also take a close look at the efficacy of the company’s revenue forecasting model. Across the CRO industry, shifting client priorities and negative clinical research results have complicated every management’s ability to forecast accurately the amount of committed work in a backlog that would be translated into revenue in any given accounting period. Based on other companies’ recent financial reports, however, it seems that PRXL is having more difficulties with revenue generation than its peers.

PRAH reported strong results in the last quarter of 2016, and guided investors to expect another strong financial performance in 2017. On the conference call providing more details, management discussed many positive aspects of the strategic relationship with Takeda. That company has announced its intention to give the majority of its full-service development work to PRAH; analysts suspect it could generate as much as $200 million in annual revenue within a couple of years. Experience with the ramp-up of the infrastructure needed to support such a large client has caused some analysts to express caution about the near-term trend of PRAH’s profit margin. The EBITDA margin slipped just a bit from September 2016 to December, due largely to the cost of hiring staff to handle the anticipated Takeda work. PRAH has been a model of consistency, generating successively higher amounts of net new business awards, ending backlog, revenue, and operating income in almost every quarter during the past two years. As it breaks the $1.8 billion revenue level in 2017, continuing to show that stair step pattern of growth may become more challenging.
Analysts’ instant analyses of Q’s December results suggested the company reported higher-than-expected EPS but lower-than-expected revenue. Management’s 2017 guidance suggested lower-than-expected revenue growth but higher-than-expected EPS growth. As has been the case for the past few quarters, CRO analysts are still trying to understand the different business rhythms of this combined clinical services/information services company. The company is no longer providing detailed information about organic revenue growth by business segment and gross and net new business wins. Like LH, it has revamped its book-to-bill calculation to show only the net backlog of business that is under contract. Management sometimes discloses a specific new business win, and sometimes describes a contract that includes service elements from each of the company’s three business segments. They do indeed discuss the quarterly revenue and margin contributions of the Commercial Solutions, R&D Solutions, and Integrated Engagement Services segments. But they also try to tell the story of the long-term potential of Q’s integrated approach to marketing various combinations of those services to drug, biotechnology, and health care clients.

The largest outsourcing service providers generated decent if unspectacular results in the most recent quarter. Investors seem pleased at the ongoing evolution of many of them into providers of a broader range of services. They do not seem as pleased about some the new complexities required when predicting and analyzing their near-term financial results.
What Will the 21st Century Cures Act Do For The Clinical Research Enterprise?

After two years of deliberating Public Law 114-255, **The 21st Century Cures Act** was passed by votes of 344 to 77 in the House of Representatives and 94 to 5 in the Senate. President Obama signed it on December 13, 2016.

Advocates and critics agree on most of the words used on the bill’s 996 pages. But they differ in their evaluation of their meaning and their merits. In perhaps its most widely praised provisions, the act provides almost $5 billion of funding to support the National Institutes of Health (NIH) research programs on precision medicine, neuroscience, and cancer, as well as $1 billion in state grants to increase opioid prevention and treatment services.

We suspect our readers are more interested in the impact of several provisions aimed at easing and accelerating the pathway to the market for investigational drugs. Among the most meaningful seem to be sections requiring the FDA to establish the following:

- a formal review pathway for biomarkers and other drug development tools,
- a program to evaluate the potential use of “real world evidence” from sources other than randomized clinical trials to support the approval of new indications for existing drugs, and to satisfy post-approval requirements,
- a new breakthrough pathway for medical devices, and
- an expedited review pathway for “regenerative medicine”.

Other sections grant the FDA new authorization to:

- use “qualified data summaries” when evaluating the approval of new indications, and
- permit drug companies to distribute to payers more types of “health care economic information (HCEI)” that is “related to” an FDA-approved indication.

The act also contains provisions dealing with combination products, genetically targeted drugs for rare diseases, pediatric treatments, adaptive clinical trial designs, centralized IRBs, and medical software. It also creates an ombudsman office within the Centers for Medicare and Medicaid.

We’re not sure the 21st Century Cures Act will improve the prospects of any particular companies in 2017. But we think it will be helpful to the broad drug development enterprise.
What’s The Outlook for the Drug and Biotech Industries?

Judging from the comments made in conference calls to discuss last year’s results and presentations made at the annual J.P. Morgan Healthcare Conference, it seems like the outlook is pretty good. We didn’t attend that conference. But it’s easy to summarize some key messages as reported by company press releases and trade industry articles.

- Most firms have sufficient capital to execute their plans.
- Most products are proceeding successfully through the clinical trial phases.
- Most CEOs expect the FDA to continue working with them to accelerate the approval process.
- Optimistic merger talk was everywhere.

Many speeches, presentations, and panel discussions offered optimistic views of topics such as Big Data, precision medicine, rare disease research, and the Cancer Moonshot. But they also touched on a few flies in the ointment.

- Several pharmaceutical company CEOs joined the “10% price hike group”, hoping that by showing some restraint on pricing the industry can avoid any administrative or legislative efforts to impose restrictions from the outside. But not every executive believes that’s the right response to the uproar over prices. Pricing a drug to appropriately account for its “value” is a better option. (See p. 11 for more on that issue.)

- Investors showed just how concerned they are about potential price restrictions by shaving several billion dollars off two major indices of drug and biotech stock prices the day then-President Elect Trump accused the industry of “getting away with murder” and stated his desire to initiate new bidding procedures for federal spending on drugs.

- Patent disputes are taking center-stage across several fronts. The most contentious involves the time lag between the date of FDA approval of a biosimilar and the date the company can launch the product. Some attendees suggested the industry’s hardball tactics regarding patents are contributing to the public’s negative attitude toward the industry.

- Pipeline activity is robust. But while some companies shared good news about the progress of an important drug, others had to admit to some setbacks in their activities.

The overall outlook is good. We hope the industry’s CEOs will exhibit some restraint in using heavy-handed tactics regarding the controversial issues of pricing and patents.
Will We See More Value-Based Pricing By Drug Companies?

Back in November voters in California rejected Proposition 61: The Drug Pricing Standards Initiative, which would have capped the payments that state’s healthcare programs pay for prescription drugs. Also in November voters rejected Democratic Presidential Candidate Hillary Clinton, perhaps reflecting a dislike for her implicit and explicit plans to restrict the drug industry’s ability to set the prices for its products. Drugs account for only about 10% of the country’s spending on healthcare. Yet we continue to believe that “the high cost of drugs” is an issue that will not go away.

In 2017 we expect to see both drug companies and third-party payers make more use of value-based pricing models when establishing prices for new products and adjusting prices for existing ones. Constructing such a model is not a trivial task. It requires quantifying both tangible and intangible elements and doing so on both a near-term and a long-term basis. Recent articles by prominent healthcare observers suggest several key elements of a credible value-based pricing system.

Tools to Measuring Outcomes:

- compare rates of survival and/or disease progression,
- acknowledge the achievement of specific clinical endpoints such as major molecular responses and clinically relevant biomarkers.

The Use of Patient-Focused Metrics:

- measure quality of life indicators,
- note the avoidance of adverse events or delayed time to metastasis,
- measure the length of treatment-free intervals,
- measure the duration of therapy,
- note problems of the administration and complexity of therapy and related adherence to treatment.

Considerations for the Healthcare System:

- measure a drug therapy’s reduction in the number and cost of hospitalizations and physician visits,
- evaluate the efficiencies of drug therapy at home and in alternate care settings.

Considerations for Society:

- Measure the overall economic and social impact of using effective medicines to enable patients to lead productive lives.

Drug companies need to develop new models to justify their products’ prices. This is just one of them.
What's The Outlook for The Outsourcing Industry?

As reported by CapIQ and shown in the table below, analysts expect the companies in both the clinical services and non-clinical services sectors to post relatively modest revenue growth that ranges from 4-7% for some and 11-14% for others. Organic or “same stores” growth rates may be different; most companies have made an acquisition that influences the 2016 to 2017 year-to-year comparison. The analysts also believe that most companies will post higher growth rates for their EBITDA profits. As we’ve noted in previous reports, we prefer to track profitability using *Earnings Before Interest, Taxes, Depreciation, and Amortization* since it ignores decisions managements make about non-operating expenses.

### Clinical Services Companies

<table>
<thead>
<tr>
<th>$ in millions</th>
<th>Revenue</th>
<th>EBITDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICON</td>
<td>$1,503</td>
<td>$1,575</td>
</tr>
<tr>
<td>INC Research</td>
<td>810</td>
<td>915</td>
</tr>
<tr>
<td>LabCorp</td>
<td>6,012</td>
<td>8,506</td>
</tr>
<tr>
<td>Medpace</td>
<td>290</td>
<td>320</td>
</tr>
<tr>
<td>Parexel</td>
<td>1,994</td>
<td>2,056</td>
</tr>
<tr>
<td>PRA Health</td>
<td>1,267</td>
<td>1,376</td>
</tr>
<tr>
<td>Quintiles</td>
<td>4,165</td>
<td>4,326</td>
</tr>
</tbody>
</table>

### Non-Clinical Services Companies

<table>
<thead>
<tr>
<th>$ in millions</th>
<th>Revenue</th>
<th>EBITDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMRI</td>
<td>$277</td>
<td>$402</td>
</tr>
<tr>
<td>Cambrex</td>
<td>374</td>
<td>434</td>
</tr>
<tr>
<td>Catalent</td>
<td>1,847</td>
<td>1,835</td>
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<tr>
<td>Charles River Labs</td>
<td>1,298</td>
<td>1,363</td>
</tr>
<tr>
<td>Eurofins</td>
<td>1,707</td>
<td>2,118</td>
</tr>
<tr>
<td>Lonza Group</td>
<td>3,664</td>
<td>3,798</td>
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<tr>
<td>Patheon</td>
<td>1,931</td>
<td>1,723</td>
</tr>
<tr>
<td>Sartorius</td>
<td>1,079</td>
<td>1,211</td>
</tr>
<tr>
<td>Siegfried</td>
<td>317</td>
<td>480</td>
</tr>
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Whether it’s the result of product/service mix, expense management programs, currency gains or losses, or one-time restructuring efforts, the evidence continues to suggest that the managements of these firms are very capable of enhancing their profitability even while generating only modest revenue growth.
Are the Stocks of Those Companies Likely to Continue Advancing?

We do not opine directly on the potential performance of any stocks. But we can show the two charts below that demonstrate investors’ preferences for the stocks of the clinical and non-clinical service companies discussed on the previous page over others in the healthcare service industry and the market in general as measured by the S&P Healthcare Services Industry Index and the S&P 500 Index, respectively.

The “rises” continued to outpace the “falls”.

It’s logical to expect that the continuation of strong revenue and profit growth by these companies will be accompanied by strong market performance for their stocks. But the stock market is not always logical!
Will We See Any New Pricing Models By The Clinically-Oriented CROs?

CROs provide a service; the largest component of a typical study budget is the cost of the people conducting it. When responding to an RFP and issuing a price quotation a CRO needs to be as accurate as possible in evaluating this and other variables:

- the number of people from each department (monitoring, data management, medical writing, et al.) who will be needed for the study,
- the number of weeks/months/years it will take to complete each phase of the study,
- the likelihood of potential changes in the study design that will necessitate any change orders, and
- the potential for outside factors to change the timing and/or scope of the study.

Most CROs use a variable pricing model that assigns a cost to the different types of “units” needed to conduct a study, and estimates the number of such “units” that will be required to complete it. But drug development involves the unpredictability of biology not the certainty of engineering; things happen that were not predicted at the time of a study's design. Expensive change-orders are frequently needed to continue a study; time delays due to unanticipated findings are necessary but disruptive elements to the process; and shifting competitive priorities of a sponsor can even disrupt the conduct of studies that otherwise appear to be on-time and on-budget.

Would a fixed-pricing model work better for the industry?

- Would many CROs accept the responsibility for absorbing cost increases they should have anticipated when issuing such a contract?
- Would many drug companies give their CROs as much information as requested up-front (it seems that they rarely do so) in exchange for a fixed-price contract that is based on a more complete assessment of the study than is typically possible?

Does risk-sharing between sponsors and CROs make sense?

- Would a service company like a CRO accept a share of the potential rewards of a successful drug in exchange for a lower price to conduct studies on that compound?
- Would a drug company be willing to share those potential post-marketing rewards in exchange for a lower cost of development?

We don’t have the answers to these questions. But we wonder if both sponsors and CROs shouldn’t be more adventurous in experimenting with different pricing models.
What Type of New Business Combinations Will We See This Year?

The New Year was only twelve days old when we read of the merger of Sarah Cannon, the Cancer Research Institute of Hospital Corporation of America and Genospace, LLC, a cloud-based software company focused on advancing personalized medicine. It’s not a merger we would have predicted, but it’s not one that surprises us either. We do expect to see more unusual combinations in a few different segments of outsourcing.

- In several Monitors in 2016 we noted the evolution of one new type of business combination – the acquisition of investigative sites by CROs. As the year ended we counted a handful of large CROs that collectively owned more than 200 separate sites. In addition, we noted several healthcare delivery organizations that complemented their businesses by owning a number of sites. We continue to believe that consolidation will continue among the providers of investigative sites. We expect to see many individual sites join existing or newly established networks; and we believe many networks will seek to become part of larger organizations that can optimize the value of their sites.

- Last year we also noted how many CROs expanded the scope of their activities by establishing or purchasing business units providing services to the commercialization departments of drug companies. Market research firms suggest that drug companies spend $160 billion each year on those services, compared to $130 billion in R&D. Moreover, the outsourcing opportunities seem to be much larger in the former category than the latter. The vast majority of activity in this arena occurs in the United States. Healthcare delivery companies and third-party payers are also potential buyers of service companies providing related information, technology, and analytics services.

- Specialty chemical companies and drug manufacturing companies are also expanding their businesses into complementary service categories. Many acquisitions relate to the increasing use of biologics around the world, as well as the development of more biosimilar versions of many off-patent drugs. Analysts of “contract research” companies are covering more firms offering “contract commercial development” services. Similarly, those following “contract manufacturing” firms are expanding their sights to include firms providing services involving ADMET, formulation, drug screening, and supply chain activities.

We are almost never surprised when Company A acquires Company B and thus diversifies its business and its customer base.
How Will Drug Companies And CROs Adjust Their Working Relationships?

Magazine articles, conference presentations, trade press editorials, and market surveys continue to suggest that so-called “strategic partnerships” between drug sponsors and CROs are not meeting the expectations of either party. What’s wrong? We just address two issues here.

- We suspect some disappointment about the effectiveness of many partnerships involves an unfortunate but realistic aspect of drug development - *most drugs fail somewhere in the development process*. After a compound fails in the clinic it’s easy to point fingers and ascribe the blame for the failure to what one party did or didn’t do to ensure the trial’s success.

- It’s also apparent to us that tremendous personnel turnover within both sponsor and provider organizations has proven disruptive to the smooth functioning of the many teams engaged in long-term projects.

Companies are trying to adopt tactics to deal with each of these issues.

- Sponsors and providers are recognizing the importance of aligning interests and expectations at the start of a strategic relationship. We see new partnerships focusing not only the specific goals of individual trials but also the broader objective of using each other’s resources to enhance the objectives of an overall development program. Many collaborations call for embedding personnel within a partner’s organization. More partners are enhancing their “lessons learned” programs even after the completion of successful projects. And more sponsors are using advanced IT tools to improve every partner’s access to information and enable instant feedback about problems as they occur, rather than letting them fester until the next project team meeting.

- Dealing with personnel turnover seems more difficult. In December the consulting firm HR+Survey Solutions noted in its 18th annual CRO survey that turnover in clinical monitoring jobs throughout that industry was 25% in 2015, virtually unchanged from the 2014 level. Sponsors seem to be particularly aware of the disruptions such high turnover can produce. Many surveys note that they are using small, specialized CROs more frequently than ever. Others suggest that having relatively low turnover rates can give such firms a strong competitive advantage over their larger, full service competitors.

But these are certainly not the only issues that need addressing.

It’s not magic; operating executives using creative management techniques can indeed make a difference.
What Will Be The Pace of M&A Activity?

We believe the strategic and financial imperatives that have been leading both corporate buyers and private investors to pursue acquisitions in the pharmaceutical outsourcing industry still remain in place. Thus, we expect to see many more deals completed in 2017, assuming of course that overall economic conditions remain reasonably strong and interest rates remain relatively low. In trying to predict the names of the targets to be acquired this year it seems rational to start by noting some large companies that have been owned by a private equity firms for at least four years. During the past twelve months, six of the companies we listed in our January 2016 Monitor have been acquired.

<table>
<thead>
<tr>
<th>Company</th>
<th>Private Equity Firm</th>
<th>Date Acquired</th>
</tr>
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<tbody>
<tr>
<td>aptuit</td>
<td>WCAS</td>
<td>April 2006</td>
</tr>
<tr>
<td>Worldwide Clinical Trials</td>
<td>The Jordan Company</td>
<td>January 2008</td>
</tr>
<tr>
<td>NextPharma</td>
<td>Sun European Partners</td>
<td>February 2011</td>
</tr>
<tr>
<td>PPD</td>
<td>Carlyle Group; Hellman &amp; Friedman</td>
<td>December 2011</td>
</tr>
<tr>
<td>dDrugDev</td>
<td>Invesco Perpetual</td>
<td>May 2013</td>
</tr>
<tr>
<td>alcami</td>
<td>American Capital</td>
<td>October 2013</td>
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Space does not permit a listing of all PE-owned companies. It’s difficult to list all the business units of large diversified companies that may be put on the market. And it’s impossible to list the most likely acquisition candidates among the large number of companies owned by entrepreneurs.

The reader will just have to wait until the deals are announced to find out which of these many, many potential acquisitions will in fact occur in 2017.
How Soon Will Brexit Affect the Pharmaceutical and Outsourcing Industries?

The United Kingdom’s (UK) June 2016 vote to leave the European Union (EU) may not affect those industries directly this year. But we suspect we’ll be hearing more from various sponsors and providers throughout the year about their plans for coping with the uncertainties that vote has triggered.

In January Prime Minister Theresa May addressed one point of uncertainty by stating firmly that Britain would pursue a definitive break from the EU via the so-called “hard Brexit” option. Doing so will require the UK to give up access to the single EU market and require it to strike new trade laws with its former partners as well as all non-EU countries. It will require separate passports for UK and EU citizens and restrict the mobility of three million EU citizens now living and working in the UK and two million UK citizens currently living and working in the EU. As separate nations the UK and EU will be free to impose tariffs on imported goods.

In February Prime Minister May indicated her intention to trigger Article 50 of the European Union’s Lisbon Treaty before the end of March. The House of Commons has already approved a bill authorizing her to do so; the House of Lords is expected to approve a similar bill very soon.

Triggering Article 50 will give the EU’s 27 other members formal notification of Great Britain’s intention to voluntarily leave that Union. After triggering it, government officials can begin negotiating the terms of that withdrawal. Those “divorce” talks can take up to two years to conclude.

Published reports suggest that UK officials are already talking with their counterparts around the world about possible terms of reciprocal trade agreements. One suggestion has the UK offering to adopt all EU tariff schedules, with the goal of minimizing the disruption of trade that would occur immediately after the UK formally leaves the EU.

It is not yet clear whether some officials from the UK and EU can carry on talks about a future trade agreement at the same time other officials are discussing the terms of the political split. Nor is it clear how Brexit will affect the drug approval process in the UK or the EMEA.

Knowing about the definitive choice of the “hard Brexit” option should give drug development companies and outsourcing service providers sufficient time to adjust their operations to cope with the eventual exist of the UK from the EU. Investors need to remain aware of those evolving plans.
Will Biosimilars Be Big In The United States?

Perhaps the largest unresolved issue that could influence the ultimate size of the biosimilar market in the United States is interchangeability. Throughout the European Union pharmacists can automatically interchange a biosimilar product when a branded drug is prescribed. In the United States, they can make that substitution with most small molecule drugs but not with a biosimilar.

Sometime this year the FDA is expected to provide Guidance on the studies that will be required to justify the approval of a biosimilar as “interchangeable” with its reference product. In a mid-December presentation Janet Woodcock, Director of the FDA’s Center for Drug Evaluation and Research (CDER), did not specify a timeline for producing that Guidance document.

Dr. Woodcock did share a few statistics on the progress of biosimilars:

- Four biosimilars have been approved, although only two are on the market pending the resolution of certain patent issues.
- The FDA is evaluating 12 additional applications.
- The agency is working with manufacturers on 66 other biosimilar development projects.

At the DIA Biosimilars Conference last October, John Jenkins, the Director of the Office of New Drugs within CDER, shared some Key Concepts and Lessons Learned about developing biosimilars:

- The evaluation of a potential new molecule leans heavily on pivotal clinical studies; the evaluation of a potential biosimilar leans heavily on analytical studies.
- Novel methods and approaches used to demonstrate biosimilarity must be justified and supported by adequate data and information.
- Extrapolating data from reference product studies raises significant concerns.
- Conducting clinical studies not strictly necessary for approval can reduce the cost advantage of a biosimilar product.
- Biosimilarity requires a product to be “highly similar” to its reference product AND (not OR) show “no clinically meaningful differences” to that product.

He ended by suggesting that manufacturers strictly follow the agency’s stepwise “Evidence Development” program and meet regularly with FDA officials managing the agency’s Biosimilar Development Program.

We continue to see the potential for meaningful incremental revenue for outsourcing firms supporting their clients’ biosimilar development programs.
Why Isn’t Patient Recruiting Getting Easier and More Effective?

Here’s another issue that’s the topic of a plethora of conference presentations, trade industry articles, webinars, and corporate capabilities demonstrations. Many discuss the expanding use of technology, the availability of new tools such as wearables, and the use of social media and web-based virtual trials to reach and engage more potential patients. But it’s not clear that any of these new approaches or tools have made the recruiting process more effective.

- Patient recruitment continues to consume about 30% of the typical trial’s cost.
- “Recruiting difficulties” is the most commonly cited reason for delays in clinical trials.
- About 80% of studies fail to meet their enrollment timelines.
- Almost 48% of all investigative sites under-enroll patients.
- Up to 25% of enrolled patients drop out of their study, thus necessitating additional “rescue recruitment efforts”.

Ken Getz at the Tufts Center for the Study of Drug Development (CSDD) has just released the annual update of his “Engaging Healthcare Providers…” survey. Contrary to what many clinical research professionals still seem to think, nearly 91% of the physicians and 72% of the nurses queried felt comfortable discussing the opportunity to participate in a clinical trial with their patients.

Other studies suggest that physicians would refer more of their patients to trials if they could develop working relationships with clinical investigators. Those practitioners acknowledge their inability to spend the time and gain the knowledge necessary to become more effective advocates for clinical research.

Still other studies suggest that 7 out of 10 people express a willingness to participate in a clinical trial if only someone would make them aware of one that’s relevant to them.

If both practicing physicians and individual patients are willing to become more involved in the clinical research enterprise…and if sponsors and CROs are using a new array of tools and approaches to recruit patients for their trials…back to our question “Why isn’t recruiting getting easier and more effective?”

We look forward to seeing more than just a handful of individual case studies that can document the counterfactual answer to our admittedly cynical question.
And Finally...

Once again, we bring our list of questions up to the magic number (17 this year) by noting some issues we’ve been exploring for some more in-depth discussion in a future edition of our Monitor.

**How Will the Regulatory Environment Change?**

Shortly, new people will be taking over the positions Secretary of Health and Human Services, Administrator of the Centers for Medicare and Medicaid, and possibly Commissioner of the FDA. Historically, the appointees of a Republican President have acted differently than those of a Democratic one. This year the FDA and other agencies will begin implementing the provisions of the 21st Century Cures Act. Also, the European Union will be trying to finalize EU Regulation No. 536/2014, which is intended to make that territory a more attractive place to conduct clinical research.

**Is The Use of Wearable Technology in Clinical Trials Really A Game-Changer?**

A November 2016 survey confirmed the findings in earlier studies examining the relatively slow roll-out of companies’ usage of wrist bands, watches, patches, and special clothing in clinical trials. It noted concerns about validation, cost, and both investigator and patient familiarity, and suggested these were serious issues that must be overcome if the question is going to be answered in the affirmative.

**Will We See More Integration Of The Clinical Research and Healthcare Delivery Enterprises?**

Probably. But it’s still an open question whether such activity will occur only in local geographies or across broader coverage landscapes. Coping with changes to the Affordable Care Act and adapting to further consolidation among healthcare providers may take up so much room on executives’ plates that they may not be willing or able to aggressively pursue this integration of the two ecosystems.

**What Questions Do You Have For Us?**

Last year, the feedback we received on this question prompted us to explore several specific issues in subsequent Monitors. So we again pose it to our readers with the expectation that we’ll do our best to address your concerns as we move through 2017.
About the Author

Michael A. Martorelli is a Director at Fairmount Partners. He joined the company after a long career as a research analyst covering a variety of healthcare companies for both buy-side and sell-side firms. During the past fifteen years, he has focused his efforts on a variety of pharmaceutical service companies. He participates in conferences run by the Drug Information Association (DIA), Institute for International Research (IIR), and other organizations. Mr. Martorelli has written a regular Financial Analysis column for the trade publication Contract Pharma. He continues to provide guest commentary for other publications.

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  Acquired By
  Cinven

- CFS Clinical
  Acquired By
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