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Bio/Pharmaceutical Outsourcing Report

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Business Conditions

PE-Owned Companies in Line to Change Hands

Mergers and acquisitions are a hot topic in the contract services industry these days, and there is a lot of curiosity about which companies are likely to change hands. Of course, any company is a target at any time, especially when the price is right, but insight to likely acquisition candidates can be gained by looking at the list of companies owned by private equity (PE) firms. On average, PE firms tend to hold onto their investments for about five years, so companies that were acquired at least four years ago are likely targets in the next year or two.

The table on page 2 lists 23 CMC services companies that are PE-owned; the list was derived from the PharmSource *Strategic Advantage* database "Search by Ownership" feature. It is sorted by the year each company was acquired, and suggests that at least 13 CMOs and CDMOs are ripe for a transaction in the foreseeable future.

The sale of one company, **Marken** (Durham, N.C., USA), was announced just this month (*see news item, Page 3)*; another, **Capsugel** (Morristown, N.J., USA), has been mentioned in the business press as being prepared for an ownership change. Other companies in the list have been rumored from time-to-time to be on offer.

Who might buy these acquisition candidates is an interesting question. Many are likely to just pass from one PE firm to another; this is especially likely for European CMOs like **Unither** (Amiens, France) and **NextPharma** (Surrey UK), which are focused on the highly competitive European market and have older facilities that are not likely to be attractive to a strategic buyer. A case in point: Cathay Capital acquired CMO **Cenexi** (Fontenay-Sous-Bois, France) from its first PE owner, Chequers Capital. A few—like **Ritedose** (Columbia, S.C., USA), **CMC Biologics** (Copenhagen, Denmark) and **Alcami** (Wilmington, N.C., USA)—have capabilities that could enhance or expand a strategic buyer's operations. The largest ones, **Aenova** (Stamberg, Germany) and Capsugel, may even have an IPO opportunity in their futures.

Some of the companies on the list have been owned by their PE backers for considerably longer than the typical five-year holding period. The longer holding periods could reflect a strategic preference by the PE firm to hold businesses for a longer period, or it could reflect performance issues that have made the company difficult to sell.

Despite the uncertainty following the US election, the current industry and financial markets environment is probably conducive to getting deals done. We should expect a number of the listed companies to be the subject of acquisition announcements in the next six to 12 months.

PE-owned CMC Services Companies, by Year Acquired

Company	Parent Company	Year Acquired
Accupac	H.I.G. Capital	2003
Aptuit, Inc.	Welsh, Carson, Anderson & Stowe	2004
CordenPharma	International Chemical Investors Group (ICIG)	2006
CMC Biologics A/S	Monitor Clipper Partners	2008
EAG Laboratories	Odyssey Investment Partners	2008
The Ritedose Corporation	Olympus Partners	2009
Marken	Lloyds Bank	2009
Aphena Pharma Solutions, Inc.	Enhanced Equity Funds	2011
Capsugel	KKR, Kohlberg Kravis Roberts & Co. L.P.	2011
NextPharma Technologies	Sun Capital Partners	2011
Unither Pharmaceuticals	Equistone Partners Europe	2011
Aenova Group	BC Partners	2012
Alcami	American Capital	2012
Denison Pharmaceuticals	Brookstone Partners	2013
ShangPharma Corporation	TPG Capital	2013
Synerlab Group	21 Partners S.p.A.	2013
Ampac Fine Chemicals	H.I.G. Capital	2014
Novasep	Fonds Stratégique d'Investissement	2014
Paragon Bioservices, Inc.	NewSpring Capital	2014
Ricerca Biosciences LLC	Main Market Partners	2014
Accuratus Lab Services	Ampersand Capital Partners	2015
Halo Pharmaceutical	SK Capital Partners	2015
Cenexi	Cathay Capital	2015

Commercial Dose Manufacturing and Packaging

New Manufacturing Deal, Temporary Closures and Recall for Patheon

Patheon (Durham, N.C., USA) will manufacture Auryxia tablets, used to treat chronic kidney disease, for Keryx Biopharmaceuticals (New York, N.Y., USA) through 2021, under an agreement that Keryx announced in a Securities & Exchange Commission (SEC) filing earlier this month. Keryx entered the new agreement with Patheon after its original CMO, Norwich Pharmaceutical Services, halted production due to processing problems.

Patheon also disclosed that the temporary closure of three commercial sites in October has had a $15 million negative impact on revenues and $12 million adverse impact on EBITDA in its fourth fiscal quarter. The Greenville, N.C., USA, dose manufacturing site and Florence, S.C., USA, small molecule API site were impacted by Hurricane Matthew, while the Manati, Puerto Rico, dose manufacturing site was closed due to an interruption of electrical power on the island.

It was also announced recently that Patheon was the CMO that produced sub-potent birth control pills that are the subject of a Class III recall by Endo Pharmaceuticals (Chadds Ford, Pa., USA). Patheon made the Gildess (norethindrone acetate/ethinyl estradiol) tablets for Endo at its Whitby, Ontario, Canada facility. Endo's Par Pharmaceutical unit is handling the recall.

Learn More

*For more information on the business and capabilities of Patheon, click on on "Learn More" at left or go to **www.pharmsource.com** and search by company name. If you need your access codes, just call 1-703-383-4903 (ET).*

Commercial Dose Manufacturing and Packaging in Brief

Fresenius Kabi (Bad Homburg, Germany) has added a small volume parenteral filling line with an integrated freeze dryer, intended to boost capacity for third-party manufacturing of lyophilized aqueous and liposomal formulations, at its Graz, Austria injectables production site. The 19-square-meter line has capacity for vial sizes of 2-30 mL, and can handle high-potency and biological APIs.

Pharmaceutics International Inc. (PII – Hunt Valley, Md., USA) manufactured about 43,000 bottles of paricalcitol that were recalled last week by Teva (Petah Tikva, Israel) due to failed stability testing for impurity levels.

PharMEDium Services (Lake Forest, Ill., USA), a compounding pharmacy, has recalled several lots of injectable products due to stability data that does not support labeled expiration dates. Affected products included atropine sulfate, ephedrine sulfate, fentanyl citrate/bupivacaine HCl, fentanyl citrate, glycopyrrolate, heparin sodium, hydromorphone HCl, ketamine HCl, labetolol HCl, lidocaine, methadone, midazolam HCl, morphine sulfate, neostigmine methylsulfate, phenylephrine HCl, remifentanil HCl, rocuronium bromide and succinylcholine chloride.

PL Developments (PLD – Westbury, N.Y., USA), a developer and manufacturer of OTC and nutritional products for the private label market, has acquired diagnostic developer and manufacturer Health – Chem Diagnostics (HCD – Pompano Beach, Fla., USA) for an undisclosed sum. HCD offers analog and digital diagnostics for family planning, cholesterol monitoring, glucose monitoring, drug and alcohol screening and infectious disease detection, along with other categories of diagnostic testing kits. PLD will continue manufacturing the HCD products at the Pompano Beach production facility.

Saneca Pharma (Hlohovec, Slovakia) will manufacture enteric-coated, controlled-release pellets for a product of the Italian pharmaceutical company Menarini Group. The pellets are made using extrusion/spheronization and coated using Wurster fluid bed technology. Under the five-year agreement, Saneca Pharma will invest in its Hlohovec facility to increase the scale at which it can perform Wurster coating of the pellets. Saneca has already manufactured the pellets at the 100 kg scale.

Wockhardt (Mumbai, India) is undertaking a £10 million ($12.52 million) expansion of its sterile drug manufacturing plant at its Wrexham, Wales site. The facility is slated to open in December, according to a *BBC News* report.

Clinical Dose Manufacturing and Packaging

Marken to be Acquired by UPS

Marken (Chiswick, UK), a provider of logistics services for clinical trials, will be acquired by UPS in a deal that will close by year-end. Financial terms were not announced.

Marken provides a broad range of capabilities for handling clinical trial supplies, including courier services, clinical supply depots, cold chain assurance, shipment tracking, direct-to-patient delivery and logistics consulting. It handles both outbound shipments of clinical trial supplies to investigator sites, and collection of biological samples from those sites. According to its financial filings in the UK, it handles more than 50,000 shipments per month.

According to its UK financial filings, Marken had 2015 revenues £116 million ($143 million at current exchange rates), up nearly 11% from its 2014 performance, and EBITDA of £17.3 million ($21 million), up 19% from 2014.

The company said its outbound business, which has been a major strategic focus, grew twice as fast as its in-bound business.

Private equity firm Apax Partners (London, UK) acquired Marken in 2009 for nearly £1 billion, or about $1.6 billion at exchange rates at the time. Thanks to a decline in bio/pharma industry R&D spending following the global financial crisis, Marken's performance deteriorated, and in 2012, Apax was forced to cede its ownership to the bank that had funded the acquisition, taking a £600 million loss as a result.

WHAT IT MEANS > > >

Logistics services for bio/pharmaceutical clinical trials has been become a hotly competitive business, driven by globalization of clinical trials and the growing share of temperature-sensitive compounds, especially biologics, in the development pipeline. The competition has become intense in the commercial arena, as well, thanks again to biologics and growth in direct-to-patient shipping of self-injected products like autoimmune therapies (Humira, Enbrel, etc.).

UPS competes in this arena with FedEx, DHL and World Courier (now owned by **AmerisourceBergen**) and a number of smaller companies like Yourway. The Marken acquisition strengthens UPS's competitive position by coupling its enormous air and ground shipping and delivery network with the specialized services to ferry clinical trial materials and samples among transportation hubs and clinical sites in compliance with GMP, GCP and import/export regulatory requirements.

Most of the other industry participants have pieces of the value chain (e.g., FedEx has the air and ground delivery network, **World Courier** has the specialty clinical logistics capability, **Parexel** has the depots) but none have all the pieces to offer a fully integrated solution. The UPS-Marken combined offering could prove to be highly attractive to global bio/pharma companies looking to consolidate their business with fewer vendors.

It will be interesting to see how the deal affects the strategies and prospects of other participants in the clinical logistics business. Several of the leading clinical packagers, notably **Fisher Clinical Services** and **Almac**, have invested in expanding their logistics capabilities as part of their clinical trial materials management offering, including adding depots and subsidiary packaging sites to their networks. Parexel has built a depot network of its own, but lacks the upstream (i.e., packaging) or shipping capabilities to enable it to compete with more integrated suppliers. It would not be surprising to see Parexel divest its CTM services business, especially if Marken's owners got an attractive valuation for their business.

Learn More

*For more information on the business and capabilities of Marken, click on on "Learn More" at left or go to **www.pharmsource.com** and search by company name.*

Clinical Dose Manufacturing and Packaging in Brief

Avrio Biopharmaceuticals (Irvine, Calif., USA) has completed technology transfer of Hemispherx Biopharma's (Philadelphia, Pa., USA) Ampligen® manufacturing processes to Avrio's facility, including performance of a test engineering run; the first cGMP lot of the drug is expected to be completed this month and released in December. Hemispherx tapped Avrio earlier this year to provide compounding and fill/finish of clinical and commercial supplies of Ampligen, a chronic fatigue syndrome treatment.

BioDuro (San Diego, Calif., USA) has expanded the spray-drying capabilities at its San Diego manufacturing facility, adding an SPX Anydro MicraSpray 150 at the site. BioDuro currently performs clinical manufacture using its existing MicraSpray 35 spray-dryer; the new addition will boost capacity to the 100 kg scale, with speeds up to 15 kg/hour. The new spray-dryer will be operational in the first quarter of 2017.

Catalent Pharma Solutions (Somerset, N.J., USA) will provide Phase I-II clinical supplies of Moderna Therapeutics' (Cambridge, Mass., USA) mRNA personalized cancer vaccine. Catalent will manufacture the candidate vaccine at its Madison, Wis., USA facility through 2018, while Moderna Therapeutics builds out a clinical manufacturing facility in Norwood, Mass. Clinical trials of the vaccine are slated to begin in 2017.

Cryoport (Irvine, Calif., USA) recently announced that it now provides cryogenic services to more than 100 clinical trials, 16 of which are in Phase III. New or expanded agreements include cryogenic logistics support for Heat Biologics' (Durham, N.C., USA) Phase II trial of HS-410 (vesigenurtacel-L) for non-muscle-invasive bladder cancer and Phase I trial of HS-110 (viagenpumatucel-L) for non-small cell lung cancer. Cryoport also is providing services for studies of Kite Pharma's (Santa Monica, Calif., USA) KTE-C19 for chemorefractory, aggressive non-Hodgkin lymphoma, as well as a Phase I trial of Unum Therapeutics' (Cambridge, Mass., USA) antibody-coupled T-cell receptor for relapsed or refractory CD20-positive, B-cell non-Hodgkin lymphoma. Other clients include Gradalis (Dallas, Texas, USA), Immuno-Cellular Therapeutics (Calabasas, Calif., USA), Perseus PCI (Simpsonville, S.C., USA) and Stemedica (San Diego, Calif., USA), among others.

IDT Australia (Boronia, Victoria, Australia), a clinical scale contract manufacturer, will sell its CMAX clinical trial business to I'rom Group (Tokyo, Japan) for a minimum of $14 million in a staged transaction. I'rom Group initially will acquire 61% of the clinical trial business for $10 million, which will allow the Japanese company to integrate CMAX. I'rom Group will acquire the remaining shares over the next 12 months for a minimum payment of $4 million; this payment may increase if CMAX exceeds an undisclosed revenue target for 2017.

Lonza (Basel, Switzerland) has opened a new drug product services laboratory facility in Basel. The 1,300-square-meter site will provide formulation development, drug analytical development and quality control services, such as particle testing, trace impurity detection, container/closure integrity testing and extractables and leachables testing.

Marken (Durham, N.C., USA) has opened a new clinical supply facility in Brisbane, Australia. The new site can serve trial sites in Singapore, as well as other sites in the US and Europe, with real-time tracking available that includes location, temperature and package condition, including light exposure.

Patheon (Durham, N.C., USA) will manufacture Phase IIb clinical supplies of the candidate age-related macular degeneration treatment Macuneos for Biophytis (Paris, France). Patheon will perform industrial scale-up, in addition to manufacture of clinical batches of the drug.

Quay Pharma (Deeside, UK) will manufacture clinical supplies of Redx Pharma's (Macclesfield, UK) candidate pancreatic, gastric and biliary cancer treatment, RXC004. First-in-human studies are slated to begin in early 2017.

Side Effects: Impacts of Key Events on CMOs and CROs

Side Effects identifies CMOs and CROs that might be impacted by key events affecting their clients, including company acquisitions, product acquisitions and licenses, product approvals, late clinical product terminations and FDA rejections.

Contractor	BioPharma Company	Event	Product	Relationship
		POTENTIALLY POSITIVE		
Shaanxi Hanjiang	Janssen	FDA approval	Vermox	Small-molecule API manufacturing
Recipharm (Lusomedicamenta Sociedade Tecnica)	Janssen	FDA approval	Vermox	Solid dose manufacturing
Baxter Biopharma Solutions	Baxalta	EMA approval	Onivyde	Parenteral manufacturing
Hubel Haosun Pharmaceutical Co.	Baxalta	EMA approval	Onivyde	Small-molecule API manufacturing
Lonza	AstraZeneca	NICE approval for locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer in adults	Tagrisso	Small-molecule API manufacturing
Vetter	UCB	NICE approval for rheumatoid arthritis in adults for whom other disease-modifying antirheumatic drugs (DMARDs) have failed	Cimzia	Parenteral manufacturing
Lonza	UCB	NICE approval for rheumatoid arthritis in adults for whom other disease-modifying antirheumatic drugs (DMARDs) have failed	Cimzia	Large-molecule API manufacturing
Bend (Capsugel)	Merck & Co	NICE approval for genotype 1 or 4 chronic hepatitis C in adults	Zepatier	Solid dose manufacturing (solubility enhancement by amorphous solid dispersion)
Fujifilm Diosynth Biotechnologies	OncoGenex	Positive Phase II results	Apatorsen (OGX-427)	Oligonucleotide manufacturing
Piramal	Celldex	Positive Phase II results	CDX-011	Antibody-drug conjugation
Lonza	Celldex	Positive Phase II results	CDX-011	Large-molecule API manufacturing
Patheon	Flexion	Positive Phase III results	Zilretta (FX-006)	Parenteral manufacturing
Catalent	Palatin Technologies	Positive Phase III results	Bremelanotide	Parenteral manufacturing
Boehringer Ingelheim BioXcellence	Amgen	Positive Phase III results	Xgeva	Large-molecule API manufacturing

Source: PharmSource Lead Sheet

API — Large Molecule

Samsung BioLogics Completes IPO

Samsung BioLogics (Incheon, South Korea) began trading as a public company Nov. 10, 2016. The company raised nearly $2 billion by selling 16.6 million shares at an average price of 136,000 won ($119) per share, the top end of its price band. The 16. 6 million shares included 11 million newly issued shares and 5.5 million sold by Samsung Electronics. Samsung C&T, the holding company for most Samsung assets, still owns the majority of the company.

The IPO valued the company at nearly $8 billion. By comparison, **Lonza** (Basel, Switzerland), the largest current participant in contract biologics manufacturing, has a market cap of $9.4 billion, but revenues of more than $4 billion (from multiple business lines, not just biologics) and is profitable, while Samsung BioLogics will have revenues of about $200 million this year and lose money.

The company had contract manufacturing revenue of KRW 109 billion ($100 million) in the first six months of 2016, up from KRW 4 billion ($3.6 million) during the same period, as the number of batches produced grew from three in the first half of 2015 to 95 in 2016.

Samsung BioLogics is a CMO with substantial capacity in mammalian cell culture and injectable fill/finish; it also has substantial ownership stakes in two biosimilar ventures, Samsung Bioepis and Archigen Biotech. The company plans to use the money raised to fund an announced increase in biomanufacturing capacity, pay down debt and further capitalize Bioepis.

The company's manufacturing facility in the Songdo area of Incheon already has 180,000 L of mammalian cell culture capacity, and Samsung BioLogics has announced plans to build an additional 180,000 L to come on stream by the end of 2018. It also will open a 2000 L clinical scale suite by the end of this year. When the second facility comes on line, Samsung BioLogics will have the largest installed capacity of any CMO. Its fill/finish suite has capacity for 25 million vials, including lyophilization capacity.

The CMO business has targeted large strategic relationships with global biopharma companies rather than one-off projects. It has announced strategic manufacturing relationships with Bristol Myers-Squibb and Roche. However, much of its capacity will be used to manufacture products for its biosimilar joint ventures.

Samsung BioLogics owns 91.2% of biosimilar developer Samsung Bioepis; the remaining interest, which expires sometime in 2018, is held by Biogen-Idec. Bioepis has six biosimilars under development, including versions of Enbrel, Remicade, Lantus, Avastin, Herceptin and Humira. Biogen-Idec is manufacturing the first product, the biosimilar for Remicade at is facility in Denmark, but Samsung BioLogics will manufacture many of the products in Songdo. US-based Merck is a commercial partner on all six drugs.

Biogen-Idec, under an option that expires in 2018, has the right to acquire additional shares in Bioepis giving it a 50% ownership of the joint venture. Samsung BioLogics believes that Biogen-Idec is likely to exercise its option.

Archigen Biotech, also a biosimilar company, is owned with AstraZeneca; each company has a 50% interest. It is developing a biosimilar version of Rituximab.

Learn More

*For more information on the business and capabilities of Samsung BioLogics, click on on "Learn More" at left or go to **www.pharmsource.com** and search by company name.*

API — Large Molecule in Brief

IDT Biologika (Dessau-Roßlau, Germany) won a contract to provide live virus fill/finish services for the US Dept. of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA). IDT Biological will provide services for live virus/vectored vaccines and possibly for small- and large-molecule injectables, monoclonal antibodies and other products. The deal includes an initial payment of $100,000 and task orders that could total up to $50 million. IDT is one of the few CMOs with live virus fill/finish capacity and has significant scale thanks to its proprietary vaccine business.

Lonza (Basel, Switzerland) reported a strong third quarter 2016 has put it on track to see an EBITDA of CHF 1 billion ($1.02 billion) by the end of 2017 and return on net operating assets above 20% in 2017. Lonza credited strong performance in its Pharma & Biotech—both in commercial manufacturing and clinical development—and Specialty Ingredient business segments for the positive third-quarter results.

API — Small Molecule

Air Liquide (Paris, France) subsidiaries Seppic, a healthcare specialty ingredients maker, and Schülke, a hygiene specialist, have begun construction on a $60 million pharmaceutical and cosmetic ingredients manufacturing facility in Sandston, Va., USA. The plant is expected to begin operations in the first half of 2018.

Dottikon Exclusive Synthesis (Dottikon, Argau, Switzerland) reported net sales of CHF 67.6 million ($69.25 million) for the first half of its business year, which closed Sept. 30. This figure represented a 56% net sales growth compared to the previous year, which the company described as "rather weak." By the end of the full business year (March 31, 2017), Dottikon anticipates a further increase in net sales and income compared to the previous year.

Lonza (Basel, Switzerland) will provide clinical supplies of the highly potent API rucaparib, a PARP inhibitor under development by Clovis Oncology (Boulder, Colo., USA) as a potential treatment for various cancers, including advanced ovarian cancer. Lonza will build a dedicated production train for the product at its Visp, Switzerland manufacturing site, which is expected to be operational by the beginning of 2019. In the meantime, Lonza will make rucaparib at its existing facilities at the Visp site.

Recipharm (Jordbro, Sweden) has added a GMP kilo lab at its facility in Paderno Dugnano, Italy. The new lab has capacity to manufacture batches up to the 5 kg scale and capabilities for flow chemistry, chromatography and hydrogenation. The total investment in the expansion has been €1.2 million ($1.31 million). The company said it plans to double the number of R&D staff at the site over the next two years.

VWR International (Radnor, Pa., USA) has acquired two companies: small-molecule API maker **Reliable Biopharmaceutical** (St. Louis, Mo., USA) and **BioArra** (Eagleville, Pa., USA), a provider of semi-processed serum. Terms of the deals were not disclosed.

Wockhardt (Mumbai, India) problems with the US FDA may hinder approval in this country of Cempra's (Chapel Hill, N.C., USA) solithromycin to treat community-acquired pneumonia. An FDA advisory panel voted earlier this month to recommend approval of the antibiotic. However, Wockhardt's Ankleshwar, India plant, which supplies the API for the product, was placed under an FDA import alert after Cempra submitted its NDA to the agency for approval. In a recent quarterly SEC filing, Cempra noted that, while the problems at the Ankleshwar facility are not directly related to solithromycin, it's unlikely that the agency would approve the drug with API sourced from that facility. As a back-up, Cempra may be able to acquire API from a **Uquifa** (Barcelona, Spain) API facility in Cuernevaca, Mexico, the company indicated.

Analytical Services

Biosimilars and Novel Products Drive Demand for Biologics Characterization Services

Biopharmaceuticals are continuing to expand their share of the new drug pipeline, as traditional monoclonal antibody and recombinant protein products are joined by biosimilars and more novel therapies like antibody-drug conjugates (ADCs), bi-specific antibodies and gene and cell therapies. However, the cost and technical challenges inherent in working with larger, more complex molecules continue to affect movement of these products through the pipeline.

PharmSource has identified 44 companies providing biologic characterization testing services (*see table Pages 10-11*).

Technology-driven niche

Large-molecule products, whether they are innovative biologics or biosimilar drugs, are complex and variable, with characteristics that ensure safety, efficacy and quality highly process-dependent. Thus, it is critical that these products be well-characterized during development, using appropriate analytical tools that are sensitive to product-specific differences in defined quality attributes.

For instance, stability, purity, homogeneity and bioactivity must be analyzed, in addition to some key factors that are specific to protein characterization, including:

- Size;
- Molecular weight;
- Peptide mapping;
- Post-translational modification analyses, such as phosphorylation and glycosylation;
- Extinction coefficient; and
- Physicochemical analyses, such as pI and pKa.

"From the perspective of equipment, it takes a continuous investment of capital to stay on the cutting edge," Michael McDowell, vice president of business development and project management at **Eurofins Lancaster Laboratories** (Lancaster, Pa., USA), said, noting that current leading methodologies include mass spectrometry (MS), ultra- and high-performance liquid chromatography (UPLC/HPLC), capillary electrophoresis (CE) and iCE, cell-based and ELISA potency assays and polymerase chain reaction (PCR) analysis.

And despite availability of a plethora of technologies and methods for biologics characterization, the niche faces many challenges.

Mario DiPaola, scientific director at **Charles River Laboratories** (Wilmington, Mass., USA), noted that methods sensitivity remains a problem, saying, "While there has been significant progress in detecting non-enzymatic post-translational modifications (PTMs), such as oxidation, de-amidation using peptide mapping with LC-MS/MS, when these PTMs are present at concentrations of less than 1-2%, it becomes difficult to detect and quantify them. Additionally, sample manipulation through the course of the peptide mapping can induce some level of de-amidation, thus complicating interpretations of the results. If there are unusual linkages in the glycan species associated with glycoproteins and if such linkages are present in low abundance, then these linkages can go undetected."

Another significant challenge is the analysis and quantification of aggregates, which can range in size from a few nanometers up to a few millimeters in diameter. The unknown nature of formed aggregates "represents a major obstacle, as no single method is currently available to cover this range," DiPaola said.

That means that a combination of several techniques, each with its own strengths and weaknesses, is necessary to assess biologics for aggregates. And since those methods differ in their physical measuring principle, the observed results and types of information obtained will likewise vary.

Providers of Biologics Characterization Services

Contractor	Country	Facility
Ajinomoto Althea	USA	San Diego, Calif., USA
Alcami	USA	Durham, N.C., USA
		Wilmington, N.C., USA
Anabiotec	Belgium	Evergem, Belgium
Aragen Bioscience	USA	Morgan Hill, Calif., USA
Areta International	Italy	Gerenzano, Italy
Batavia Biosciences	The Netherlands	Leiden, The Netherlands
Biodextris	Canada	Laval, Québec, Canada
BioGenes GmbH	Germany	Berlin, Germany
Biomnis Group	France	Lyon, France
BioOutsource Ltd.	UK	Glasgow, Scotland, UK
BioPharmaSpec	UK	St. Saviour, Jersey, UK
BioReliance	UK	Stirling, Scotland, UK
	USA	Rockville, Md., USA
BSL BIOSERVICE Scientific Laboratories GmbH	Germany	Planegg / Munich, Germany
Catalent Pharma Solutions	USA	Kansas City, Mo., USA
		Morrisville, N.C., USA
Charles River Laboratories	Germany	Cologne, Germany
		Erkrath, North Rhine, Germany
	Ireland	Ballina, Co. Mayo, Ireland
	Scotland	Edinburgh, Scotland
	USA	Malvern, Pa., USA
Covance, Inc.	USA	Greenfield, Ind., USA
		Madison, Wis., USA
Cipla Biotec	India	Goa, India
CMC Biologics A/S	Denmark	Copenhagen, Denmark
Cobra Biologics	UK	Keele, UK
Coriolis Pharma	Germany	Martinsried, Germany
EAG Laboratories	USA	Columbia, Mo., USA
Eufets AG	Germany	Idar-Oberstein, Germany
Eurofins Scientific Group (incl. Eurofins Lancaster Laboratories)	Denmark	Glostrup, Denmark
	Ireland	Dungarvan , Ireland
	USA	Lancaster, Pa., USA
Intertek	UK	Manchester, UK
	USA	San Diego, Calif., USA
KBI Biopharma	USA	Durham, N.C., USA
NDA Analytics	UK	Alconbury, Cambridgeshire, UK
Nuvisan Pharma Services	Germany	Neu-Ulm, Germany
Particle Sciences	USA	Bethlehem, Pa., USA
Platine Pharma	France	Lyon, France

Contractor	Country	Facility
PPD	USA	Middleton, Wis., USA
ProJect Pharmaceutics	Germany	Martinsried, Germany
Protagen Protein Services	Germany	Heilbronn, Germany
		Dortmund, Germany
Quality Assistance	Belgium	Donstiennes, Belgium
Rentschler Biotechnologie GmbH	Germany	Laupheim, Baden-Wuerttemberg, Germany
SGS Life Science Services, S.A.	Belgium	Wavre, Belgium
	Canada	Mississauga, Ontario, Canada
	Germany	Freiburg, Germany
	Switzerland	Geneva, Switzerland
	UK	Wokingham, Berkshire, UK
	USA	Fairfield, N.J., USA
		Lincolnshire, Ill., USA
		West Chester, Pa., USA
Sinensis Life Sciences (Eurofins)	The Netherlands	Oss, The Netherlands
Solvias AG	Switzerland	Kaiseraugst, Aargau, Switzerland
Tepnel Pharma Services	UK	Livingston,, West Lothian , UK
Texcell SA	France	Evry, France
	USA	Frederick, Md., USA
Vela Laboratories	Austria	Vienna, Austria
Virocyt	USA	Broomfield, Colo., USA
VxP Pharma Services	USA	Indianapolis, Ind., USA
WuXi AppTec	China	Suzhou City, Jiangsu Province, China
	USA	Marietta, Ga., USA
		Philadelphia, Pa., USA
		St. Paul, Minn., USA
XenoBiotic Laboratories Inc.	USA	Plainsboro, N.J., USA

Source: PharmSource Strategic Advantage

Additionally, determination of secondary, tertiary and, in some cases, quaternary structures in biologics provide major challenges. The use of multi-dimensional nuclear magnetic resonance and X-ray crystallography can provide detailed information on a biologics' secondary and tertiary structure, but are expensive, time-consuming and applicable only to a small subset of protein molecules, DiPaola said. For most biologics, high-order structure information is obtained via low resolution methods, such as circular dichroism, Fourier-transform IR spectroscopy, fluorescence, calorimetry, analytical ultra-centrifugation and light scattering. But while results from these techniques can be used to construct the shape or at least obtain folding aspects of a protein, the individual results from each technique can be prone to inaccuracies, especially those requiring mathematical deconvolution, and can yield contradictory data, he added.

In biosimilar development, multiple batches of the originator molecule must first be tested via multiple, orthogonal analytical techniques to establish the quality target product profile. Then, regulatory characterization requirements call for head-to-head comparative studies between the reference product and the biosimilar.

The demand for precise characterization means that the technology and methodology used in biologics characterization play a crucial role. And this means that having the right equipment to perform analyses is critical.

Fiona Greer, global director, biopharma services development at **SGS Life Science Services** (Mechelen, Belgium), pointed to techniques for sizing biologics and elucidating higher-order structure, such as LC-MS and peptide mapping using proteolytic digestion. Techniques to determine primary amino-acid sequence and protein structure—such as N-terminal sequencing using either Edman degradation or MS—and amino acid analysis are also imperative, she said. Biophysical techniques, such as circular dichroism (CD), Fourier transform infrared spectroscopy (FTIR), dynamic light scattering (DLS), analytical ultracentrifugation (AUC), size exclusion chromatography-multi-angle laser light scattering (SEC-MALLS), are also important.

Additionally, techniques to analyze the stability of a biologic such as particle counting, analysis of protein aggregates are necessary.

Min Park, product manager, biologics and specialty sterile technologies at **Catalent Pharma Solutions** (Somerset, N.J., USA), pointed to chromatography systems with different detection modes and high-resolution mass spectrometry as among the most critical techniques for biologics characterization, along with bioassays, electrophoresis, metals analysis and kinetic binding.

Many of the biologics being characterized currently are biosimilars. A major challenge in this arena is to make these products economically viable, Greer said. Obtaining batches of originator molecules, for instance, is not easy and quite expensive.

ADCs are another class of biologics that Greer said pose challenges for many routine analytical techniques.

"In general, at the laboratory level, a significant technical challenge is the compliant handling, processing and storage of the extensive data generated by multiple analytical instrumentation used for biologics characterization," she explained.

Additionally, development and scale-up of manufacturing processes must be planned into development and formulation efforts—and tested—when it comes to biologics and biosimilars, noted Alistair Kippen, director of analytical biotechnology at MedImmune (presentation at the 2014 NIST/University of Maryland Biomanufacturing Technology Summit). Changes in manufacturing processes can lead to changes in quality attributes; these issues often show up during scale-up activities, he said.

Keeping up with the technology Joneses

And it's not enough to have the current technology available. Keeping up with evolving technologies is a key challenge—from both a cost and an expertise perspective—for CROs providing biologics characterization services, Park said, adding, "New types of compounds or regulatory needs may require different or newer technologies which lead to efforts to procure, train, and gain the necessary expertise around them."

Among the future techniques that might be employed, Greer forecast, are those allowing some insight linking higher-order structure to biological activity, such as hydrogen-deuterium exchange (HDX) mass spectrometry, will be used more in the future, particularly as manufacturers have worked hard to improve the practicalities of the technique.

Park added that advancements have been developing in chip-based technologies, higher-end mass spectrometry and the ability to look at particulates.

Improvements in software for the analysis of chromatography and MS data, as well as improvements in user interface are among technological advancements that are helping to improve biologics characterization. In particular, hydrogen-deuterium exchange MS, which has been around for several years, has recently been used more widely for higher-order structural analysis, DiPaola said. Ion-mobility MS is another technique that is becoming more widely available and used to characterize complex biologics.

DiPaola also noted that two-dimensional IR spectroscopy—currently used primarily by a few labs in

academia—is an up-and-coming technology that could prove useful for characterizing higher-order structures in proteins.

A new technology using a combination of tunable laser IR spectroscopy with microfluids technology is also being developed for concurrent determination of protein quantitation, aggregation and secondary structural analysis.

And while advanced equipment can be purchased easily enough, it's equally important that the scientists performing biologics characterization be skilled and experienced in its use, Greer emphasized.

For instance, they need to be expert designers of analytical strategies that will allow use of the least amounts of protein sample, as well as being skilled in sample preparation techniques to ensure that the tested proteins are in the correct format and concentration for the specific analytical technique applied. Knowledge of regulatory requirements for biotech drugs is also important. Other key expertise includes:

- Knowledge of the instrumentation and software required for protein analysis, including the pros and cons of each technique; and
- Understanding of data processing and data interpretation for each analytical technique. For example, peptide mapping and analysis of glycans requires analysis of mass spectrometry data. This is currently a lengthy process, requiring specialist knowledge of how to interpret the peaks within the mass spectrum.

DiPaola added that the specific required skill sets can depend on the technology used. For bioassays, for instance, a degree in cell biology and expertise in cell culture are necessary, for instance. For higher structural analysis, the scientist must be fluent in protein chemistry, as well as skilled in setting up and running sophisticated instrumentation and interpreting data from various sources.

Park added that analysts need to have a good understanding of biologics and structure, as well as manufacturing processes and mechanism of action (MOA).

Pre-qualified assays for biosimilars

Greer noted that growth in interest in developing biosimilars is yielding "an explosion in the requirements for both analytical and biological characterization." Interest has been so high in some biosimilar APIs, in fact, that some companies have begun to offer pre-qualified assays for certain APIs, the idea being that drug makers can save some of the time and money that would be dedicated to acquiring and testing the originator biologics.

Eurofins, for instance, offers pre-qualified potency assays for "most innovators coming off-patent," McDowell said. These include assays for trastuzumab (Herceptin), bevacizumab (Avastin), cetuximab (Erbitux) and adalimumab (Humira), according to the company's website.

And Sartorius Stedim Biotech's BioOutsource subsidiary offers ready-to-use assays for testing biosimilars of tocilizumab (Actemra), ustekinumab (Stelara) and ranibizumab (Lucentis). CRL also offers a portfolio of ready-to-use assays for impurity analysis, such as residual contaminants, and a separate set for full characterization of biosimilars.

While these pre-qualified assays may offer a level of convenience, "no two products or manufacturing processes are identical," McDowell said. "Therefore, even with platform methods, you must perform a validation for cGMP compliant data."

Time saving come in method development; a client can expect that timeline to be shorter, but this is just a fraction of the overall cGMP method establishment timeline, McDowell said.

Analytical Services in Brief

BioAgilytix Labs (Durham, N.C., USA) has entered an agreement with biological materials and standards developer ATCC (Manassas, Va., USA) to develop cell-based assays for use in bio/pharmaceutical R&D. BioAgilytix will use ATCC custom-engineered cell lines and primary cells with its existing assays; ATCC will provide tool and reagent development and storage services.

Charles River Laboratories (CRL – Wilmington, Mass., USA) saw third-quarter 2016 revenues of $425.7 million, up 21.8% from the previous year, largely due to growth in biologicals manufacturing support and discovery and safety test services, the company reported earlier this month. Biologics manufacturing services generated $89 million in revenue, up 21.4% from third-quarter 2015; discovery and safety assessments contributed $120.9 million, up 2.6% over 2015. The CRO anticipates total revenue growth of 21-22% for full-year 2016.

EAG Laboratories (San Diego, Calif., USA) is expanding capacity at its Easton, Md., USA testing facilities. Part of a 33,000-square-foot expansion, the latest addition includes dedicated laboratories for ecotoxicology, environmental fate, metabolism and other testing services for makers of pharmaceuticals and specialty chemicals, along with other products. The expansion includes four life-cycle rooms, six endocrine test units, test systems for acute and sediment tests and gene expression and cell biology labs, along with space for additional culturing facilities.

Idifarma (Noáin, Navarra, Spain) announced earlier this month expects 2016 revenues to total €5.3 million ($5.77 million), up from €3.5 million ($3.81 million) in 2014. The CDMO also forecast that it expects to have 100 employees by the end of 2016, up from 75 in 2014.

Neopharm Labs (Blainville, Quebec, Canada) has expanded into the US with acquisition of **Averica Discovery** (Marlborough, Mass., USA), which specializes in early-stage contract research and analytical development, for an undisclosed sum. The Marlborough Averica site will continue to provide its current services, while also serving as a US office of Neopharm.

Pharmaceutical Product Development (PPD – Wilmington, N.C., USA) has expanded its Athlone, Ireland laboratory facility, adding an additional 400 square meters of analytical testing space to the site and bringing the total space at the facility to 3,800 square meters. Services provided include analytical testing, method development and validation, stability testing and QC and release testing, with particular emphasis on bio/pharmaceutical inhalation products.

Sartorius Stedim Biotech (Aubagne, France) opened a new bioanalytical and biosafety testing laboratory in Boston, Mass., USA, targeting biosimilars development. The site will provide the company's BioOutsource brand assay platforms in North America. Testing services include antibody-dependent cell cytotoxicity, complement-dependent cytotoxicity and surface plasmon resonance, along with cell-based assays and ELISAs.

Phase II-IV Clinical Research

BioStorage Technologies (Indianapolis, Ind., USA) will expand sample storage capacity in the US and bioprocessing capabilities in China. The company plans to boost freezer capacity at its Indianapolis biorepository by 55%, while expanding the facility's size by 30%. The expansion will include sample management automation and cryogenic storage capabilities. In addition, BioStorage Technologies has entered an agreement with Shanghai Outdo Biotechnology (Shanghai, China) and RUCDR Infinite Biologics (Piscataway Township, N.J., USA) to provide sample bioprocessing services at the Outdo BioBank (Shanghai).

Cytel (Cambridge, Mass., USA), a biometrics CRO and provider of clinical research software, has expanded, adding new offices in Barcelona, Spain and Paris, France. The Barcelona location will also

serve as a hub for Cytel's data science group. The additions bring the company's total number of locations in Europe, India and the US to 10.

INC Research (Raleigh, N.C., USA) will participate in The Leukemia & Lymphoma Society's (LLS') master trial of treatments for acute myeloid leukemia (AML). INC Research and other CROs and bio/pharma companies will examine several candidate therapies for AML in an umbrella trial of newly diagnosed AML patients with specific molecular mutations known to drive the disease; patients will be matched to specific targeted therapies for those specific aberrations.

Science37 (Culver City, Calif., USA), a virtual clinical research service provider, completed a $31 million Series B financing led by Redmile Group and with further funding from Series A lead investors Lux Capital and dRx Capital, plus additional investment from Sanofi Genzyme BioVentures.

Drug Discovery

Envigo (Huntingdon, Cambridgeshire, UK) has collaborated with **Intertek** (London, UK) and OCSiAI (Leudelange, Luxembourg) to meet EU Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) standards for OCSiAI's TUBALLTM single wall carbon nanotubes, used to increase the efficiency in drug targeting and delivery.

Eurofins (Kraainem, Belgium) subsidiary Eurofins Genomics (Louisville, Ky., USA) has launched a new DNA sequencing laboratory in Toronto, Ontario, Canada via its Eurofins MWG Operon (Toronto) company. The facility will provide high-speed sequencing services using the Sanger method to researchers in Canada.

Evotec (Hamburg, Germany) will provide *in vitro* pharmacology services to UCB (Brussels, Belgium) in support of discovery work in central nervous system disorders, along with other target classes of drug candidates. Services under the three-year agreement will include assay development, compound profiling and mechanistic studies.

Evotec also has made an offer to acquire preclinical CRO **Cyprotex** (Cheshire, UK) for approximately £55.36 million ($68.98 million). The transaction is expected to close by the end of this year. Cyprotex reported first half 2016 revenues of £8.73 million ($10.88 million), with EBITDA of £2.34 million ($2.92 million).

Horizon Discovery (Cambridge, UK) entered a licensing agreement with an unnamed partner for access to its engineered bioproduction cell lines for use development of the partner's therapeutic products. The partner also gains early access cell lines that Horizon may develop at a 50% discount over the next five years. The deal is valued at a minimum of £500,000 ($625,925).

Metrion Biosciences (Cambridge, UK) will profile and validate induced pluripotent stem cell (iPSC)-derived cells and tissues for preclinical applications for biotech company Axiogenesis (Cologne, Germany). The iPSC cells will be used to develop assays to predict cardiac arrhythmia and neuronal risk in support of drug discovery activities.

Captive Capacity

Bristol-Myers Squibb (BMS – New York, N.Y., USA) plans to re-align its manufacturing and R&D businesses "in alignment with its product focus and priorities," the company announced as part its third-quarter 2016 earnings release. The company did not give any specifics regarding the re-alignment, but did note that approximately 75% of its pipeline is focused on biologics and said it would continue to invest in biologics capacity while streamlining small-molecule operations. Industrial real estate firms

contacted by PharmSource said they had not heard of detailed facility divestiture plans as yet.

Earlier this year, BMS completed a $280 expansion of its Devens, Mass., USA biologics manufacturing site (*June 2016 B/POR*). The company is also building a biologics plant in Cruiserath, Ireland, which is expected to become operational in 2019 (*June 2016 B/POR*). BMS reported third-quarter 2016 revenues of $4.9 billion, up 21% compared to the previous year.

Endo Pharmaceuticals (Dublin, Ireland) will sell its Charlotte, N.C., USA manufacturing site, slated to close by Dec. 31, to an unnamed buyer. Endo subsidiary Qualitest Pharmaceuticals (Huntsville, Ala., USA), which operates the Charlotte plant, on Oct. 31 filed a Worker Adjustment and Retraining Notice (WARN) Act notice with the North Carolina Dept. of Commerce announcing the layoffs associated with the closure. Endo also plans to close the Qualitest facility in Huntsville.

GlaxoSmithKline (GSK – London, UK) will close its Sydney (Ermington), Australia manufacturing facility in 2020. The closure, which will eliminate about 223 jobs, will be conducted gradually over the next four years, transferring production at the Ermington site to other GSK facilities and CMOs.

Merck (Darmstadt, Germany) has completed a €15 million ($16.71 million) investment into its biotech facility in Madrid, Spain to boost production of fertility and growth hormone disorder treatments by 50%. The plant makes API for Merck's fertility treatment Gonalf and endocrine/metabolic disorder drug Saizen.

Pfizer (New York, N.Y., USA) plans to close two of its UK facilities in the near future, according to reports by such news outlets as BBC and Reuters and confirmed by a Pfizer spokesperson. The company will close its Hospira UK site in London, which is known as the Park Royal site and employs about 100, by August 2017; it will complete production in May 2017. The building lease is expiring on the Park Royal site; additionally, Pfizer noted that the aging facility would have required significant investment in the near future to maintain operations. The company will move some of the Park Royal work to its similar site in south London.

Pfizer will also close its global cold chain packaging and distribution site in Havant, Hampshire, which has about 270 workers, by the end of 2020. Work currently performed at the Havant site will move to Pfizer's Puurs, Belgium facility. Pfizer plans to sell this facility.

Sterinova (Saint-Hycinthe, Quebec, Canada) has completed a new C$70 million ($52.23 million) injectables manufacturing facility at its existing sterile biologicals site Saint-Hyacinthe. The 6,225-square-meter plant, which can produce products in syringes or premix solution containers, doubles the size of the Saint-Hyacinthe manufacturing campus.

Medical Device CMOs

Bespak (Norfolk, UK) has launched a new autoinjector—known as Syrina AR 2.25—for self-administration of viscous formulations. The injector can deliver volumes up to 2 mL using a standard 2.25 ml prefilled syringe.

CSSi Lifesciences (Glen Burnie, Md., USA) has launched a fully integrated medical device CRO; services offered include design engineering and testing, clinical study planning, monitoring and reporting and regulatory filings to agencies in the US and other countries.

CTI Clinical Trial and Consulting Services (CTI – Cincinnati, Ohio, USA), a CRO with expertise in cell therapy and immunology products, is providing clinical trial and regulatory support to Sernova (London, Ontario, Canada) for the latter's Cell Pouch System, an implantable and scalable medical device for use in delivering therapeutic cell products, such as insulin, to patients with chronic diseases.

Unilife (York, Pa., USA) plans to shift its focus away from its prefilled syringe business in favor of increased work in wearable injectable technologies, the company revealed during a conference call to discuss its fourth-quarter results. The device manufacturer has wearables-focused deals in place with Amgen (*January 2016 B/POR*), MedImmune and Sanofi. Unilife reported revenue of $6.3 million for the fourth quarter of its fiscal 2016, and $14.8 million for the entire year, up from $3.5 million and $13.2 million for fourth-quarter and full-year 2015, respectively. The company saw a net fourth-quarter loss of $7.7 million and full-year loss of $100.8 million, compared to $26.1 million and $90.8 million for the same periods last year. The fiscal 2016 loss included a primarily non-cash $26.6 million asset impairment charge related to some of the company's non-wearable injector equipment.

Regulatory Developments

The US FDA and the European Medicines Agency (EMA) could have a mutual recognition agreement for GMP inspections in place by January 2017, according to a European Commission report on results of negotiations held in New York, N.Y., USA last month. The GMP inspection mutual recognition deal is part of the larger proposed Transatlantic Trade and Investment Partnership. An outstanding issue is the question of trade secret information and exchange of confidential information, as inspections include review of specifications that are considered proprietary information, the commission report said. The EMA is also emphasizing collaboration on antimicrobial resistance and seeks to include veterinary products in the scope of the pharmaceutical text of any agreement.

Outsourcing Events

Antibody Engineering & Therapeutics
December 11-15, 2016, San Diego, Calif., USA
www.ibclifesciences.com

DCAT Week 2017
March 20-23, 2017, New York, N.Y., USA
www.dcat.org

INTERPHEX
March 21-23, 2017, New York, N.Y., USA
www.interphex.com

91st DCAT Annual Dinner 2017
March 23, 2017, New York, N.Y., USA
www.dcat.org

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