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Bio/Pharmaceutical Outsourcing Report

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AGC Acquires CMC Biologics

AGC Asahi Glass (AGC – Tokyo, Japan) has agreed to acquire biomanufacturer **CMC Biologics** (Copenhagen, Denmark) in a deal valued at ¥60 billion ($500 million). PharmSource estimates that the price represents a multiple of about 3.3x revenues and more than 10x EBITDA. The selling shareholders are three private equity firms: Monitor Clipper Partners; European Equity Partners; and Innoven Partenaires. Closing is expected this month.

CMC Biologics has manufacturing sites in Copenhagen, Bothell, Wash., USA and Berkeley, Calif., USA. The three sites have nearly 30,000 L of bioreactor and fermenter capacity, including batch-fed and perfusion mammalian cell culture and microbial fermentation. The company also has a proprietary expression technology known as CHEF1 with which it promises to produce clinical supplies of monoclonal antibodies in 12 months for €2 million ($2.1 million). The company has 530 employees at its three sites.

WHAT IT MEANS > > > This is AGC's second acquisition of a biomanufacturing business in the past six months. In September 2016, it acquired **BIOMEVA** (Heidelberg, Germany), a provider of microbial fermentation contract manufacturing services with scale to 1000 L. The company also has two sites in Japan (*see table on following page*).

With AGC's acquisition of CMC Bio, only two biologics CMOs with significant scale remain independent: **Cook Pharmica** (Bloomington, Ind., USA) and **Rentschler Biotechnologie** (Laupheim, Germany). The rest are all part of larger, mostly public, corporate parents.

It remains to be seen how AGC will seek to leverage its large scale, multi-continent capabilities. Capacity is tight across the biomanufacturing industry in both mammalian cell culture and microbial fermentation. AGC has the deep pockets to fund further expansion, but so do the other corporate parents, but most have moved very incrementally to increase capacity, or not at all.

The greatly improved yields achieved in biomanufacturing technology, the shift to niche indications and evolution of single-use (disposable) bioreactor technologies, have combined to greatly reduce the need for and cost of biomanufacturing capacity. Still, customer waits for capacity are still long, and the decreased capital requirements work against the industry as much as they do for it.

AGC Facilities and Capabilities Following CMC Biologics Acquisition

Facility	Business Unit	Capability	Fermentation Capability
Chiba, Japan	AGC		4500 L, 400 L, 300L
Yokohama, Japan	AGC		300 L, 400 L
Heidelberg, Germany	Biomeva		1000L, 100 L
Copenhagen, Denmark	CMC Biologics	Steel tank: 750 L (2), 100 L Disposable: 3x2000 L, 2000 L, 500 L, 100 L Perfusion: 750 L (2), 500 L, 100 L	1500 L (2), 100 L
Bothell, Wash.	CMC Biologics	Steel tank: 3000 L (2), 750 L (2) Disposable: 6x2000 L, 2000 L, 500 L (2), 100 L	
Berkeley, Calif.	CMC Biologics	Steel tank: 3000 L, 500 L Disposable: 2000L, 500 L, 100 L	

Learn More

*For more information on the business and capabilities of CMC Biologics, 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).*

API — Large Molecule in Brief

Abzena (Cambridge, UK) licensed an undisclosed antibody sequence to biotech company Trieza Therapeutics (Cambridge, Mass., USA), which specializes in immunomodulatory oncolytic viruses. Trieza will use the antibody sequence in conjunction with its own viral vector technology for oncology drug development.

Abzena also saw group revenue increase 157%, from £3.5 million ($4.3 million) to £9.0 million ($11.0 million), and underlying revenue growth of 46%, to £1.6 million ($1.96 million), for the six months ended Sept. 30, 2016, according to results released Nov. 30, 2016. The growth was driven by acquisitions, including the purchase of PacificGMP in September 2015, which helped boost manufacturing revenues to £2.0 million ($2.45 million), up from £0.5 million ($0.6 million) a year earlier. Revenue from manufacturing process development and GMP production at Abzena's San Diego, Calif., USA business grew 47% to £1.4 million ($1.7 million). Cell line development more than doubled, providing £0.6 million ($0.73 million) in revenues, while chemistry research services revenues grew 66% to £3.5 million ($4.3 million), versus £2.1 million ($2.6 million) the same period last year. Gross profit rose 133%, to £3.8 million ($4.6 million) from £1.6 million ($1.96 million) a year earlier. The company saw an adjusted EBITDA loss of £3.0 million ($3.7 million), compared to £2.9 million ($3.6 million) a year earlier.

Apceth (München, Germany) will make clinical supplies of two bluebird bio (Cambridge, Mass., USA) candidate products: Lenti-D for cerebral adrenoleukodystropy and LentiGlobin for transfusion-dependent β-thalassemia. Under the new agreement, Apceth will also perform process validation and eventual commercial manufacturing if the products gain marketing approval.

Brammer Bio (Lexington, Mass., USA) has acquired Biogen's (Cambridge, Mass., USA) 66,000-square-foot manufacturing site in Cambridge. Biogen had announced plans to either close or sublease the facility in June of last year (*June 2016 B/POR*). Brammer Bio will provide about half of Biogen's gene therapy manufacturing requirements. Because fewer staff are needed for Brammer Bio's operations at the site, Biogen laid off about 93 workers at the Cambridge site.

Catalent Pharma Solutions (Somerset, N.J., USA) will develop and manufacture antibodies for a malaria vaccine under a new agreement with PATH under the nonprofit health organization's Malaria Vaccine Initiative. Catalent will use its GPEx cell line technology to perform the work at its Madison, Wis., USA facility.

CSSi LifeSciences (Glen Burnie, Md., USA) has teamed with **BioMARC** (Fort Collins, Colo., USA), a unit of Colorado State University, to offer biologic and vaccine development services from discovery to commercialization. CSSi will provide preclinical, regulatory and clinical expertise, while BioMARC contributes biopharmaceutical production for non-clinical, clinical and commercial use.

Dalton Pharma Services (Toronto, Ontario, Canada) will provide formulation development, cGMP liquid filling, analytical method validation, quality control release testing and ICH stability services for rare and orphan disease treatments in Cerium Pharmaceuticals' (Gaithersburg, Md., USA) development pipeline.

MilliporeSigma (Billerica, Mass., USA), the North American life sciences business of Merck (Darmstadt, Germany), will build two new bioprocess development facilities near Boston, Mass., USA and Shanghai, China. Services provided will include cell line development, upstream and downstream process development and non-GMP clinical production. MilliporeSigma already operates a similar facility in Martillac, France.

Emergent BioSolutions (Gaithersburg, Md., USA) has expanded an existing development agreement with Soligenix (Princeton, N.J., USA) to include scalable clinical-to-commercial production of the protein antigen for RiVax, a vaccine candidate to protect against ricin exposure that would not require cold chain shipment and storage. Manufacturing will take place at Emergent's Baltimore, Md. facility. Emergent previously had performed process development work on RiVax.

Fujifilm Diosynth Biotechnologies (Morrisville, N.C., USA) parent Fujifilm Corp. (Tokyo, Japan) will acquire reagent manufacturer Wako Pure Chemical Industries (Osaka, Japan) via a tender offer from Takeda Pharmaceutical Co. (Osaka) scheduled to begin Feb. 27 that is expected to total ¥154.7 billion ($1.37 billion). Takeda and its subsidiary Nihon Pharmaceutical Co. together held 71.2% of Wako shares as of last month. Wako's chemical synthesis and cell culture medium manufacturing technology and capabilities will be added to Fujifilm Diosynth's CDMO offerings, as well as supporting Fujifilm's regenerative medicine and in vitro diagnostics businesses.

Lonza (Basel, Switzerland) will manufacture clinical and future commercial supplies of voclosporin API for Aurinia Pharmaceuticals (Victoria, British Columbia, Canada). The product is currently in Phase III trials as a lupus treatment. The agreement provides an option to have Lonza exclusively supply the API for up to 20 years.

Meanwhile, Lonza earlier this month concluded divestment of its peptides business to **PolyPeptide Group** (Malmo, Sweden) for an undisclosed sum (*December 2016 B/POR*). Lonza booked a non-cash related write-off of CHF 44 million ($43.91 million) and will book a CHF 29 million ($28.94 million) non-cash currency translation impact in the first half of 2017.

MasTHerCell (Gosselies, Belgium) has entered a master service agreement with Servier (Neulilly-sur-Seine, France) under which it will develop a manufacturing platform for allogenic cell therapies using chimeric antigen receptor (CAR) T-cells.

Oxford Genetics (Begbroke, UK), which specializes in DNA design, protein and viral expression systems and cell line engineering, won a £1.61 million ($1.99 million) Innovate UK grant for development of new mammalian bioproduction and synthetic biology technologies such as bispecific proteins and viral vectors for gene therapies.

Paragon Bioservices (Baltimore, Md., USA) has won the opportunity to compete with other CDMOs for contracts let by the National Institute of Allergy and Infectious Diseases. Under terms of the agreement, Paragon may compete to bid on task order awards up to $159 million for development of manufacturing processes and analytical methods, as well as product characterization, to support development of new therapies.

PharmaCell (EV Maastricht, The Netherlands) will provide clinical and eventual commercial manufacturing of candidate *ex vivo* autologous gene therapy products currently in Orchard Therapeutics'

(London, UK) pipeline. Orchard's pipeline includes treatments for primary immune deficiency disorders and inherited metabolic disorders, such as adenosine deaminase deficiency severe combined immunodeficiency and mucopolysaccharidosis IIIA.

Wacker (München, Germany) biotech division Wacker Biosolutions, has acquired a large-scale fermentation plant in León, Spain from Antibióticos de León (León). Wacker will use the 800-square-meter facility to produce cysteine by fermentation for pharmaceutical and food use, and plans to invest about €30 million ($32.1 million) over the next few years to modernize the site and add production equipment.

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				
Patheon	Boehringer Ingelheim	FDA approval	Synjardy XR	Solid dose manufacture
Vistin Pharma	Boehringer Ingelheim	FDA approval	Synjardy XR	Small molecule API manufacture
Lonza	Clavis Oncology	FDA approval	Rubraca	Small molecule API manufacture
Patheon	AstraZeneca	NICE recommendation for preventing atherothrombotic events in conjunction with aspirin in adults who had a myocardial infarction and are at high risk of a further event	Brilique	Solid dose manufacture
Patheon	Eisai	NICE recommendation for treatment of locally advanced or metastatic breast cancer in adults (subject to discount)	Halaven	Parenteral manufacture
Boehringer Ingelheim BioXcellence	Merck & Co	NICE recommendation for treatment of locally advanced or metastatic PD-L1-positive non-small-cell lung cancer in adults subject to company providing price discount	Keytruda	Large molecule API manufacture
Caladrius	Kite Pharma	Positive PI data	KTE-C19 (eACT)	Cell therapy
Hovione	Achaogen	Positive PIII data	Plazomicin	Small molecule API manufacture
POTENTIALLY NEGATIVE				
Patheon	Actelion	Negative IQWIQ analysis due to lack of comparative data	Opsumit	Solid dose manufacture
Jet Pharma	Actelion	Negative IQWIQ analysis due to lack of comparative data	Opsumit	Small molecule API manufacture
Lonza	Actelion	Negative IQWIQ analysis due to lack of comparative data	Opsumit	Small molecule API manufacture

Source: PharmSource Lead Sheet

Commercial Dose Manufacturing and Packaging

Horizon Pharmaceuticals (Riviera Beach, Fla., USA) received a warning letter from the US FDA alleging GMP violations Riviera Beach manufacturing facility. Among the deficiencies noted in the warning were invalidation of non-sterility findings, specifically contamination of several lots of sterile ophthalmic rinse with the spore-forming *Bacillus mycoides*, without a scientific basis. Additionally, the company released partial batches of AVR eye drop vials after discovering leaking product at the transfer plate to the blow-fill-seal machine in the cleanroom, the agency alleged. Horizon's investigation into failed stability results for CMC eye drops also lacked scientific data and rationale, the letter stated, and some stability failures were not investigated at all. Other violations noted included: inadequate facility maintenance, including leaking pipes in a cleanroom ceiling and particulates and dust found on tanks next to ingredient charging ports; and insufficient cleaning and disinfection procedures, including failure to use a sporicidal agent.

IDT Biologika (Dessau-Roßlau, Germany) has established an animal vaccine business in North America, dubbed IDT Animal Health Americas. José Ochoa will head the new business unit, while maintaining his position as chief business officer at IDT Biologika's Rockville, Md., USA location.

Pharma Tech Industries (Athens, Ga., USA) has added a high-speed bottling line at its Union, Mo., USA manufacturing facility. The line, which has capacity up to 300 bottles/minute, includes unscrambling, filling, check-weighing, metal detection, capping, induction sealing, bundling and case packing equipment. It has a bottle size capacity of 5 inches diameter and 10 inches in height. The bottling line is part

of Pharma Tech's overall expansion at the Union site, which included addition of 55,000 square feet of manufacturing space and 20,000 square feet housing an analytical/microbial lab and warehousing space.

Pocono Coated Products (Cherryville, N.C., USA) received a warning letter from the US FDA alleging unresolved GMP violations noted during an October 2015 inspection of its Cherryville finished product manufacturing plant. According to the warning, FDA analysis of samples collected during the inspection revealed one subpotent drug, a finding that led to Pocono Coated Products' client issuing a recall of all lots of the unnamed product. Other violations noted included: failure to validate the manufacturing process for transdermal patches and failure to include in master batch records a statement of theoretical yield, percentage of theoretical yield and limits beyond which an investigation is required. The company responded to the inspectional observations in November 2015, but in the warning, the FDA requested more detail on corrective and preventive actions taken.

Sterling Pharma Solutions (Cramlington, UK) will manufacture TPI Enterprises' (Cressy, Victoria, Australia) codeine phosphate for sale in the UK market at its Dudley site near Newcastle, UK. Sterling was formed last year by a buyout of the Dudley manufacturing site from Strides Shasun (Bangalore, India) by the facility managers for an undisclosed sum (*October 2016 B/POR*).

Tedor Pharma (Cumberland, R.I., USA) will add 5,400 square feet to its existing 40,000-square-foot Cumberland site. New manufacturing suites will be included, and will house a 60-cubic-foot V-blender and a fluid bed processor. The suites will be able to use such mobile equipment as high-speed tablet presses and encapsulators for solid oral dose manufacturing. Completion is slated for May of this year.

Tesaro (Waltham, Mass., USA) received a complete response letter (CRL) from the FDA regarding its application for a new IV version of Varubi to treat nausea and vomiting due to chemotherapy. The CRL requested more information about the two contractors that will make the finished product for the biotech firm, including the company's rationale for the validation it used and some additional test results. The agency did not raise questions about the API supplier, Hovione. Patheon manufactures the already-approved solid dose form of Varubi.

Clinical Dose Manufacturing and Packaging

3M Drug Delivery Systems (St. Paul, Minn., USA) is providing its Hollow Microstructured Transdermal System (hMTS) for use with Panacea Pharmaceuticals' (Gaithersburg, Md., USA) investigational cancer vaccine. The first patient in a Phase I clinical study has been dosed with the vaccine using the hMTS.

AB BioTechnologies (Bloomington, Ind., USA) will build a $10.5 million, 23,000-square-foot manufacturing facility in Bloomington. The new site will be able to provide injectables formulation, filling, freeze-drying and packaging capabilities at the clinical scale.

Albany Molecular Research Inc. (AMRI – Albany, N.Y., USA) client Nemus Biosciences (Costa Mesa, Calif., USA) recently announced achievement of a synthetic pathway to manufacture clinical-grade tetrahydrocannabinol-valine-hemisuccinate (THCVHS) for drug candidates NB1111 an NB2111, including the ability to scale-up production, along with API purity exceeding FDA requirements of at least 99.5% purity.

AMRI will perform formulation for NB1111 for delivery into the eye to treat glaucoma; **Catalent Pharma Solutions** (Somerset, N.J., USA) will provide formulation for NB2111, a candidate treatment for chemotherapy-induced nausea and vomiting.

Almac (Craigavon, UK) has launched a web-based training and educational program for clinical develop-

ment professionals. It has two parts; the Library offers free access to case studies, white papers and other documents from Almac and other industry experts on such topics as biostatistics, regulatory compliance, biologics development, cold chain management, clinical trial supply management and interactive response technology (IRT). The Academy is offered exclusively to Almac clients and users of the company's IRT product IXRS and provides custom-developed training modules, online assessments and certifications in IXRS use.

Catalent Pharma Solutions (Somerset, N.J., USA) will evaluate Jupiter Orphan Therapeutics (JOT – Jupiter, Fla., USA) resveratrol formulation JOTROL—under development as a potential treatment for rare diseases linked to single gene deficiencies, such as Friedreich's ataxia and mucupolysaccharide diseases—for delivery via Catalent's softgel technology. Under a new agreement, Catalent will assess its own OptiShell gelatin-free technology, as well as conventional softgel technology to determine the optimal oral dosage form for JOTROL and manufacture supplies for human PK studies and Phase II clinical trials. Work will be performed at Catalent's St. Petersburg, Fla., USA site.

Dalton Pharma Services (Toronto, Ontario, Canada) will provide contract manufacturing services to the US Army Medical Material Development Activity for malaria treatments under development. Specific services include sterile powder filling, aseptic liquid filling, quality control release testing and ICH stability services.

PCI Pharma Services (Philadelphia, Pa., USA) has entered a partnership with Suvoda LLC (Conshohocken, Pa., USA), under which PCI will integrate Suvoda's IRT/IWRS technology for subject randomization and trial supply management into its own packaging and logistical services for clinical trial supplies.

Quotient Clinical (Nottingham, UK) division CoFormulate Ltd. will perform pediatric formulation development work on several unnamed off-patent compounds for Proveca (Daresbury, Cheshire, UK). CoFormulate developed a taste-masked formulation of Proveca's first pediatric medicine, Sialanar (glycopyrronium bromide oral solution).

Symbiosis Pharmaceutical Services (Stirling, UK) will provide clinical scale fill-finish services for Catalyst Biosciences' (S. San Francisco, Calif., USA) marzeptacog alfa, a Factor VIIa product intended for treatment of hemophilia. Catalyst Biosciences, which recently secured rights to the manufacturing process for marzeptacog alfa from Pfizer subsidiary Wyeth LLC, also has an agreement with **CMC Biologics** (Copenhagen, Denmark) for cell cultures for the product (*May 2016 B/POR*).

API — Small Molecule

Novasep (Pompey, France) completed US FDA inspections at three manufacturing sites with no Form 483 observations. The agency inspected Novasep's facility in Mourenx, France, which produces APIs and advanced intermediates, its Le Mans, France site (highly potent cytotoxic APIs, antibody-drug conjugate payloads and advanced intermediates) and its Leverkusen, Germany plant, which makes and sells preformulated nitroglycerin products and has hazardous chemicals capabilities.

Wockhardt (Mumbai, India) GMP deficiencies at its Ankleshwar, India API manufacturing site (*November 2016 B/POR*) were noted in a complete response letter (CRL) to Cempra (Chapel Hill, N.C., USA) regarding its application for approval of a solithromycin product to treat community-acquired pneumonia; the CRL stated that the deficiencies, which were not detailed in the letter, must be resolved before the drug can be approved. Cempra's original 2013 contract manufacturing agreement with Wockhardt calls for purchase of at least 70% of its annual solithromycin supply from the CMO. The CRL also called for an

additional study of approximately 9,000 patients to better determine the risk of hepatoxicity in patients with community-acquired pneumonia.

YProtech (Alderley Park, Alderley Edge, UK), a CDMO focused on chemistry services, has added a high potency facility for synthesis and non-GMP manufacture of highly potent cytotoxins for cancer treatment development. YProtech can produce cytotoxic compounds on the multigram scale to support preclinical development efforts. The facility includes a clean room with an isolator, dedicated high-containment chemistry lab with multiple fume cupboards, automated purification capability and LC/MS and NMR for compound analysis. YProtech plans to add another cGMP high-containment facility capable of manufacturing clinical supplies of cytoxins in the next 12 to 18 months.

Analytical Services

Growth in Parenterals, Bio/pharmaceuticals, Single-Use Manufacturing Technology Ups Demand for Extractables/ Leachables Testing

Extractables/leachables testing has become an important specialty segment of the analytical testing industry in recent years. Its specialized nature has meant that extractables/leachables testing is almost entirely outsourced, even by global bio/pharma companies.

Demand for extractables/leachables testing is being driven by several factors, all related to the growing presence of biologics and their susceptibility to adverse efficacy and safety effects resulting from leachable impurities. Those factors include:

- The adoption of single-use manufacturing systems for products produced by mammalian cell culture. Those systems use bags made from polymers that can leach into the drug substance;
- The general growth in in injectable delivery, where key components like vials, syringe barrels and stoppers must be tested;
- The broader interest in novel delivery systems, including proprietary injectable, inhalation and transdermal technologies, and the growing number of combination (drug plus device) products.

Increased demand is also coming from the medical device industry.

PharmSource has identified 16 companies that current offering contract extractables/leachables testing services (*see table on page 9*). Responding to the trend, several contract labs have recently invested in additional capacity for extractables/leachables testing.

- **SGS Life Science Services** (Mechelen, Belgium) last year opened a 500-square-meter facility in Wiesbaden, Germany dedicated to extractables/leachables testing, previously provided at its Taunusstein, Germany laboratory (*September 2016 B/POR*). SGS also added extractables/leachables testing capabilities, among others, at its Shanghai, China laboratory (*June 2016 B/POR*).
- **PPD Laboratories** (Wilmington, N.C., USA) commission a new, expanded extractables/leachables laboratory in early 2016 that effectively doubles its lab preparation space and equipment areas for extractables/leachables studies.
- **WuXi PharmaTech** (Shanghai, China) launched preclinical medical device services in 2016 at its Shanghai and Suzhou, China sites that include extractables/leachables testing.

Technology matters

Technologies required for extractables/leachables testing cover equipment and instrumentation to extract component materials, prepare those extracts for analysis, and analyze the extracts for the detection and quantification of extractable and leachable compounds. Without accurate identification of the chemical structures of these compounds, toxicologists cannot perform adequate safety assessments, Nixford explained.

And extractable/leachable compounds typically occur at trace levels, so specialized equipment is necessary to accurately identify and quantitate them. Commonly used methods include headspace-GC/MS/FID for detection and quantitation of volatile compounds, direct injection GC/MS/FID for semi-volatile compounds, HPLC-MS/UV for non-volatile compounds, analysis for anions by ion chromatography, and ICP-MS for metal species.

Because of the extraordinarily sensitive instrumentation, special anti-contamination precautions are needed. For instance, presence of aerosolized organic vapors from constituents of a mobile phase preparation in one area of a laboratory may be sufficient to contaminate the preparation of a leachable sample in another area, noted Derek Wood, associate director, extractables/leachables and GC/MS services at the PPD Laboratories GMP Lab (Middleton, Wis., USA). Contamination from glassware or pipets is also possible.

Companies Providing Extractables/Leachables Testing

Contractor	Country	Facilities
BioScreen Testing Services	USA	Torrance, Calif., USA
Catalent Pharma Solutions	USA	Kansas City, Mo., USA
Encompass Pharmaceutical Services	USA	Norcross, Ga., USA
Eurofins Scientific Group	Denmark	Glostrup, Denmark
	USA	Lancaster, Pa., USA
Halo Pharmaceutical	USA	Whippany, N.J., USA
Intertek	UK	Melbourn, Royston, Cambridgeshire, UK
	USA	Whitehouse, N.J., USA
iuvo BioScience	USA	Rush, N.Y., USA
Maxxam Analytics	Canada	Burnaby, British Columbia, Canada
Microbac Laboratories, Inc.	USA	Wilson, N.C., USA
NAMSA	USA	Northwood, Ohio, USA
PPD	USA	Middleton, Wis., USA
Quality Chemical Laboratories	USA	Wilmington, N.C., USA
SGS Life Science Services, S.A.	China	Shanghai, China
	France	Clichy, France
	Germany	Berlin, Germany
	India	Taramani, Chennai, India
	Singapore	Singapore, Singapore
	Taiwan, R.O.C.	Taipei County, Taiwan, R.O.C.
	USA	Fairfield, N.J., USA
Sharp Packaging Services	USA	Phoenixville, Pa., USA
Whitehouse Laboratories	USA	Lebanon, N.J., USA
WuXi AppTec	USA	Marietta, Ga., USA

Source: PharmSource ADVANTAGE

Adequate extraction of compounds is important before detection can occur. Common techniques include reflux or Soxhlet extraction, sonication, autoclave, heated-oven extraction and, in some cases, such

automated techniques as accelerated solvent extraction (ASE) and microwave-assisted solvent extraction, Wood said. Material pre-treatment may be required, including use of such equipment as a liquid nitrogen freezer-mill (cryo-grinder). Sample clean-up techniques, like solid-phase extraction (SPE), may be required prior to analysis.

For complex packaging systems, there are two ways of testing, Tino Otte, senior scientific consultant at Intertek (London, UK) said: extraction of each assembly part and subsequent screening of extracts; or screening of the single assembly parts directly with thermodesorption (TDS) coupled with GC/MS, plus later extraction of the assembled packaging system, including analysis of extracts with such techniques as GC/MS, GC-HS/MS, HPLC/MS or ICP-MS, which is particularly useful for metal impurity testing.

"TDS-GC/MS gives a nearly complete overview about the components which will potentially be found in the later extractables study, which simplifies the work and reduces the risk of missing a component," he said.

It's also important that testing include incubating packaging systems at elevated temperatures with the real drug formulations to allow detection of compounds that may migrate over time into packaging, such as from labels or inks attached to the outer surface of the packaging, Otte added.

Another major challenge, said Andreas Nixdorf, team manager, extractables and leachables testing at SGS, is to sustain a qualified status from lot to lot, because the starting materials used to make polymeric materials are often not well-controlled along the supply chain to production of the final product. Impurities may be introduced at any point along the supply chain, meaning a material may have been qualified as safe and fit for intended use, but another lot produced later could have a more critical profile of which the end-user would not become aware.

"Impurity control in those materials is the biggest hurdle to ultimately producing a safe product," he said.

If there are unknown compounds to be tested for, such as special additive degradation products, it's also important to have toxicologists available to also evaluate the potential toxicity of those compounds, which is necessary to define a proper analytical threshold for later leachables monitoring under GMP requirements, Otte noted.

Mistakes in extractables/leachables testing can include use of pre-fabricated screening routines, which may not be correctly adapted to the application, Otte said. If the testing procedure is not correctly adapted to the packaging system being evaluated, the data obtained will not be in agreement with guidelines; for instance, the limit of detection could be too high or proof of method suitability lacking.

In addition, overly harsh extraction conditions may be applied, well in excess of the worst-case scenario recommended by regulators, which leads to more extractables found than would happen in reality because the polymer was partially dissolved or degraded.

These mistakes mean additional evaluation will be needed to gain approval from such regulators as the US FDA or the European Medicines Agency (EMA), thus increasing the costs of development and testing of products.

Regulatory demands

Regulatory requirements for mainly focus on expectations for the categories of products and manufacturing scenarios for which extractables/leachables should be evaluated. Typically, guidance from the US FDA and other regulators does not specify the exact approach or procedures for an extractables/leachables study, with the exception of recent FDA and EMEA guidances for elemental impurities.

"Although largely the same regulatory guidances have been in place for many years, these mainly only specify the requirements to perform extractables/leachables testing," Wood explained. "The specific details on how to conduct these studies and an approach to establishing thresholds were not put in place until more recently."

USP has recently added pertinent new chapters that cover assessment of extractables associated with pharmaceutical packaging and delivery systems (USP 1663), assessment of drug product leachables associated with pharmaceutical packaging (USP 1664) and delivery systems on plastic packaging systems and their materials of construction (USP 661).

"Since approximately 2001, [regulatory] authorities and several working groups have developed strategies and recommendations on how to organize extractables/leachables assessments," Nixdorf noted.

Important industry documents and recommendations include the Product Quality Research Institute (PQRI) 2006 best practices recommendations, which helped define proper procedures and considerations for extractables/leachables studies for inhaled products, Wood said. Other industry recommendation documents have been established since then or are in progress, such as a new PQRI recommendation for parenteral and ophthalmic drug products and a standardized extractables protocol published by the BioPhorum Operations Group for evaluating single-use system components in biomanufacturing.

The PQRI documents do not address metal species, but US FDA and EMEA guidance documents provide specification information for allowable limits of certain metal compounds.

Analytical Services in Brief

SGS (Geneva, Switzerland) will soon have available a new strain of influenza virus for use as a challenge agent in clinical trials of flu drugs and vaccines. The H3N2-type virus is undergoing adventitious and purity tests; final safety and activity data from first-in-human studies are expected to be presented in April 2017.

XenoGesis (Nottingham, UK) has opened a bioanalysis suite at BioCity that includes two new mass spectrometers for use in identifying and quantifying candidate molecules made for drug discovery efforts. The Thermo Scientific Q Exactive Focus Hybrid Quadrupole-Orbitrap and Thermo Scientific TSQ Quantiva Triple Quadrupole mass spectrometers will be used for screening, quantitating, identifying and confirming targeted and untargeted compounds for XenoGesis clients. Both are paired with a Thermo Scientific Vanquish Flex Binary ultra-high-performance liquid chromatography system.

Phase II-IV Clinical Research

INC Research (Raleigh, N.C., USA) will move its corporate headquarters from Raleigh to Morrisville, N.C., USA as part of its plans to invest $37.9 million into expanding that facility. The expansion, which will create about 550 new jobs, is partially funded by a Job Development Investment Grant from the North Carolina Economic Investment Committee, which could total as much as $8.4 million over eight years.

Early Development

Alpha Genesis (Yemassee, S.C., USA), a provider of primates for pre-human clinical studies, plans to invest $2 million to expand and renovate its 50,000-square-foot Yemassee facilities this year. The expansion is expected to add 30 new jobs at the site by the end of 2017.

iPharma Ltd. (Hong Kong, China) earlier this month announced capabilities to provide inhalation product design, development and testing services, including formulation development of dry powder, liquid or suspension-based products, particle engineering via spray drying and support of inhaler design and modeling. iPharma can also provide characterization and clinical release testing, method development and validation and inhalation device testing.

Pharmaron (Beijing, China) has acquired **Xceleron** (Germantown, Md., USA), which specializes in highly sensitive accelerator mass spectrometry (AMS) technology used to identify and analyze both small and large molecules at low concentrations. Pharmaron will pair Xceleron's AMS expertise with its own radiolabelled compound manufacturing and metabolism capabilities.

Drug Discovery

Investment in Client, Acquisition and New Agreement for Evotec

Evotec (Hamburg, Germany) will invest in Eternygen GmbH (Berlin, Germany), a developer of treatments for metabolic diseases for which it has provided drug discovery services. Evotec will join a consortium of investors to participate in Eternygen's latest €8 million ($8.3 million) funding round. Evotec will continue to provide discovery services for small-molecule sodium-coupled citrate transporter (NaCT) inhibitors in an effort to identify treatments for diabetes, non-alcoholic fatty liver disease and obesity, among others.

Late last year, Evotec also acquired preclinical CRO **Cyprotex** (Macclesfield, Cheshire, UK) for £55.7 million ($68.6 million), or approximately £1.60 ($1.97)/share. With the purchase, Evotec gained Cyprotex's ADME-toxicology capabilities.

The CRO will also provide phenotypic screening platforms for use with Merck's genome editing technologies, including such genetic reagents as viral CRISPR and shRNA, in primary and induced pluripotent stem cells and *in vivo* disease models.

Learn More

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

Drug Discovery in Brief

Aptuit (Greenwich, Conn., USA) will provide discovery services aimed at providing candidate treatments for idiopathic pulmonary fibrosis for Chiesi Farmaceutici (Parma, Italy). Aptuit will provide medicinal chemistry, pharmacology and DMPK testing to identify compounds that warrant further preclinical development.

Eurofins Scientific (Kraainem, Belgium) will acquire Villapharma Research (Murcia, Spain), which provides organic synthesis and medicinal chemistry services, for an undisclosed amount. The transaction is expected to close next month.

Horizon Discovery (Cambridge, UK) has gained full commercial rights to ERS Genomics' (Dublin, Ireland) CRISPR edited cell lines for manufacture of biotherapeutics. Horizon has also entered into a collaboration with Solentim (Dorset, UK), developer of the Cell Metric and dedicated instrumentation for cell line development, to develop automated approaches for gene editing of cell lines; that collaboration is being funded with a £523,000 ($645,453) grant from Innovate UK.

InVivo Biotech Services (Hennigsdorf, Germany) has been acquired by Bruker (Billerica, Mass., USA) for an undisclosed amount. Bruker will use InVivo Biotech's monoclonal antibody and similar capabilities to support its translational pathology research with the MALDI Tissuetyper. InVivo, which had 2016 revenues of approximately $5 million, will continue to operate under its existing name and management team.

Captive Capacity

Aerie Pharmaceuticals (Irvine, Calif., USA) has leased a facility in Athlone, Ireland from the Industrial Development Agency (IDA) of Ireland to house the company's first manufacturing plant. The 30,000-square-foot facility will make commercial supplies of Aerie's candidate glaucoma treatment Rhopressa (netarsudil), for which Aerie submitted an NDA to the US FDA in September 2016. The company

estimates that construction and equipment costs will total about $25 million; the site is expected to begin producing commercial supplies of Rhopressa by 2020 if the product gains marketing approval.

Akorn Pharmaceuticals (Lake Forest, Ill., USA) last month completed a re-inspection of its Decatur, Ill., injectables manufacturing site by the US FDA with no Form 483 observations. An agency inspection in June had found quality control issues, including inadequate documentation of batch control testing. News of the successful re-inspection gave Akorn stock a bump in mid-December, with shares hitting $20.21.

Asterias Biotherapeutics (Fremont, Calif., USA) earlier this month completed validation and start-up of a new GMP manufacturing facility at its Fremont site. The new plant initially will make clinical supplies of AST-OPC1, Asterias' candidate product intended to help victims of cervical spinal cord injuries gain improved function in the fingers, hands and arms.

AstraZeneca (London, UK) opened a new £120 million ($148.98 million) cancer treatment manufacturing plant at its existing Macclesfield, UK site last month.

Aurobindo (Hyderabad, India) will acquire Generis Farmacêutica (Venda Nova, Portugal) for €135 million ($143.54 million), the company announced in a filing with the National Stock Exchange of India. The acquisition includes a solid-dose manufacturing facility in Amadora, Portugal with a capacity of 2.2 million tablets/year. Generis was estimated to have sales of about €64.8 million ($68.87 million) for 2016.

Bristol-Myers Squibb (BMS – New York, N.Y., USA) will close three of its US R&D facilities, the company announced last month. BMS will phase out its 1 million-square-foot Hopewell, N.J., USA laboratory facility over the next 10 years. Additionally, the company does not plan to renew its lease at the Lake Union Steam Plant site in Seattle, Wash., USA when it ends in 2019. Work at that facility has focused on discovery and manufacture of early clinical supplies of therapeutic proteins. BMS will also close its Wallingford, Conn., USA facility at the end of 2018 and has nixed plans to build a Connecticut development site. Work from these three sites will be transferred to other US locations, such as a still-planned research facility in Cambridge, Mass. and expansion of two other sites—the Redwood City facility in the San Francisco Bay area of California and the recently opened Lawrenceville, N.J. site. BMS initially announced plans to rework its manufacturing and R&D business as part of its third-quarter 2016 earnings release (*November 2016 B/POR*).

Europharma DK (Esbjerg, Denmark) has had its manufacturing authorization and GMP certificate suspended by the Danish Medicines Agency due to GMP violations found during a December 2016 inspection of its Esbjerg site. In its report to EudraGMDP, the Danish Medicines Agency alleged that Europharma deliberately hid information, took deliberate action to hinder inspectors and falsified the expiry date on some products.

GlaxoSmithKline (GSK – London, UK) is adding about 9,300 square meters to its laboratory facility in Providence, Pa., USA, at a cost of about $45 million. Construction is slated for completion in October of this year.

GSK also extended a development agreement with Puridify (Stevenage, UK) to make clinical-scale batches using Puridify's Protein A in place of packed bed chromatography columns for monoclonal antibody purification. The companies had previously conduced proof-of-concept studies at the 50L scale.

Intega Skin Sciences (Laval, Quebec, Canada) received a warning letter from the US FDA alleging GMP violations at its Laval manufacturing site, formerly owned by Valeant (Laval). Among the violations listed in the warning were: failure to investigate out-of-specification aerobic microbial counts for a batch of product released for distribution, or to investigate whether other lots might be affected; lack of critical procedures—such as review of out-of-spec results, complaint handling and change control—for its quality unit; failure to validate cleaning procedures for non-dedicated production equipment to ensure that they would prevent contamination; and lack of written procedures for handling written and oral complaints.

Laboratorio Angulema (Madrid, Spain) has had its manufacturing temporarily suspended in the wake of GMP issues found during a November inspection by the Spanish Agency of Medicines and Medical Devices (AEMPS) of its Leganes, Spain site. In its statement of noncompliance report filed with EudraGMDP, AEMPS listed several deficiencies that it termed "critical," including: lack of an effective pharmaceutical quality system; release of vaccine and autovaccine batches without required sterility testing; process validation not performed; medial fill process simulation for aseptic process not performed; lack of validation of terminal sterilization of sterile vaccines and autovaccines; and lack of validation of inactivation process for bacterial vaccines and autovaccines. Laboratorio Angulema makes subcutaneous sterile bacterial and allergenic vaccines, along with subcutaneous sterile bacterial autovaccines primarily for the Spanish market.

PL Developments (Westbury, N.Y., USA), a private-label OTC maker, will build a logistics and manufacturing site in Piedmont, South Carolina. The $45 million facility will be constructed with help from a $750,000 grant from Greenville County for site improvements. PL Developments already has distribution centers in Clinton and Duncan, SC, along with another manufacturing site in Clinton, SC. The Piedmont site could add as many as 450 jobs once fully operational.

Medical Device CMOs

Raumedic AG (Helmbrechts, Germany) will provide the single-use component of scPharmaceuticals' (Lexington, Mass., USA) sc2Wear Infusor for subcutaneous administration of products that currently require intravenous or intramuscular injection by a healthcare professional. The sc2Wear delivery device is based on Sensile Medical's (Hãgendorf, Switzerland) SenseCore micro-piston pump, for which scPharmaceuticals has an exclusive global license for certain therapeutic categories, including heart failure and infectious disease.

Commodity Suppliers

GEA (Düsseldorf, Germany) and **Siemens** (Munich, Germany) have partnered to provide an integrated continuous tablet manufacturing line. GEA's ConsiGmaTM continuous manufacturing platform will be equipped with Siemens' Automation & Industrial IT packaging, including Sipat for PAT data management. The line will offer both wet granulation and direct compression.

MilliporeSigma (Billerica, Mass., USA), the North American life sciences business of Merck (Darmstadt, Germany), has opened a facility in Mollet des Vallès, Spain dedicated solely to manufacture of meglumine, an excipient for pharmaceuticals and a component of medical imaging contrast media.

Regulatory Developments

FDA Issues Flurry of Draft and Final Guidances at Turn of Year

In recent weeks, the US FDA released several draft and final guidances pertinent to manufacturers of clinical and commercial drug products, including contract manufacturers.

For instance, according to draft guidance on submission of that information in electronic format, issued at the close of 2016, the FDA may stop accepting non-electronic submissions of manufacturing establishment information (MEI) as early as 2019. The draft document said that all MEI in NDAs, ANDAs and BLAs, along with amendments, supplements and resubmissions of any application, should be provided electronically using the Health Level 7 Version 3: Structured Product Labeling (SPL) standard and consoli-

dated into a single list including the establishment name and address, unique facility identifier, contact information for the person responsible for scheduling inspections and specific manufacturing operations conducted at the site. These expectations would take effect 24 months after the guidance is finalized.

The FDA's much-anticipated draft guidance on how it expects drug manufacturers to demonstrate biosimilar interchangeability recommends that drug sponsors conduct one or more switching studies to demonstrate that patients can alternate between the two products safely and without diminished efficacy. The draft guidance—entitled *Considerations in Demonstrating Interchangeability with a Reference Product* and issued in mid-January—focuses primarily on the data needed to support interchangeability. It also addresses considerations for switching study design and analysis. The agency also makes clear that specific requirements will vary based on the biosimilar submitted for approval. For instance, factors to consider when determining the amount and type of data needed to demonstrate interchangeability should include the complexity of the biosimilar and product-specific immunogenicity risks.

The FDA also earlier this month released final guidance explaining its GMP expectations for combination products. It addresses such issues as design controls for early-phase investigational products, cross-labeled products and GMP information required in marketing applications. The guidance document also includes hypothetical situations to clarify how companies are expected to comply with certain combination product GMP requirements. Issuance of the final guidance, *Current Good Manufacturing Practice Requirements for Combination Products*, followed on the heels of the FDA's final rule on postmarket safety for combination products, released last month.

The agency also released final guidance on repackaging of biologics by pharmacies or registered outsourcing facilities (aka compounders) this month. A key feature of that document—*Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*—was its focus on when it may be acceptable to mix or dilute a biologic as part of repackaging procedures. The agency also clarified its definition of repackaging and outlined situations in which it does not intend to enforce certain federal regulations regarding repackaging activities.

Regulatory Developments in Brief

The Japanese Pharmaceutical and Medical Devices Agency late last year agreed to share information from its inspections of API manufacturing sites with the US FDA, the European Medicines Agency and other regulators. At minimum, participating inspectors are expected to share with other regulatory bodies the names of APIs produced at a site, the site master file, product quality review data, manufacturing process descriptions and the buildings and/or production lines inspected. The international regulatory inspection program, in place since 2012, allows participating agencies to request another participant to extend the scope of a planned inspection to cover particular areas of interest.

Outsourcing Events

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

AACR Annual Meeting 2017
April 1-5, 2017, Washington, D.C., USA
www.aacr.org

2017 PDA Annual Meeting
April 3-5, 2017, Anaheim, Calif., USA
www.pda.org

ACRP 2017
April 29-May 1, 2017, Seattle, Wash., USA
s4.goeshow.com/acrp/annual/2017/expo.cfm

InformEx 2017
May 16-18, 2017, Philadelphia, Pa., USA
www.informex.com

Bio/Pharmaceutical Outsourcing Report

9870 Main Street
Fairfax, Virginia 22031 USA
Voice: +1-703-383-4903
Fax: +1-703-383-4905
E-mail: info@pharmsource.com
Website: www.pharmsource.com

Editor-in-Chief: James C. Miller
Director of Market Intelligence: Saul Richmond, Ph.D.
Managing Editor: Elizabeth (Lisa) Tilley Hinkle
Industry Analysts: Nanthida (Judy) Nanthavong, Brooke Wilson, Scotty Chung-Siu, Mahdia Hashimy, Katie Leuth
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