PharmSource ADVANTAGE Briefing

PharmSource ADVANTAGE: Sourcing Intelligence for Intelligent Sourcing

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In This Issue:

Tel. 703-383-4903
Fax. 703-383-4905
www.pharmsource.com
info@pharmsource.com

Welcome to the *PharmSource ADVANTAGE Briefing*!

Welcome to the March 2010 issue of the ***PharmSource ADVANTAGE Briefing***, a complimentary newsletter designed to provide actionable intelligence to bio/pharmaceutical and contract service professionals. Inside each issue, you will find a snapshot of our flagship newsletter, ***Bio/Pharmaceutical Outsourcing Report***, along with a company profile developed from our comprehensive **PharmSource ADVANTAGE** contractor database.

This month, we analyze GlaxoSmithKline's decision to move the manufacture of Avodart to its facility in Poland and the impact this will have on **Catalent Pharma Solutions**. In addition, we outline how best to evaluate CMOs for HPAPI manufacture. We also profile **Therapure Biopharma** and discuss the company's new multiyear manufacturing agreement with LFB Biomedicaments. And don't miss the information on our latest report, The *Market for Analytical Testing and Development Services* on page 3.

Enjoy the issue!

Feature Story

GSK Moving Manufacture of Avodart to New Facility in Poland

GlaxoSmithKline (GSK - London, UK) announced plans to invest PLN 70 million (USD 24 million) into its manufacturing plant in Poznan, Poland. The company plans to spend the majority of these funds, PLN 54 million (USD 19 million), rebuilding the infrastructure and upgrading the equipment at the site. As a result, the plant will have an expanded annual capacity of 600 million capsules and will have the capability to mark drugs via laser printing.

In addition, GSK announced its intention to move the manufacturing and packaging of Avodart (dutasteride) soft gelatin capsules from **Catalent Pharma Solutions**' (Somerset, N.J., USA) facility in Beinheim, France, to the Poznan plant. Commercial production is scheduled to begin at the new facility in January 2011, and the company plans to export the drug, which is a treatment for benign prostatic hypertrophy (BPH), to 80 markets around the world.

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In 2009, Avodart generated revenue of GBP 530 million (USD 840 million); however, this number is expected to jump further, as the drug recently demonstrated a significant ability to reduce the risk of developing prostate cancer among middle-aged men with elevated PSA levels. GSK has in the works a new treatment for BPH, Duodart, that is expected to usurp Avodart as the therapy of choice for BPH. Avodart is scheduled to lose patent protection by 2013 or 2015.

What it means

The move of the manufacture of Avodart to GSK's new facility in Poland is a considerable blow to Catalent. Based on projected future sales of USD 1 billion, Catalent could lose between USD 30 million and USD 50 million in annual revenue. On the other hand, GSK is expecting to see notable cost savings on the production of the drug by moving to a site in an emerging-market country with presumably lower cost. This is important, as competition is sure to mount with the drug's looming patent expiration.

Side Effects

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	Pharma Company	Event	Product	Relationship
Potentially Positive Side Effects				
Angelini Fine Chemicals	Labopharm	FDA Approval	Oleptro	Small molecule API manufacturing
Elan Drug Delivery	Acorda Therapeutics	FDA Approval	Ampyra	Solid dose manufacturing
Gland Pharma	Innopharma/ Bioniche Pharma	ANDA Approval	Ibutilide Fumarate	Injectables manufacturing
HollisterStier	Auxilium Pharmaceuticals	FDA Approval	Xiaflex	Injectables manufacturing
Patheon	Acorda Therapeutics	FDA Approval	Ampyra	Solid dose manufacturing (second source)
Regis Technologies	Acorda Therapeutics	FDA Approval	Ampyra	Small molecule API manufacturing
Potentially Negative Side Effects				
Lonza	Alexion Pharmaceuticals	EU approval of Alexion's manufacturing plant	Solaris	Biomanufacturing

Source: PharmSource Lead Sheet

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PharmSource Special Report

New Study Sizes the Analytical Testing Market

PharmSource is pleased to announce the publication of our new report, *The Market for Analytical Testing and Development Services.* The report presents the findings of our extensive effort to model expenditures on GMP analytical development and testing in both the clinical and commercial phases and to understand the factors that will drive outsourcing of analytical activities over the next five years.

The heart of the study is our model of spending for CMC development, including API process development, formulation, CTM manufacture and associated analytical testing. We have constructed a model driven by the new product pipeline and the outsourcing behavior of the major end-customer segments. A separate model breaks down spending for analytical testing of commercial products.

Based on our model, PharmSource estimates industry spending for CMC development services at about USD 9.3 billion, divided almost equally among process and formulation development, analytical development and testing, and CTM manufacture. We estimate that as much as two-thirds of that spending is already outsourced, either to CDMOs or dedicated contract labs. Growth in the market will be constrained by a likely shrinkage in the development pipeline, and North American and European contractors will be challenged by emerging competition from Asia.

More information on *The Market for Analytical Testing and Development Services* is available at http://www.pharmsource.com/productsservices/special-reports/.

Business Conditions

How to Evaluate CMOs for HPAPI Manufacture

You need to manufacture a cytotoxic compound. How do you identify and evaluate an appropriate CMO to do this? Two basic rules will get you started:

> **Rule #1:** Know your own product - physical, chemical, and biological characteristics; toxicology; therapeutic dose; and process complexity and scale. A good CMO will ask you about all of these points because they need detailed product information to assess the controls that are appropriate for your product.
>
> **Rule #2:** Get to know the CMO, and let them get to know you. This is critical because relationships built on trust and communication are critical to project success, and especially critical in cytotoxic production.

What is a Cytotoxic Compound?

At present, there is no official guidance regarding the categorization of cytotoxics or high potency APIs (HPAPIs). In the absence of this, the industry has evolved several different classification systems. The one most widely accepted by CMOs and many pharmaceutical companies is the SafeBridge system. This system ranks compounds for potential potency on a scale of I to IV. Category I covers low-irritant drugs. Category II, currently the largest, contains drugs that can cause organ toxicity. Category III is the first tier of potent drugs that cause genetic effects, plus organ toxicity. Category IV contains the most potent

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compounds, with characteristics including extreme acute and chronic toxicity, potentially non-reversible effects, moderate sensitizing activity, poor or no warning properties, quick absorption rates, suspected or known "genic" effects, and requiring moderate to immediate medical intervention.

How can you evaluate your own compound? SafeBridge can do it for you, as can other independent testing laboratories. As we noted, it is critical to categorize your compound before starting the search for a CMO.

Evaluating a CMO: Ask the Right Questions and Do Your Homework

You may talk to several CMOs before deciding on one. These discussions can yield useful information that will help you make your final selection. What should you be asking? What do you need to know beforehand? Alex McClung, Director of Quality Assurance for Pharmaceutics International, Inc., a CMO that handles cytotoxic compounds, offers these key suggestions:

- Who are you talking to from the CMO? Remember that consistent responses are a good sign, divergent responses are a bad sign. Business people, engineers, and the quality/regulatory staff may represent the CMO's capabilities quite differently. Ensure and insist that you talk to a number of different people in the organization.
- What questions are the CMO asking? A CMO experienced in handling HPAPIs should require you to complete a product profile questionnaire or to provide detailed information about your product up front. Lack of questioning along these lines is an indication that they are not qualified.
- How do they respond? Be sure to drop key phrases and industry buzzwords into your discussions and gauge the CMO's response. The phrases "beta lactams," "cytotoxic compounds," and "SafeBridge Category IV products" will elicit specific responses in qualified CMOs. Especially for Category IV products, the controls required are so different from normal production processes that the CMO that can manufacture them will respond accordingly.
- Watch for specific indicators: If you get a blank look when you mention "Category IV," walk away! If the CMO says immediately, "We can do that," ask them to show you how.

"In addition, be sure to look for specific examples of control and isolation strategies," McClung says. "For Category IV manufacturing, the necessary equipment and controls will be obvious when you walk through the facility." CMOs who can handle Category IV compounds will have self-contained outfits for operators, isolator technologies, and clearly dedicated equipment. If a CMO handles only Category III compounds and below, the special controls may not be obvious but ask for them to be pointed out—they should not just be described in SOPs. Look for:

- HVAC controls
- Material, equipment and personnel flows
- Isolators and other containment equipment
- Gowning controls

Also important is finding out the scope of the CMO's current regulatory licensing and regulatory inspection history. In some instances, regulators may expect to see dedicated facilities. (While regulatory agencies will not provide a list of how compounds must be handled, they will expect dedicated facilities and equipment for Category IV compounds.) In others, regulators want to see validated cleaning and decontamination processes. Can your CMO adequately demonstrate to regulators dedicated facilities or appropriate controls to manage the risk? And, does the CMO understand the regulatory environment?

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Always Perform Due Diligence

Due diligence is the final and most important aspect of CMO evaluation, and you should perform a due diligence audit before you sign the contract and ensure your auditor is qualified to assess cytotoxic production capabilities. "You and your auditor need to understand the regulations and requirements for the production process in order to appropriately evaluate a CMO," McClung says. "Conduct an audit. Know what you're looking for. Our CMO, for example, does not handle Category IVs. We do have the ability to control processes and production for Category IIIs and below, however, to a degree acceptable to regulators, including appropriate facility design, engineering controls, and procedural controls. We are happy to show these controls to auditors." Reputable CMOs will explain what they can and cannot handle and what regulators will expect from your product manufacturing.

"The bottom line is do your homework, and maintain open and honest communication," McClung emphasizes. "You need to get to know the CMO your are working with, and a good CMO will always ask questions about your product, and will spend time getting to know both your product and your company."

PharmSource ADVANTAGE: Contractor Profile

API – Biomanufacturing

Therapure Biopharma Signs Multiyear Manufacturing Agreement

Therapure Biopharma (Mississauga, Ontario, Canada) signed a multiyear manufacturing agreement with LFB Biomedicaments, a wholly owned subsidiary of French biopharmaceutical company LFB. The financial terms of the contract were not disclosed.

Under the terms of this agreement, Therapure Biopharma will produce two plasma proteins. The company also agreed to modify its facility to allow for the installation of LFB proprietary technology and processes needed for manufacture of the proteins. LFB will remain responsible for the regulatory approvals and marketing of the products.

Modifications at Therapure Biopharma's Mississauga site are expected to be completed in 2011, with qualification and validation being performed in 2012. The regulatory approval process is anticipated to be concluded in 2013.

Therapure Biopharma

Headquarters: Mississauga, ON, Canada

Services:

- **API - Biomanufacturing**
  - **Blood products**
  - **Process development**
  - **Cell culture**
- **Clinical Dose Manufacturing and Packaging**
  - **Injectable Phase I/II CTM and Formulation**

In addition, Therapure Biopharma signed an agreement with Stellar Pharmaceuticals to provide fill-and-finish services for Stellar's natural viscosupplement, NeoVisc, in prefilled syringes.

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Below is a part of an actual profile from the **PharmSource ADVANTAGE** database of contract service providers. The database provides detailed information about contractor capabilities in dose and API manufacturing, packaging services, formulation and more. Qualified companies are listed in PharmSource's contractor database **free of charge**, based on their relevance to our data sets. Along with each profile, you'll find information about known clients, mergers/acquisitions/alliances, company financials and our comprehensive archive of proprietary articles.

The **PharmSource ADVANTAGE** database of contract service providers can be used to create a shortlist of contractor candidates, or for benchmarking. It can help you save weeks of searching, researching and due diligence.

Therapure Biopharma

Mergers/Acquisitions **News & Analysis** **Known Clients**

Corporate Profile:

Address:	2585 Meadowpine Blvd. Mississauga, ON L5N 8H9 Canada
Voice:	905 286 6200
Fax:	905 286 6300
Website:	www.therapurebio.com
E-mail:	info@therapurebio.com
Ownership:	Private: private equity or venture capital
Parent Company:	Catalyst Capital Group
Primary Business:	Contract Services

Contract Business:

Contract revenues:	$0-24 million
Corporate Head contact:	**Thomas Wellner** Voice: +1 (905) 286-6200 E-mail: ceo@therapurebio.com

Contract Services:

API - Biomanufacturing
- Blood products
- Process development
- Cell culture

Clinical Dose Manufacturing and Packaging
- Injectable Phase I/II CTM and Formulation

Therapure Biopharma Inc.

Mississauga - ON - Canada Facility
2585 Meadowpine Blvd.
Mississauga, ON L5N 8H9 Canada
Phone: 905 286 6200 Fax: 905 286 6300
info@therapurebio.com

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Specifications for "Cell Culture"

Biologics products

Diagnostic antigens:	No
Monoclonal antibodies:	Yes
Plasmid DNA:	Yes
Polyclonal antibodies:	Yes
Recombinant proteins:	Yes
Vaccines - recombinant:	Yes
Viral vaccines and vectors:	No

Project acceptance criteria

Special Materials

BL 1 organisms:	Yes
BL 2 organisms:	Yes
BL 3 organisms:	No
Spore-forming agents:	No
Viruses:	No

Cell lines

Baculovirus:	No
CHO:	Yes
Glutamine synthetase (GS - Lonza):	No
Hybridoma:	Yes
Myeloma:	No
NS0:	No
PER.C6 (Crucell):	No
Proprietary cell lines:	HEK-293, multiple test lines

Bioreactor technologies

Production scale

500 L and smaller GMP:	Yes
500 L to 4999 L GMP:	Yes
5000 L and larger GMP:	No
Pre-clinical materials (Non-GMP):	Yes

Batch/Fed-batch

Batch/fed batch:	Yes
Bioreactor size (number):	10L – 3,000L

Perfusion

Bioreactor size (number):	50 L
Perfusion:	Yes

Other bioreactor technologies

Hollow fiber:	No

Single use bioreactors

Single use bioreactors:	Yes
Single use bioreactors - types/sizes/number:	Wave, 20-200 L

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Downstream recovery and purification	
Cell homogenization:	Yes
Centrifugation-batch:	No
Centrifugation-continuous:	No
Chromatography:	Yes
Cold rooms:	Yes
Membrane separations - microfiltration:	Yes
Membrane separations - nanofiltration:	Yes
Membrane separations - ultrafiltration:	Yes
Precipitation/crystallization:	Yes
Solvent extraction:	Yes
Solvents accepted:	Multiple
Related services	
Analytical methods development:	Yes
Biosafety testing:	Only for manufacturing clients
Cell banking:	Yes
Fill and finish:	Yes
Formulation development:	Yes
Molecular biology:	Yes
Process development:	Yes
Stability testing and storage:	Yes
Regulatory approvals and certifications	
Canada - HPB:	Yes
Europe - EMEA or constituent countries:	No
UK - MHRA:	No
USA - FDA:	No

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