

sp2

February 1, 2008

---

## **Contract Research Services Support API Manufacture**

Ash Stevens Inc (ASI) was originally founded to serve the chemical research needs of the US Federal Government but has since become a full-service contract manufacturer of API's with the expertise in contract process development and chemical regulatory affairs. Company president and CEO Dr. Stephen A Munk describes ASI's evolution and its vision for the future.

Founded in 1962, Ash Stevens Inc. (ASI) is a contract research organization focused on low-volume, high-value API's produced using the company's more than 40 years experience in chemistry, process development, materials and quality requirements of products. ASI's corporate offices and research facilities are house in the Detroit Research Park, Michigan, USA, and has six research laboratories and support facilities.

The company's customer base includes both the private sector and the US Federal Government. Services include chemical research and development, support of clinical trials through synthesis of drug candidates, and manufacturing of API's post regulatory approval. This support has led to approvals on API's in many areas including oncology. The company was recently approved to manufacture the active ingredients in Velcasem, Vidaza and Clolar With these approvals, it now has 11 FDA-approved drug substances in its portfolio.

"We support all the facets of chemistry manufacturing and controls preparation related to API's, including structure elucidation, specifications development, methods validation, and drug substance stability, as well as preparation of documentation for submission," says Dr. Stephen A. Munk, the company's president and CEO.

"Ash Stevens had been a long-time Government contractor and one of the compounds that we were developing with the National Cancer Institute, Fludarabine Phosphate became interesting commercially. The company followed that drug to the market and we continue to support the brand, Fludara, 17 years after approval! That initial approval re-focused our investment programme to ensure that we continue to modernize our operations in line with current pharmaceutical and GMP thinking. That was a major driver for our 2000-2003 plant upgrade and expansion."

### **Investment in process development and drug manufacture**

ASI's process development and drug manufacturing facility is located in Riverview, Michigan. The 28,000 sq ft facility now houses nine chemical drug development and production laboratories, three full-scale production areas, as well as two analytical laboratories for quality control. Projects at this facility typically involve cGMP manufacture of material for toxicological and clinical

studies through to commercial production after approval of the drug product. Major production equipment includes glass-lined batch vessels (up to 500 gallons), hydrogenation and other pressure vessels, centrifugal, nutsche and Rosenmund filter-dryer equipment, and vacuum and convection tray drying ovens, plus barrier isolation systems. Last October, ASI announced that it had recently brought two new Rosenmund filter-dryers and a 100-litre pilot plant with cryogenic capabilities online at Riverview, representing an investment of more than \$2.5 million. The large filter-dryer, a 0.3 cubic metre unit, is equipped with glovebox technology to facilitate handling of air-sensitive materials at plant scale. The smaller filter-dryer, a 0.03 cubic metre unit, is designed to be used with the company's new cryogenic pilot plant, which has the capability of maintaining temperatures as low as -80 degrees C and can operate seamlessly to 200 degrees C. The new systems are modeled an ASI's process laboratories with pocket filters and vessels using the same geometries as those found in the main plant.

"These new capabilities facilitate the rapid scale-up of processes to support product requirements throughout clinical development and post-launch" says Munk. "It's our mission to translate client discoveries into new products to help seriously ill people. By upgrading our facilities with scaleable systems and assuring rapid product supply, we are investing in our customers' success in the form of faster drug approvals.

"Ash Stevens thinks in detail about specifications not only from a technical perspective but from a regulatory perspective. Often, while things might make chemical sense, specifications are inadequate from a regulatory perspective. We additionally have a real understanding of pharmaceutical needs and timelines and are able to help optimize material management issues with our clients. This allows us to be nimble and ensure that material of adequate quality is available quickly for toxicology work while we prepare for the clinical side of the programme."

### **Niche product manufacture**

ASI's products are sold globally and the company has been audited by a large number of Ministries of Health including in Europe, Japan, Korea, and Australia. The company produces API's for both large pharma clients (for Fludarabine Phosphate and Clofarabine) as well as emerging pharma clients. Munk says its flexible, robust systems allow it to work efficiently with a variety of clients:

"Many in our industry have the same physical infrastructure as Ash Stevens. What distinguishes Ash Stevens is the depth of our systems and our understanding of the needs of pharmaceutical companies in contrast to the needs and requirements of organisations focused mainly on chemicals. This is reflected in the large number of New, Innovator, and Developed Chemical

Entities that we were recently approved to produce- three in a period that has seen less than 100 for the entire world.”

Munk says ASI’s capacity is well suited for niche products, as its largest vessels are 500 gallons: “This limits our ability to deliver many metric tons quickly but we are very nimble organization and understand the very timelines for ensuring the survival of our client companies. Since we also have a lot of ‘Big Pharma’ regulatory and manufacturing experience, our systems are robust enough to meet the depth and demands of larger pharma clients as well.”

### **Level playing field**

Munk is very positive about the company’s future: “Chinese and Indian companies will ultimately need to comply with tougher regulatory standards and that will level the playing field in terms of price,” he says. “Wages are also rising in those parts of the world, but I feel the financial advantage that producers from that part of the world enjoy is largely driven by the cost of regulatory compliance.

I think that the out look for competent contract research and development organisations is very positive going forward. We are certainly positive for the future and continue to invest in our business. We brought low-temperature capabilities online last year and purchased new, contained isolation technology-filter- dryers with glovebox technology. We have just completed commissioning of a new 400 MHz NMR. Emerging pharmaceutical companies will continue to be formed with exciting concepts from academic laboratories as well as licensing from Big Pharma as they realize that they cannot pursue all of the great opportunities that they have before them. There will be opportunities for those organisations to realize value from products that do not fit their company objectives and that will create opportunities for new companies to take up the challenge of converting those ideas in products.

It is a great time to be in the contract R&D/manufacturing environment. Those with a good understanding of pharma needs and the financial resources to invest will thrive as outsourcing grows in importance for Big Pharma as well as new companies whose business model does not include a full complement of chemical development and manufacturing expertise,” he concludes.