

## Pharmaceutical Technology

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### Ash Stevens Plots a Steady Growth Path

The playing field for contract manufacturing organizations (CMOs) of active pharmaceutical ingredients (APIs) is highly competitive as CMOs face cost pressures from suppliers from Asia, recent overcapacity, and increased purchasing power from pharmaceutical companies. Amidst these changing fundamentals, however, certain companies are prospering. Such is the case with Ash Stevens (Detroit, MI), which has managed to grow at healthy rates and secure contracts for several recently approved APIs.

#### From research to contract manufacturing

Ash Steven's strategy has been to focus on smaller volume, more chemically complex APIs while leveraging its US-based manufacturing base. Cal Stevens, PhD, a professor at Wayne State University in Detroit, Michigan and Art Ash, the first PhD recipient from Wayne State, founded the company in 1962. The company's initial focus was in contract research with government agencies, including the National Cancer Institute (NCI). The company took the step of transforming itself into a contract manufacturer of APIs in the early 1990s with the commercial manufacture of fludarabine phosphate, the API in the anticancer drug "Fludara," now marketed by Bayer Healthcare (Wayne, NJ).

This initial success was followed with the company's manufacture of brimonidine tartrate, the API in the glaucoma drug "Alphagan" by Allergan (Irvine, CA), explains Stephen Munk, president and CEO of Ash Stevens. Munk took the helm of Ash Stevens in 1997. Before joining Ash Stevens, he led the adrenergic discovery team at Allergan.

Ash Stevens now manufactures 11 APIs that have been approved by the US Food and Drug Administration. This total includes three recent approvals: "Velcade" (bortezomib) by Millennium Pharmaceuticals (Cambridge, MA), "Vidaza" (5-azacitidine) by Pharmion (Boulder, CO), and "Clolar" (clofarabine) by Genzyme (Cambridge, MA). The company manufactures these APIs at its 30,000-ft<sup>2</sup> facility in Riverview, Michigan. The company's total reactor capacity is 1500 gallons (5.6-m<sup>3</sup>).

Bortezomib is produced using standard peptide coupling chemistry. The unusual, boron-containing amino acid is produced using a Matteson reaction. The actives 5-azacitidine and clofarabine (1) are both produced from simple sugars and appropriate bases.

#### Promising APIs

Although commercial development and manufacturing of APIs represents between 85-95% of its business, Ash Stevens is also keeping to its roots in

working with the government on promising APIs. In October 2006, the company was awarded two multi year contracts from the NCI totaling \$12.4 million for synthesis-related work in medicinal chemistry in support of preclinical and clinical quantities of small molecules.

#### Strategy paying off

The company's strategy is reaping its rewards. Although a small company (with annual sales of roughly \$10 million), the privately held Ash Stevens has increased its revenues at double-digit to high single-digit growth per year for the past several years, and Munk is also optimistic for 2008. "We expect growth of roughly 10% in 2007, and see similar growth for 2008."

Reflecting that optimism, the company is investing in its facilities. Ash Stevens recently invested \$2.5 million for a new 100-L pilot plant with cryogenic capabilities at its Riverview, Michigan, development and manufacturing site. The new pilot plant has the ability to maintain temperatures as low as  $-80^{\circ}\text{C}$  and as much as  $200^{\circ}\text{C}$ . The investment also includes the addition of two new Rosenmund filter-dryers.

The  $0.3\text{-m}^2$  filter dryer is equipped with glove-box technology for handling air-sensitive materials and Category 3 and 4 potent materials at plant scale. The  $0.03\text{-m}^2$  filter dryer will be used in the new cryogenic pilot-plant system.

The addition of cryogenic capabilities is the latest investment for the company. Between 1999 and 2003, the company invested \$13.5 million to build its contract-manufacturing activities.