



The Key to Success in High-Potency APIs

US contract API manufacturer Ash Stevens Inc. (ASI) has extensive expertise in the manufacture of high-potency anti-cancer pharmaceutical ingredients and is seeing increased demand for its services from European pharmaceutical companies. We asked company CEO Dr. Stephen A. Munk about the changes affecting the marketplace and prospects for future growth.

TM: What's the single most important issue facing the API manufacturing sector today?

SM: In my opinion the most important issue facing the API manufacturing sector today is the very large number of players operating in the sector, which means that the FDA and other regulatory bodies are spread very thin trying to manage regulatory oversight; the result of this are problems like the recent issues with Heparin supply. Companies have to play by the rules, and as problems like that occur, there will be more regulations to manage those problems. Regulations in general add a level of complexity to how the industry operates, but they are necessary to avoid errors and minimise potential injury to patients. Remember, we are here to help people, not to injure people.

TM: Is there any particular issue that's important specifically for the high-potency API sector rather than for the API manufacturing sector in general?

SM: In the high-potency sector, the most important issue, particularly for smaller companies, is capital expenditure. This is because the production of high-potency APIs is an expensive business and you have to decide whether to invest in barrier isolation technology or to use the more traditional personal protective equipment procedures. For smaller companies, how they deploy their capital is a crucial issue for success. PPE items such as suits with supplied breathing air are, of course, safe but they are cumbersome for the operator. Barrier isolation technology is better in some cases, but is more expensive.

TM: How did ASI develop its particular expertise in high-potency APIs?

SM: Ash Stevens started in business as a US Government contractor working for the National Institutes of Health, and in particular for the National Cancer Institute, so the company was involved with anti-cancer drugs from a very early stage. This experience has given us a real advantage in the high-potency APIs area. About ten years ago, we started thinking about contained processes and ways to minimise operator exposure. In fact, ASI was one of the first companies to install Walker-Carlisle glove-box filtration systems. We took a novel approach: we worked through the operating procedures using mock-up systems and using placebos and then asked our operators to advise on which procedures and designs worked best for them. This included both the design of manufacturing equipment as well as equipment cleaning procedures. The result was a smoothly operating system for manufacture of high-potency APIs.

TM: Why are fast-track approvals so important in the anti-cancer area and what is ASI's experience and expertise in this field?

SM: The Food and Drug Administration Modernization Act of 1997 provided a fast-track system which allowed rapid approval for treatments for life-threatening conditions and for treatments for unmet medical needs. A good example is Velcade, the first FDA-approved proteasome inhibitor which is used in the treatment of multiple myeloma. However for these drugs, the analytical and manufacturing processes still have to be validated as in the normal approvals procedure; the manufacturing process needs to be fully understood, and a full

development report prepared just like with a standard application. This means the same amount of work needs to be done in much shorter linear time, maybe in as little as a third of the time for a normal approval. ASI has a lot of experience in this area and has developed strong project management skills, enabling us to have multiple fast-track projects running simultaneously.

One of the methods that allows us to achieve this is the use of commercial Design of Experiments software packages in which a very large number of operational parameters such as temperature, stoichiometry, stir rates, solvent composition as well as other parameters can be analysed using statistical design methods to optimise the process quickly. What we need to do is complete the same amount of process development work as in a non-fast-track project but by working intensely in a short time period. Smaller companies like ASI can achieve this because of their flexibility and their ability to shift gears rapidly and complete multiple tasks concurrently.

TM: What are the issues related to how materials handling practices and cleaning protocols meet the requirements of health & safety legislation?

SM: There aren't any formal regulations with respect to barrier isolation technology as yet, but there are issues in that the equipment is complicated, and therefore so are the cleaning procedures. What you need to do is ensure that the cleaning procedures themselves are in place rapidly so that the equipment can be used for more than one product, as barrier isolation equipment is very costly. You need to be able to measure the cleaning efficiency. The best procedure is to develop product-specific cleaning methods and analyses, for example swabbing of the equipment for analysis. One must validate swab transfer efficiencies, and we try to use HPLC retention times to determine the presence or absence of material. Tests need to be specific, for example HPLC or UV analysis, not just general ones like TOC (total organic carbon). The development of appropriate cleaning procedures is just as much of an issue as chemical process development.

When working with a client we look at the toxicology data and do a hazard assessment. Operators tend to be suited up more for charging operations. For discharging operations barrier isolation technology is readily available in our plant. Small companies need to look at their capital expenditure and decide which combination of PPE and barrier isolation technology is best for their high-potency API manufacturing process, bearing in mind that environmental and safety issues are just as important as FDA drug product requirements.

TM: What outsourcing opportunities are there for European companies with US-based contractors? How have these activities developed/expanded in recent decades and how do you see these activities developing in the future?

SM: Of late there has been a big increase in business for US-based contract manufacturers because of the weakness of the dollar with respect to both the euro and the pound Sterling. Another factor is that Chinese and Indian contract manufacturers are no longer able to offer the same low prices as in the past because of the increased wages and regulatory requirements they have to meet. Another factor in our favor is working in similar time zones. There has been substantial activity from European companies seeking US partners.

TM: Are there any other technical innovations you see impacting the high-potency API sector in the near future? What are the prospects for the sector in the medium to longer term?

SM: Clever engineering in valves, materials transport, packaging, plus new high-throughput, parallel synthesis approaches to safer process development, are issues for all API manufacturers but in high-potency manufacture it's in the area of process engineering that

the major breakthroughs will be most important. Anti-cancer APIs will remain a good business to be in, provided you make the right capital investments and pay attention to details. Effective project management and development of reproducible procedures are the keys to success. For companies with staying power and a strong capital structure, it's now a good time to be in the business. I'm proud to be involved in what ASI and others in the field are doing in the high-potency, oncology drug field: using chemistry to help sick people.

Further information

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