
Best Practices for Cancer APIs

By Paul Thomas

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Ash Stevens shares information gained from years in the business, and how it will make a new CMC alliance work with various partners.

By Paul Thomas, Senior Editor

Detroit-based **Ash Stevens, Inc. (ASI)** has nearly a half-century of experience in the development and manufacture of active pharmaceutical ingredients, but it's in the area of cancer APIs where it specializes. ASI was founded in 1962 to provide chemical research to the U.S. government and has a longstanding relationship with the National Cancer Institute.

ASI also recently made the news as a key member of the fledgling Michigan CMC Alliance, a consortium of contract service providers that have banded together to leverage their collective facilities and intellectual capital.

We spoke with ASI's Jim Hamby, Director of Business Development, to get an insider's view of the challenge of making APIs for oncology products, and on the new alliance.

PhM: What are the key considerations in the developing and manufacturing APIs for cancer drugs? What are the distinct challenges from the contract provider's perspective?

J.H.: There are several important aspects unique to cancer drug development. The drugs are often targeted to unmet medical needs for life-threatening conditions so the timelines are often accelerated. That means that the same amount of work to support a successful CMC section of an NDA needs to be completed in a much shorter period of time. This mandates a very tight, flawlessly managed regulatory program.

Cancer agents also tend to be classified as "potent". In reality, this is a euphemism for toxic compounds. A developer/manufacturer therefore needs systems and proper engineering controls to ensure that those involved in the synthesis remain safe. We have a major commitment to barrier isolation systems for this purpose. These isolation systems provide the highest level of worker and environmental safety.

PhM: What is the acceptable percentage of impurity for API of small molecule cancer drugs in GMP production?

J.H.: The level of impurity is predicated on data obtained from the acute toxicology study. For early stage development, levels as high as 3% to 5% may be "qualified" based on the tox study. Even though these levels may be acceptable, FDA may question levels that high. Levels in the range of 0.5% to 1.0% are not unusual for "qualified" impurities in early stages of development.

For some impurities, for example, Residual Solvents or Heavy Metals, Guidance documents or compendial references (sp. USP) specify generally accepted levels. Higher levels can be justified, however, due to the small administered dose.

PhM: Is it necessary to analyze the identity of impurity material?

J.H.: In early phases of development, it is not necessary to identify the structure of an impurity. It is permissible to call such an impurity “Unknown A with HPLC RRT = x”. Using this nomenclature in the tox lot and subsequent GMP lots for early phases would be acceptable. The structure of all impurities greater than 0.1% should be known prior to filing an NDA.

PhM: Do different products require a separate contained facility for API synthesis, GMP batch and packaging?

J.H.: The compounds would not require separate facilities. Ash Stevens has suitable production laboratories and potent compound handling facilities for synthesis of such materials.

The facilities are designated as “multi-use” meaning they may be used for synthesis of different products ... but only one such product could be synthesized in the area at any one time.

Ash Stevens develops, and suitably validates, cleaning procedures and cleaning verification analytical methods so that the facilities may be cleaned and demonstrated to be clean after use. This is an important part of our service, where each client relies upon the other to support programs to ensure that cross-contamination is mitigated.

PhM: Tell us more about the Michigan CMC Alliance — how did it come about? Was there a model for this?

J.H.: The Alliance, an informal arrangement of people looking to support each other, was formed as large pharmaceutical companies in Michigan began to contract. This afforded smart, entrepreneurial people the opportunities to use their expertise, gained through many years working in big pharma, to start their own businesses working with emerging pharmaceutical companies to develop novel therapies.

Michigan CMC Alliance’s purpose is to support the growth and success of life science companies. The Michigan CMC Alliance provides CMC resources and expert strategies for drug development, as well as education on the complexities of the CMC development process. In so doing, the emerging company doesn’t have to build a deep bench internally, which is a costly endeavor.

PhM: What does Ash Stevens get out of the alliance?

J.H.: We have the opportunity to work with a broad group of professionals with expertise throughout the entire CMC world, not just our own area of expertise, which is API.

PhM: How will the alliance ensure seamless, consistent service to clients with so many partners involved?

J.H.: One of the most useful assets that we have is that many in the Alliance have previously worked together and have developed a good working relationship. We are also geographically close, facilitating easy face-to-face meetings and rapid communication.