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Time is of the essence in getting new drugs to market, and delays in scale-up or process development mean lost sales. So when a new drug was fast-tracked by the FDA, contract manufacturer Ash Stevens had to act equally fast

In the early 1990s, scientists in academia discovered a novel mechanism for the treatment of cancer. The lead agent from that programme was then licensed to a biotech start-up and early stage clinical trials began. The novel drug attacks cancer from several angles – inducing cell death, inhibiting the cell cycle and overcoming cell-survival pathways.

In late 1999, clinical trials demonstrated initial success and the compound entered a phase of very rapid development. In 2002, the drug was shown to be so effective that regulatory agencies were willing to allow it onto market before the completion of Phase III trials – a year ahead of the company's projected launch.

The Food and Drug Administration and Modernization Act of 1997 provided a 'Fast Track' process for the rapid approval of treatments for life-threatening conditions and unmet medical needs. For these drugs, as with a standard application, the analytical and manufacturing

processes still have to be validated and a full development report must be prepared. However, this work needs to be done in a third of the time of a normal approval.

The biggest hurdle for the sponsor company became pulling together the manufacturing component of the New Drug Application (NDA) to meet the accelerated FDA approval timeline. When the developer of the anticancer drug had to accelerate its regulatory filings and market launch timelines, it turned to Detroit-based **Ash Stevens Inc (ASI)**, a contract manufacturer with experience of handling fast tracked approvals.

ASI had been involved with the manufacture of the API at an early stage in the development process, which included manufacture of the initial batch required to perform toxicology studies. In the 1990s, when Phase I trials for the drug were initiated, ASI made the first small batches of the API.

The sponsor now charged ASI with improving the existing manufacturing process and generating enough material to support additional clinical trials and the early launch of the drug.

Ideally, the same process that was used in the early phase clinical trials should be used for the late phase clinical trial and commercial material. Alternatively, clinical trials can be delayed until a new process is developed, in which case analytical methods would be developed once the new process was defined, and trials would resume once the resulting API from the new process was available.

Neither of these options was available in the case of the anticancer API because the process had to be improved to support the larger amounts that would be needed, and delaying the clinical trials was unacceptable.

different strategy

To meet the aggressive timelines and continue to supply ongoing clinical trials, ASI adopted a different development strategy. Material for ongoing clinical trials was prepared using the old process, while a new, more efficient process was developed concurrently with new analytical methodology, significantly reducing the project timeline.

According to Vince Ammoscato, vice president of operations at ASI, the company's biggest achievement was to reduce the process cycle times while continuing to use kilo lab equipment. 'What used to take eight to 10 weeks, we could now do in four weeks, producing significantly more material (API) with improved solid state characteristics (crystalline) and higher purity,' said Ammoscato.

ASI was also able to streamline production by significantly reducing large volumes used in the process and facilitating manufacture in a kilo lab as opposed to large-scale plant equipment, thus minimising waste.

ASI began developing the new API manufacturing process in late 2001 and demonstrated the process in April 2002. The FDA accepted the NDA for the anticancer drug in early 2003 and approved the drug in four months. The drug was launched just six days after approval.

According to ASI president and ceo Stephen Munk, the company was able to cut the number of process steps in half, reduce the solvent volume by a factor of 100, and significantly reduce the cost of making the cytotoxic drug.

Even as the sponsor continues expanding the market for the drug by pursuing approval for additional patient populations, Munk believes that the drug process ASI developed for the drug will be able to support any batch size the market should require.

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