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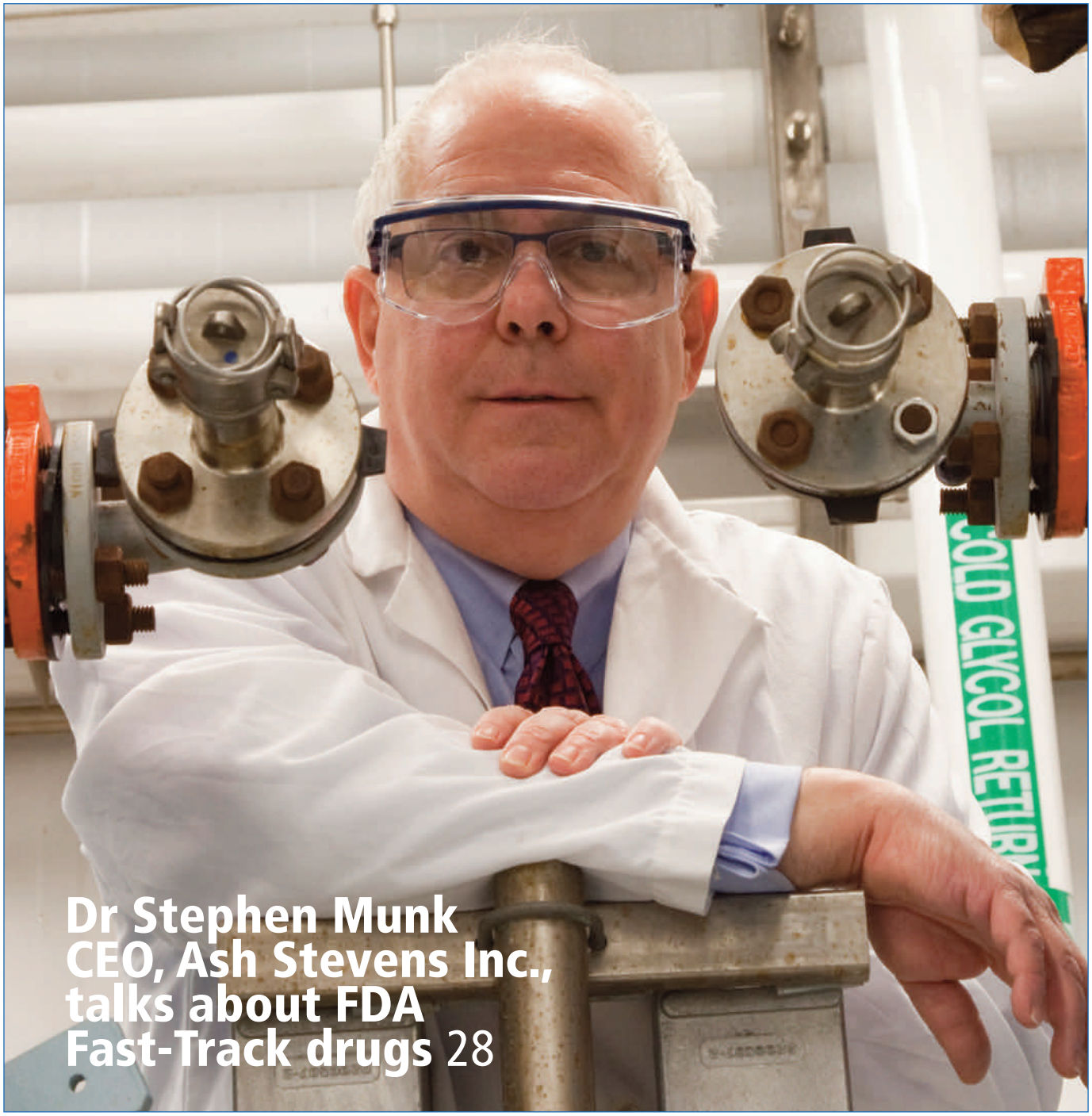

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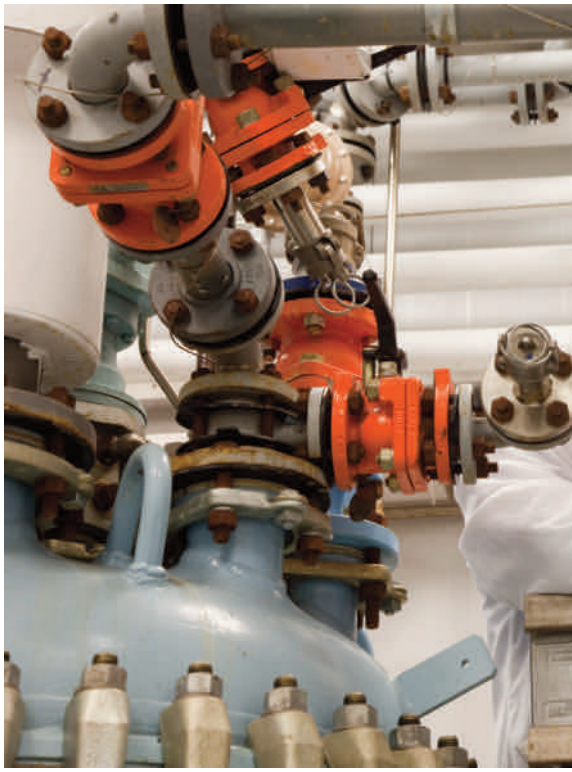
SPECIAL REPORT: INGREDIENTS

Qualities for Fast Track success

US FDA Fast Track designation is intended to expedite patients' access to promising new drugs where there exists a serious unmet medical need. **Ash Stevens** CEO, Dr Stephen Munk, discusses the strategies and tactics contract manufacturers require to meet the accelerated timelines for Fast Track projects



The pathway to regulatory approval of a new chemical entity can be extensive, taking as long as 15 years to reach the market from the initial compound discovery. In an effort to get promising new drugs to patients who desperately need them, the US FDA has put in place certain programmes to expedite the process for new drugs intended to treat serious unmet medical needs with life-threatening consequences. These fast-paced programmes require the sponsor company and its outsourcing partners to work seamlessly in unison to achieve the maximum time-saving benefits. In addition, longer development times mean higher development costs and reduced time for marketing under patent protection, which also contributes to higher overall costs to patients.

The FDA has four programmes in place designed to speed the approval of drugs that meet certain criteria while maintaining their safety and effectiveness – Fast Track, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review processes.

Drugs that treat serious or life-threatening conditions and also fulfill an unmet medical need can receive Fast Track status and accelerated approval, while those that provide a substantial improvement over available drugs on the market are considered to be break-through therapies. Priority review status is granted to drugs that have both improved safety and effectiveness compared with existing therapies and this means that the FDA will make its determination within a shorter time period (generally six months).

Fast Track designation for a new therapy must be requested by the sponsor organisation. Information demonstrating that the drug is an improvement over an existing treatment (superior effectiveness, reduced side-effects) or is the first treatment for a life-threatening disease must be provided. It is recommended that requests for Fast Track designation be submitted with the pre-investigational new drug (IND) application and at the very latest by the end of the phase II meeting with the FDA. During the early development stage, supporting evidence that the drug meets an unmet medical need can take the form of activity data in a nonclinical model, a mechanistic rationale and/or pharmacologic data. During later development stages, clinical data is required.

Companies that receive Fast Track designation for a drug candidate communicate more extensively with the FDA, with both more frequent meetings and written exchanges to ensure that the drug development programme and data collection are proceeding appropriately. In addition, Accelerated Approval and Priority Review may also be applicable for drugs with Fast Track status.

Furthermore, rather than needing to submit the entire New Drug Application (NDA) at once, a company with a Fast Track drug can submit individual sections for review – a 'rolling review'. In many cases, the Chemistry and Manufacturing Controls (CMC) section is submitted first, followed later by the Clinical section. In some cases, the FDA will also accept sections with preliminary data; additional data is provided as developed which can reduce review times.

Frequent communication with FDA, particularly during early development stages (the IND stage through phase I) is a key component of the Fast Track programme; when questions and issues about the design of clinical studies are resolved quickly, the time for approval is often reduced significantly – often to six months or even less.

To leverage Fast Track status for a drug candidate, pharma companies must have excellent communication systems and be prepared to develop and validate manufacturing processes and analytical methods while generating safety and efficacy data in far less time than is typically allotted. As the trend to outsource much of the drug development and manufacturing process continues to expand, pharma companies must rely on service providers with experience of handling Fast Track projects, working with the FDA, and the capability to meet vastly accelerated timelines.

First, it is imperative that contract manufacturing organisations (CMOs) working on Fast Track projects not only are aware of the shortened development times (by as much as a factor of three), but also have established lines of communication with the sponsor company. Project management is critical. There are many interdependent tasks along the critical path and effective, organised management of those tasks will ensure a successful outcome.

Communication with FDA regulators is

Stephen Munk, CEO of Ash Stevens

also vital and CMOs should be prepared for the additional meetings and information exchanges that are so important to reducing approval times.

Second, because both regulatory filing and market launch timelines are reduced for Fast Track drugs, CMOs must be capable of rapid process scale-up. In general, it is desirable to scale up the synthetic route used for the production of pre-clinical/toxicity testing quantities to avoid any delay in the initiation of clinical trials through the introduction of unqualified impurities. This involves optimising reaction concentrations, reaction times and temperatures, as well as reagent load. The basic synthetic strategy will generally remain unchanged but this is predicated on the scalability and safety of the early chemistry.

It is therefore important to improve the efficiency of the laboratory synthetic strategy as much as possible with respect to process cycle times, waste minimisation and yield. Increasing the productivity of kilo-scale processes for clinical trial material through the reduction of cycle-time is an important factor for accelerating the development of a Fast Track drug.

But even with such improvements, initial laboratory processes are generally not suited to large-scale or commercial production. An effective strategy for overcoming this is to produce material for clinical trials using the laboratory process while developing and validating simultaneously an efficient and cost-effective large-scale process. The scaled process should have an equivalent or better impurity profile and use improved associated analytical techniques. This approach can significantly reduce project timelines while ensuring the quality and safety of the API.

This raises the third key capability required for CMOs involved in Fast Track drug development and manufacture. Because the timelines are reduced, clinical trials involve fewer patients and the quantity (number of batches) of manufactured material subjected to testing is less than that for a compound on a more traditional development path; there is generally less information about how the process can potentially impact product API quality, which can present challenges when it comes to qualification of process performance. The team cannot regroup and repeat work due to the compressed timeline – all tasks must be completed successfully the first time through.

The CMO must be aware of this issue and work closely with the drug sponsor and FDA to identify and mitigate any potential issues before they arise. It is also very important to have experience with the development of comparability data, ensuring batch-to-batch consistency that can be used to relate initial analytical data to the data obtained using validated methods developed for process performance qualification and specification determination.

Here, the use of a quality-by-design (QbD) approach and early determination of critical quality attributes (CQAs) can help ensure that analytical methods developed under accelerated timelines still allow for the demonstration of process and product control. A QbD approach involves an integrated team to design and execute a statistically valid set of parametric studies around critical quality process parameters (CPPs; times, temperatures, reaction and reagent concentrations and related process parameters). A key member of such a team is a person formally versed in statistics, complementing traditional chemical and engineering skills.

It should also be noted that because so many activities must be completed (process, analytical and cleaning method development and validation, preparation of reference standards and impurity samples, specification setting, stability and microbiological testing, and related activities) in such a short time, it is often necessary for a pharmaceutical company to work with multiple service providers.

The use of a CMO with integrated capabilities across development through commercial manufacturing and an established network of other providers to supplement specialised capabilities can reduce the complexity of the project management needs and contribute to more compact development timelines.

Excellent project management skills are the fourth criterion that CMOs must meet if they are to be successful with Fast Track projects. Project management is critical as there are many tasks within a CMO that must be co-ordinated. If patients are to be enrolled in a study, the drug must be ready on that given date; they cannot be left waiting for delivery dates that a supplier missed.

A CMO preparing the API requires that process chemistry, engineering and manufacturing support, analytical chemistry, quality assurance, and regulatory affairs understand the timeline and where each set of tasks fits in that timeline. The project manager's mission is to ensure that each functional area is prepared for and meets its deliverables. Progress along the timeline must be clearly communicated to the sponsor.

A reliable partner

Finding a CMO that can meet all of the criteria outlined in this article can be a real challenge. To date, Ash Stevens has received 12 FDA and/or EU manufacturing approvals for innovator APIs, including four Fast Track manufacturing approvals for the active ingredients in the oncology drugs Velcade, Vidaza, Clolar and Iclusig.

Ash Stevens continues to invest in state-of-the-art development and manufacturing technology as well as outstanding training programmes to maintain a leadership position in the industry.

The organisation has a proven approach to project management and the necessary communication skills to support a successful NDA. Ash Stevens was the winner of a 2014 Lilly Global Supplier Award.

BIBLIOGRAPHY

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf
2. Drug Substance; Chemistry, Manufacturing, and Controls Information, Draft Guidance US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER); January 2004.
3. ICH Guidance Documents http://www.ich.org/cache/compo/276-254-1.html. (GMP requirements are specifically covered Q7A: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients).
4. Anderson, N.G. Practical Process Research and Development Academic Press: New York, 2000.