

More than Filling.



Vetter White Paper Edition

Five keys to reducing time-to-market

Vetter Pharma International GmbH

Introduction

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With development times measured in years, increasing costs represent a major challenge confronting pharmaceutical and biotechnology companies. As a result, reducing time-to-market is an essential component in any business strategy, particularly when the end of patent protection is considered. One solution is to partner with a contract manufacturer that provides intelligent concepts and the proper experience, not only with respect to the production itself, but also with regulatory authorities. Planning early on is crucial to speeding up the time-to-market process.

Five keys to reducing time-to-market



According to Benjamin Franklin's famous quote in *Poor Richard's Almanac*, "Time is money". The American hero of the revolution, scientist and sage illustrated his point with an example involving ten shillings and six pence. Had Franklin been writing about today's pharmaceutical industry, he might have been tempted to underscore his advice to do justice to the substantial sums involved – up to \$ 1 million daily in the later stages of developing a new drug.

The time involved can also be significant. As many as twelve years can elapse between a discovery that seems to have therapeutic value and the approval of the new drug. The processes of discovery, development, testing, manufacturing and securing approval are demanding and require close cooperation among experienced partners.

Franklin's advice also speaks of the money lost when time is not used most effectively. Time is doubly important for drug development. Not only are the costs of testing and approval great, the entire economic profile of a potential drug also depends on time. Patents enable companies to recoup the costs of discovery and development, but the duration of a patent is limited; once it expires, the original manufacturer must compete with companies that have not had to pay for the costs of bringing a compound to market. Thus the incentives to have the longest possible period of patent protection

are strong. The best way to lengthen that period is to move through the development and regulatory approval process – particularly the production and packaging processes – with the efficiency and speed that comes from working with an experienced manufacturing partner.

Among its many benefits, outsourcing drug development and production offers ways to significantly reduce the time required to bring a new product to market. An expert manufacturer should excel in five key areas, all of which play important roles in shortening time-to-market.

1. It should provide a full spectrum of services, from pre-project consultation to packaging, as this offers the best opportunities to speed up the entire process.
2. It should have the experience needed to plan and implement a project quickly; its methodological and technical competence means a much shorter learning curve.
3. It should have standardized protocols that need limited customization for each new project. This can shorten the validation process considerably and speed up the approval process with the relevant regulatory agencies.
4. It should have a positive track record with regulators. This can also make a positive contribution to the approval process and, for example, help avoid time lost in dealing with unexpected problems.
5. Finally, the expert manufacturer should have the infrastructure and capacity available in terms of both technology and personnel, especially if a request comes at short notice. Complete backup systems should also be in place to avoid potential losses.

Getting an expert manufacturer started

A manufacturer's development service provides the foundation for all of its projects. The team that completes development and clinical testing should also be involved in commercial manufacturing. This ensures that intimate knowledge of the compound and the filling process is retained when the challenges change from testing to commercial production. Continuity also avoids losing time on knowledge transfer; should any difficulties arise, those involved will know the entire history of the project. The development service and representatives of commercial manufacturing evaluate all customer inquiries. They review product specifications and manufacturing requirements as well as technical options. For example, experienced manufacturing partners can often apply a process that has already been validated, shaving off even more time-to-market. In other cases, a new process must be designed, implemented and validated. In these situations, the development service's overall experience and continuity with the project will support efficiency and a shorter time-to-market.



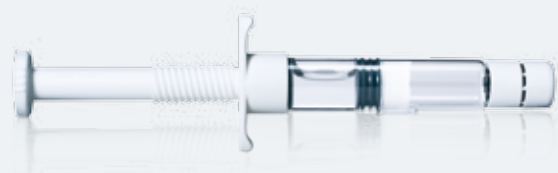
Ideally, once a project starts, a specialized manufacturing team begins to work with a team from the client. Each team has a dedicated project manager to ensure efficient communication. The two teams consult and plan intensively to determine the production process that will move the product from development to market production without significant delays. The steps in the project are defined and formulated as a checklist, including milestones to measure progress.

The primary packaging system for the compound needs to be selected at the earliest possible point in the project. An expert or specialized manufacturer should be able to offer a solution that provides the user with the greatest convenience. At the same time, the solution should be one with which the manufacturer has considerable experience, as this experience can be brought to bear in increased process efficiency. The checklist that the two companies compile at this early stage will include all the equipment that needs to be ordered in time for the commercial production phase. Thorough planning early on speeds up processes further down the line.

These three elements – intensive consulting and planning, building a unified team for development and manufacturing phases and selecting the primary packaging system – put a project on the right track from the very beginning. Time gained at the start pays off later.

The next step

The main factor in moving a project through development and testing efficiently is well-designed, integrated project management: all processes are synchronized so that they come together at the earliest possible moment. Consider the example of a lyophilized parenteral formulation, a very complex item. For this increasingly popular method of administration, Vetter has devised its own patented Vetter Lyo-Ject® dual-chamber syringe. Prefilling a plain syringe is complicated enough; in the case of lyophilized drugs, however, the Vetter Lyo-Ject® must be filled twice – once with the product to be lyophilized, and once with the solvent following the lyophilizing process. Close coordination with the developing company is required to ensure the success of this complicated process.



After selecting the primary packaging system, the development team reviews the entire filling process – the filling machine, format parts and so on – so that it can begin informing the company's own suppliers who then, in turn, can deliver the necessary parts on time. The development team also studies the compound's particular characteristics and the packing materials to make sure they are suitable in terms of light-sensitivity, filling, pumps and other parameters. Here again, the checklist and milestones developed in the planning stage keep the process on track, shortening time-to-market.



Testing feasibility

With the preliminary plans in place and a detailed process roadmap drawn up, testing and filling can begin. The first step is to perform a small-scale feasibility fill. The small-scale filling is done by hand and entirely under laboratory conditions. It constitutes a feasibility study that serves several purposes. Most importantly, it gives a quick indication of whether lyophilization is practical. Each lyophilization run, with its attendant preparation, generates a protocol that describes moisture content, reconstitution behavior, chemical stability, turbidity, appearance and mechanical stability of the lyo-cake and application functionality. These small-scale tests also determine the specifications of the product, including whether it should come in a single-dose or multi-dose packaging, what the fill volumes are and which storage conditions are necessary.



Interactions among the product, the silicon and elastomers are also examined, allowing a final decision on the primary packaging. For the initial feasibility studies, the galenic formulation candidates need to be selected. The basis for developing a safe and efficient lyo cycle is the physical-chemical data package. At this stage, the characterization of the sensitive active pharmaceutical ingredient (API) plays a role (e.g. shear sensitivity, pH-shift). One rule of thumb is that the more information the feasibility fill creates, the less time is required for adjustments during the commercial manufacture. Adjustments, changes or corrections can be performed in the laboratory much more simply than on the filling line once it has gone into operation. Some companies have specialized knowledge of very sensitive substances that can bring concrete benefits in this phase of development.

Moving from feasibility toward production

Completing the feasibility phase provides one or two galenic formulations to work with. The first milestones must be reached with care to avoid difficulties such as product stability issues that could affect the launch schedule. The lyo cycle must then be run several times, simulating large-scale conditions to fine-tune the process and determine ideal freezing, as well as primary and secondary drying conditions. Multiple runs also allow the laboratory technicians to monitor crucial factors such as freezing rates, heating ramp and radiation effects, or the impact of the pumping system. Each lyophilization run is documented and the resulting samples are stored for informal stability testing, usually at combinations of either 2–8°C, room temperature, or 40°C at 75% relative humidity.



Determining the best cycle and formulation requires approximately three months, during which time the rest of the team is working out the best approaches to scaling up the production process. The production equipment must be procured and set up. Specification

and qualification factors must be met, and the cleaning process must be validated. Raw materials and packaging materials must be selected, ordered and prepared. To ensure final success, backup supplies must be in place. An expert manufacturer should bring experience and organization to these activities, and coordinate carefully with the discovery and development company.

Whether the results of the feasibility study are applicable to bulk filling must also be tested and validated prior to commercial manufacturing. To scale up successfully, a number of steps have to be carefully evaluated and calibrated: the thawing procedure of the bulk product, for example, and the definition of bulk handling and mixing properties. Filtration is another important aspect that requires expert knowledge. What kind of tubing will be used? What is the right tubing diameter? What is the maximum filtration pressure allowed? Experience in answering these questions makes the process efficient. The filling profile is then checked against the type of pumping system and aseptic handling. Once all of these elements are in place, the lyo cycle can be tested by performing different runs on the minimum and maximum scales – including extensive moisture mapping to verify homogeneity throughout the batch. At this stage of development, the actual filling equipment will have been installed and will be ready for testing on the batches used in scaling up the processes. Once again, the initial planning pays off as tasks that had been running in parallel converge at later stages of development.



Final testing and initial manufacturing

Production of clinical batches begins as soon as scale-up success has been confirmed. To generate precise indicators for the master batch record, a minimum of three batches must be run, using a minimum of 10% of the future commercial batch size. These batches can be used for registration purposes. The critical factors in determining their success are good manufacturing practices (GMPs), which are indispensable, the possibility of human use, which must always be borne in mind, and release of the batches by quality control and the qualified person. The runs testing the process' scaling up produce material for stability batches, which can also be used for clinical studies once the stability tests have produced positive results.

In the aseptic filling process, each step in a project is geared towards greater safety and speed in the final stages. Prior to commercially manufacturing the drug, however, a detailed risk analysis must be performed for all steps of the process, followed by validation, which must be conducted on at least one full batch for the European and US markets. All critical parameters are examined and tested. These include holding times, mixing properties and full-day production (robust processing). Simulating worst-case conditions is one way to cover all of these base values. Another is to validate an optional minimum and maximum batch size to build flexibility into the commercial production process. Validation also extends to various shipping aspects, including the container, the packaging and the means of transportation. These tests and evaluations produce a validation protocol and report that are used for all future commercial batches. The customer, with support from their expert partner, submits these documents to the regulatory authorities. If the batches still have sufficient shelf life, they can also be used for the product's market launch. The end of the validation process signals the beginning of commercial manufacturing. In our experience, these steps can be optimized, allowing them to run in an efficient sequence.



Minimizing time-to-market

One of the most effective areas for reducing time-to-market for a new pharmaceutical compound is packaging and all of the elements surrounding it. The processes involved in this phase are precisely planned, and valuable time can be saved. Working with an expert manufacturer that has the know-how, expertise, and infrastructure to implement the project efficiently can lead to significant gains for a drug development company. Experienced teams, integrated process management and active communication between all units and team members are crucial. Most important, however, is careful planning in the earliest stages to ensure that all steps in the process are choreographed to save as much time as possible. An excellent track record with regulatory agencies such as the FDA, EMA and others means that companies can rely on the manufacturer's experience in maintaining the requested cGMP status and navigating approval channels. The combination of detailed technical knowledge, close coordination with project partners and deep understanding of materials enables a good specialized manufacturer to help its partners improve efficiency throughout the development process, ultimately shortening the time it takes to bring a new product to market and improving the opportunities for sales.

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