VETTER

VETTER CASE STUDY

SPEEDING UP TIME-TO-MARKET

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By leveraging its expertise and precise planning capabilities, Vetter helps a client erase months from the development of packaging processes.

THE MARKET

In the hyper-competitive pharmaceuticals and biotechnology markets, companies face a litany of challenges, from stricter regulatory guidelines and rising development costs to the pressures of globalization. To succeed under these conditions, pharmaceuticals and biotech firms are finding it critical to reduce their time-to-market, thus creating competitive advantage and maximizing near-term sales.

Unfortunately, the actual time required to develop a new product is not easy to shorten. Sometimes, however, firms can streamline the product transfer phase of development, speeding the time to commercial production. Both experience and expertise are critical in developing the correct methodology, which allows for significant reduction of development time while maintaining product quality.

THE TASK

A newly developed monoclonal antibody drug was created for the U.S. market. This drug was designed for patients of various ages who had physical disabilities, and it had to be administered subcutaneously.

The biotech manufacturer of the antibody sought an outside supplier with extensive know-how in developing a commercial manufacturing process and then packaging the drug. The company contacted Vetter, the world market leader in the aseptic filling of liquid and lyophilized drugs. Vetter was chosen for its broad-based experience in bridging the phase between formulation and filling, the aseptic filling itself and the packaging of sensitive and highly complex active substances.

The customer requested that the new drug be filled in a conventional syringe. At a later date, a more patient-friendly auto-injector would be used, since the drug was aimed at the home care segment. In addition, the biotech company required that the concentration of the active substance be between 80 and 100 mg/ml, and the planned filling volume between 0.1 and 0.2 ml.

THE CHALLENGE

At the time the biotech firm contacted Vetter, the drug (API) was in phase III of clinical development. Formulation studies, as well as comprehensive incompatibility studies and tests, had already been carried out by the biotech firm. These tests revealed that the API was sensitive to silicone and had a shelf life of at least 18 months.

The API's silicone sensitivity created challenges in both the primary packaging and manufacturing processes. Particular attention had to be paid to the desired filling volume as well, which demanded the highest precision and reproducibility.

In addition, the customer's timeline for the product launch was tight. Vetter agreed to a 15-month timeline, from kick-off to submission of the application dossier. This was much faster than the usual timeline

for development of a manufacturing process for a liquid formulation, which typically runs between 18 and 24 months.

THE IMPLEMENTATION

Project start-up (1 month)

Vetter undertook a precise planning process to ensure adherence to tight deadlines:

- A project structure and timeline were created and synchronized with the available budget
- The project was organized into several phases: project start-up, development, validation and hand-over to commercial production
- Both the customer and Vetter established project teams
- Joint communication structures were put into place, including regular telephone conferences and team meetings
- Project managers on both sides were nominated as coordinators and main contact persons for the overall process
- The team identified critical steps in the project, such as equipment procurement times, the transfer of analytical methods, and stability tests; defining these junctures early on headed off potential problems later in the process

The Vetter team included representatives from all key departments, including process development and implementation, analytical chemistry development services, packaging material development, production and quality assurance. Additional experts were introduced during specific project phases.

Feasibility studies (3 months)

Once the initial planning phase was completed, Vetter Development Service (VDS) began the development process in conjunction with the biotech firm. The parameters of manufacturing and the specifications of the packaging system were defined under laboratory conditions, using standardized and product-specific analyses. The results were all noted in a development protocol.

Key studies undertaken to develop ideal processes included:

- Compounding/mixing studies
- Compatibility study with different systems and qualities, e.g. syringe type, siliconization, stopper material, etc.
- Determination of break-loose and glide forces
- Short informal (accelerated) stability
- Filtration trails
- Assessment of various fill pump systems on shear stress sensitivity
- Determination of fill accuracy
- Visual inspection (appearance, color, clarity) to check for particulate matter formation

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» Functionality of different filled PPM systems in different types of auto-injectors

Based on past experience, Vetter experts provided access to a wide selection of processed systems and packaging components for the studies. Thus, Vetter could avoid time-consuming processes such as ordering, washing, siliconizing and sterilizing materials, saving up to several months. In addition, Vetter's laboratory already was geared specifically for commercial filling. Because its laboratory equipment and processes mimic those in Vetter's manufacturing plant, laboratory results could be directly transferred to the filling lines.

Based on studies by VDS, key compounding and fill parameters were determined for the API in conjunction with the biotech firm:

» Feasibility of liquid formulation at 100 mg/ml and 0.1 ml fill volume

» Generation of compounding protocol with optimal mixing, hold times and min/max compounding volumes

» Choice of 1 ml-long staked needle syringe as primary packing system, resulting in fewer handling steps for patients

» Choice of Teflon-coated stopper to allow drug compatibility

» Spray siliconization with 1000 cSt silicone oil for compatibility with the product and stable BLEF (break loose forces and glide forces)

» Peristaltic pump for minimal shear stress and optimal fill

» Accuracy

» Washed, siliconized and filled syringes to be inserted based on customer preference

Transfer to commercial filling (3 months)

Thanks to the results and experience gained in the lab, Process Development Specifications (PDS) were quickly drawn up and approved by the biotech firm. Vetter created documentation to display the complete filling process. Based on the PDS, Master Batch Records (MBRs) were generated. For additional efficiency, MBRs were set up in a modular fashion. Standard Vetter processes such as visual inspection could be described using standard templates. Only customer-specific processes had to be created from scratch, speeding the entire process along.

While documents were drawn up, production equipment was procured and installed in parallel. The customer transferred in raw materials, while Vetter ordered packaging materials as agreed.

Engineering batches (2 months)

Engineering batches then were used for test fillings in real-time conditions directly on the commercial filling line. These engineering runs were used for detailed evaluations of the various steps in the process. All critical parameters were con-

firmed at this time, including mixing features, hold time, fill volume and stopper position. This eased the validation process, as well as avoided wasted time and materials during validation.

Technical parameters were first tested with a placebo buffer. The final procedure then was carried out with the API. To save time, the syringes filled in this step were used for marketing studies, transport validation and informal stability studies.

In addition, Vetter conducted a risk analysis to prove the robustness of individual manufacturing steps. The compounding and fill process were deemed mature enough to progress into the validation phase. Media fills for the packaging format were in place, and production staff had been trained by the VDS team to handle the product and process.

Transfer to commercial production (2 months)

Vetter's manufacturing facility and production line already had been approved by the U.S. Food and Drug Administration. Therefore, for the API in this case, the validation phase was limited to product-specific parameters.

To provide robust data for the validation report, three representative batches of at least 10 percent of the future commercial batch size had to be filled. Vetter's VDS team worked closely with the production team throughout the entire production development phase. This cut back on the time needed for knowledge transfer. The validation batches were used for registration and as stability batches, saving up to a year of development time.

Preparing for approval (6 months)

Vetter leveraged its extensive regulatory expertise to allow quick approval for the API:

- Experience preparing for approvals worldwide
- Support in drawing up submission documents
- Creation of dossier sections required for approval (EU/US-CTD Module 3, Drug Product Section)
- Expertise presenting both product-specific and non-product-specific data, including the technical writing and grade of detail to allow a smooth review process and to avoid questions
- Experience with GMP inspections and pre-approval inspections of various authorities worldwide
- An excellent audit history with a large number of agencies, including the Gulf Central Committee, as well as the authorities in Canada, Russia, Brazil and Mexico; Vetter also has received more than 25 successful FDA approvals for client products

This experience made this phase of the process shorter than originally estimated.

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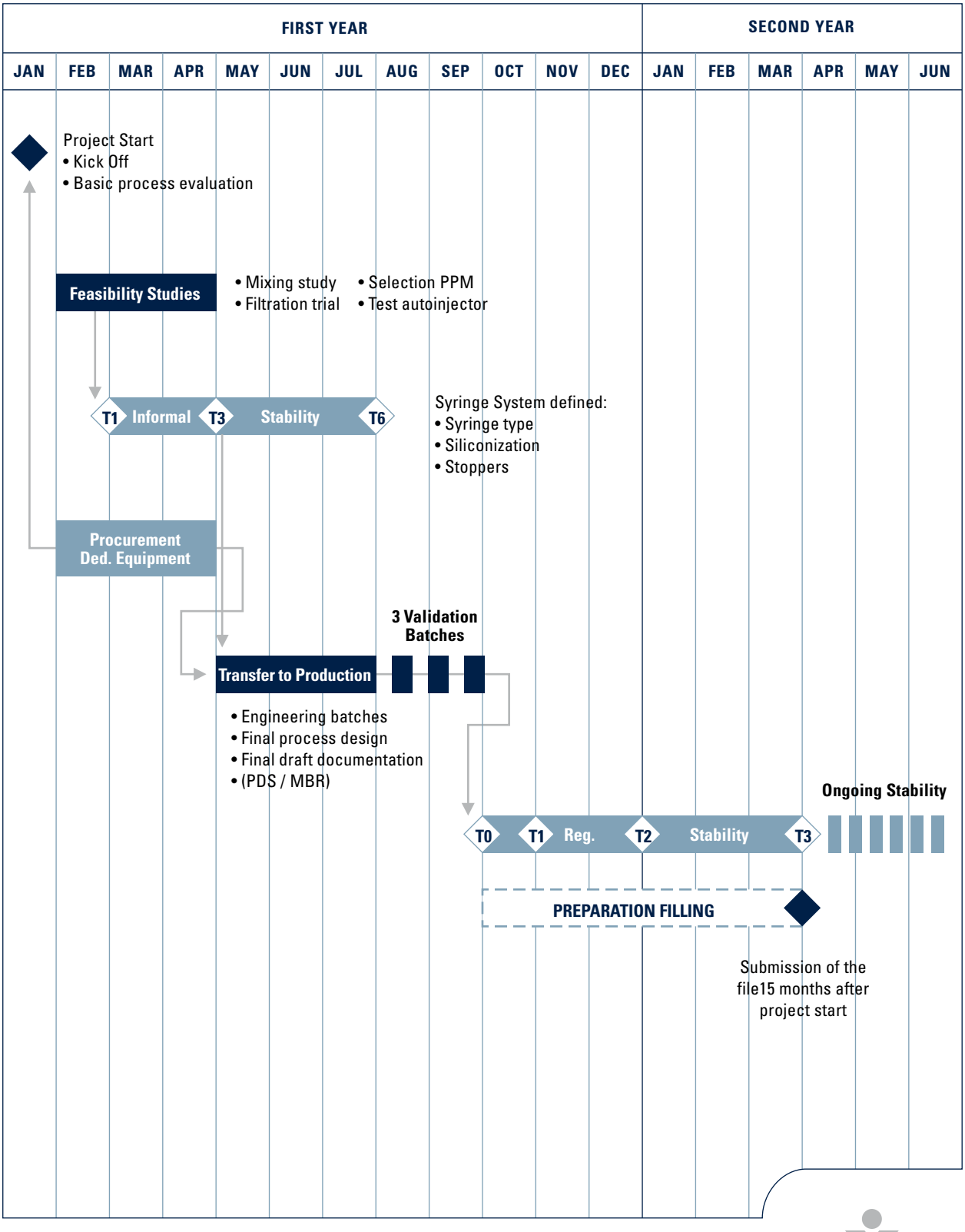
CONCLUSION: THE KEYS TO SUCCESS

Thanks to Vetter's expertise, carefully planned processes and close collaboration with the biotech firm, Vetter and its customer were able to considerably shorten the API's time-to-market. What usually takes between 18 and 24 months was accomplished in just 12 months. Several strategies contributed to this success:

- Assigning a project manager at both Vetter and the biotech firm
- Developing a precise project plan at the outset, including identification of critical steps within the project
- Leveraging the same project team for the entire process
- Including key commercial departments, such as production and regulatory affairs, on the project team
- Relying on project team members with wide experience in various packaging systems, handling and manufacturing sensitive biologics and fill processes
- Creating clear communication channels
- Leveraging Vetter's access to a wide selection of processed systems and packaging components
- Speeding up development time by using highly flexible laboratory procedures
- Relying on laboratory procedures that are designed to provide an easy transfer to commercial manufacturing, thanks to comparable processes in commercial manufacturing
- Leveraging standardized development documentation (e.g. PDS, risk analysis)
- Providing early and controlled transfer to the commercial production line
- Leveraging Vetter's experience with regulatory authorities

OVERALL TIMELINE



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