Capturing Lightning In A Bottle

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MannKind’s inhalable insulin product and delivery system changes the future of diabetes therapy

The development and commercialization of novel pharmaceutical products sometimes requires innovative processes and equipment. Such is the case for MannKind Corporation and Afrezza™, an inhalable insulin product based on the company’s Technosphere® particle technology. Afrezza is a dry powder formulation packaged in unit dose cartridges administered to patients using a reusable, breath-powered inhaler that fits into the palm of a patient’s hand. Clinical studies demonstrated that Afrezza more closely mimics the body’s natural insulin response than any other insulin product.

Afrezza’s unique formulation and drug delivery system presented a development challenge that required novel manufacturing processes which, in turn, required novel processing equipment. To prepare for commercialization, MannKind designed and built an Afrezza manufacturing facility that included adapting, and even creating, multiple pieces of processing equipment like a specialty reactor, a cryopelletizer, a powder transport system, and a cartridge filler.

The manufacturing facility comprises approximately 23,400 m² of floor space and was completed in 2008, less than 2 years after groundbreaking. The facility was built to produce Afrezza, but retains flexibility to manufacture the various products progressing through the MannKind product pipeline. MannKind’s decision to build the new plant at its existing development and operations facility in Danbury, CT was based on the belief that personnel continuity is critical for reducing both project time and expense. By building the manufacturing facility in Danbury, MannKind engaged the same employees from the earliest stages of design, through construction, and into operation. Additionally, expanding the existing facility into a neighboring abandoned manufacturing space yielded substantial cost savings over the development of a green-field site.

The design and construction of this technically advanced plant has resulted in the facility being awarded both the Equipment Innovation and Process Innovation awards in the annual Facility of the Year Awards (FOYA) program. The FOYA program, sponsored by ISPE, INTERPHEX and Pharmaceutical Processing magazine, is designed to honor and recognize pharmaceutical manufacturing plants and the teams behind their design, construction and operation.

**New Equipment Design Technology**

Afrezza powder is characterized by low density and lack of flowability, so it was necessary to design new process technology for its production and packaging. Commercial scale-up of existing laboratory equipment and techniques was not cost-effective, and the Afrezza cartridges were
incompatible with existing powder filling technology. To address these challenges, innovative solutions based on building new technology and modifying existing technology were developed.

Vessel used for adsorbing insulin onto Technosphere Particles

Process Overview

Afrezza manufacture begins with the production of a Technosphere® particle suspension that is washed and concentrated using tangential flow filtration. Subsequent insulin addition gives a
Technosphere® Insulin suspension that is flash frozen into pellets that are lyophilized (freeze-dried) to remove water. The resultant Afrezza powder is then filled/packaged into single dose disposable high density polyethylene cartridges.

*Tanks for tangential flow diafiltration*

**Specialty Reactor**

Technosphere® particles are formed in an acid induced precipitation reaction under very specific conditions of mixing time, pH, and temperature. Though these requirements may seem unremarkable, it was a particular challenge to design a reactor that could fulfill all of them. For example, during mixing, the flow rates of two convergent streams required control to a defined ratio while initiating both streams simultaneously and attaining the desired flow ratio immediately. Additionally, reactor operation over a range of flow rates while maintaining the critical stream ratios was needed. A reactor that met these needs was designed and constructed by a cross-functional team of process development engineers, design engineers, automation engineers, equipment suppliers (pump, mixer, and heat exchanger), and the process skid vendor. The resultant reactor is remarkably efficient and it takes only milliseconds to form a Technosphere particle in the homogenizer. The reactor also allows the use of process analytical technology (PAT) in the form of an in-line Lasentec FBRM (focused beam reflectance measurement) system that provides in-process control.
After Technosphere particle formation, insulin is adsorbed onto the particles to form Technosphere Insulin in suspension. The suspension is flash-frozen and then lyophilized to obtain the dry Afrezza powder. Simple quiescent freezing of the bulk suspension would result in powder agglomeration and inefficient drying and/or meltback. To avoid these issues, a new method of flash-freezing was developed and a new piece of equipment, a cryopelletizer was required. In the cryopelletizer, the TI suspension is flash frozen into small pellets (ice cubes containing Technosphere Insulin particles) that are sized appropriately for efficient lyophilization. In the laboratory, cryopelletization can be accomplished by dripping the product suspension into a pool of liquid nitrogen to form frozen pellets. Although this method produces good product on a small scale, the technique is not commercially viable. Commercial-scale production required the application and modification of equipment previously used only in the food processing industry. Similar to the laboratory technique, the commercial cryopelletizer uses liquid nitrogen to flash-freeze the product suspension, but rather than dropping or spraying the suspension into a pool of liquid nitrogen, it’s metered into a liquid nitrogen stream. Internal components in the machine separate the frozen pellets from the nitrogen, recirculate the liquid nitrogen, and add make-up nitrogen as needed. The formed pellets are loaded into chilled trays and delivered into the freeze dryer eliminating storage and transportation equipment for the frozen pellets. These pioneering efforts in cryopelletization and bulk lyophilization offer significant reductions in processing time and cost, and provide consistent pellet size. This large-scale cryopelletizer application is unique in the pharmaceutical industry.
Cryogranulator used to form Technosphere Insulin pellets prior to lyophilization

Cartridge Filler

Filling Afrezza powder into unit dose cartridges required equipment capable of dispensing 3-10 milligrams of low density, non-flowing dry powder both accurately and at high speed. These characteristics and requirements combined, presented significant challenges. For example, the powder's low density and lack of flowability dictated a specialized geometry for the hoppers feeding the fillers. The fill weight for each cartridge was orders of magnitude less than that found in traditional capsules. Filling must be conducted under low bio-burden and ISO 7 conditions and the two-part cartridge needed a specific orientation to receive powder. A cartridge filling machine was designed to meet these needs of the Afrezza powder.

Commitment To A Vision

MannKind is committed to communication and teamwork across the corporation. From earliest conception through qualification, goals and challenges were identified, and solutions were implemented. This approach allowed the design and construction of a facility to manufacture high-quality, novel insulin treatments for the millions of patients with diabetes. MannKind's decision to invest in bricks and mortar was based on the need for a facility that could accommodate a novel process while maintaining manufacturing and financial control.

Project Management

At the core of the project's success lay a series of collective management techniques and tools, covering everything from communication streams, to collaborative schedules, to effective contracting schemes, to documentation methods. Working with a small, fully-empowered team
allowed MannKind to respond rapidly to unexpected challenges. A house-designed system of distributed management ensured that individual employees’ talents and skills were leveraged appropriately. Employees felt individually connected to the process, personally valued, highly empowered, and maximally effective. A pervasive corporate culture of accountability and openness ensured that employees managed their responsibilities well and communicated any problems to their supervisors before they could become mistakes.

Communication Streams

Throughout the project, MannKind employed both circular and lateral communication streams to ensure that all participants had immediate access to relevant information. The circular stream was designed to keep upper management in communication with workers in the field and vice versa, and lateral streams were employed to facilitate communication amongst and between contractors, engineers, scientists, and managers at all levels. Utilizing the best technique for each project area and participant allowed MannKind to maintain information security, eliminate redundancy and costly communication errors, and complete the facility significantly ahead of schedule and under budget.

Conclusion

Afrezza production required the novel application of cross-sector technologies to meet specific product requirements including Technosphere® particle formation, Afrezza croypellitization, and cartridge filling. The new processing capabilities that were developed for Afrezza have the potential for use across the pharmaceutical industry. For example, MannKind’s cryopelletization technology may be applicable to the production of hundreds of drugs worldwide that require bulk lyophilization for manufacture. Overall, Afrezza manufacture is possible due to innovations in both equipment and processing that successfully meet the challenges presented by the first insulin product with the potential to change diabetes therapy.