Case study
Drug product

Scale-up and site transfer of a semi-solid product for commercial launch

A company was seeking the expertise and technological capabilities of a CDMO partner to transfer and scale up the production of an existing ointment.

This case presented critical challenges related to technology and site transfer that spanned development, process engineering, analytics, and quality control. Scale-up challenges included both those common to tech transfer and those unique to the production of semi-solid products. Cambrex provided the necessary experience, skill sets, and technology to perform the in vitro release testing needed to show bioequivalence and to meet US FDA guidance for Scale-Up and Postapproval Changes (SUPAC). Together with the essential product and process development work, having access to Cambrex's advanced equipment and methods for scaling up a high-quality, high-performance semi-solid dosage form allowed the company to avoid the potential knowledge gap that can cost time and money during the transfer of a topical product to a new manufacturing site.

Technology on the move

In this case, the technology transfer involved an FDA-approved prescription ointment that needed to be manufactured at commercial scale. The customer wanted to produce its product in both 45g tubes and 2g sample packets, requiring scale-up of production to 900kg batches.

Tech transfer of an existing product requires going back to the development stage to characterize critical product attributes and define the process design space for small-scale production, analytical testing, scale-up, and, importantly, quality control and risk management across the entire workflow. Cambrex offers the experience and expertise to provide all of the elements essential for the successful tech and site transfer of an existing product.

"Small details can have a big impact on the end result," says Maryse Laliberte, General Manager at Cambrex's Québec facility. "This is especially true with semi-solid dosage forms, for which the sensory component is critical. Creams, ointments, gels, and pastes should be smooth, non-gritty, and non-greasy and have a pleasant feel and smell."

Companies that partner with Cambrex benefit from the cost and time savings realized with a one-stop-shopping approach that combines all the technology, equipment, and scientific and engineering expertise needed to manufacture a high quality product with a diversity of active pharmaceutical ingredients (APIs) or nonprescription substances in a semi-solid dosage form at a broad range of scales.

Overview

A company wanted to transfer and scale up the manufacturing of a dermatological ointment with the help of a CDMO partner. Cambrex performed all of the necessary development work to demonstrate physicochemical similarity and bioequivalence, and all of the process design, scale-up, and analytical testing needed for cost-efficient manufacturing and packaging of product.

Challenge

Any changes to the equipment and processes used to produce a prescription or non-prescription semi-solid dosage form may affect the physicochemical characteristics, bioavailability and sensory qualities of the final product.

Solution

Cambrex provided the expertise and technology from development through scale-up and manufacturing that was needed to perform the formulation, engineering, analytical testing, and validation work critical for successful site transfer.

Results

Cambrex successfully demonstrated the similarity of the existing and new drug products using a variety of analytical methods, including in vitro release testing to show bioequivalence. Cambrex produced the ointment in 900kg quantities, packaging it in 45g tubes and 2g sample packets.

Demonstrating equivalence

During development, it is critical to demonstrate both qualitative and quantitative equivalence between the new and existing products. Classification of product similarity comprises three classes:

- **Q1 =** products have the same components
- **Q2 =** products have the same components in the same concentrations
- **Q3 =** products have the same components in the same concentrations with the same arrangement of matter (microstructure) and the same permeability rate

Whereas testing to satisfy Q1 and Q2, showing that the new drug has equivalent physicochemical characteristics, may be relatively straightforward, demonstrating the bioequivalence required for Q3 can be quite challenging for complex semi-solid dosage forms. For a prescription dermatological drug, in vitro release testing methods (IVRT) used for Q3 characterization may be sufficient to replace the need for repeat clinical studies.

Cambrex can develop and validate IVRT on product development batches to demonstrate the equivalent release profile and bioavailability of new and existing formulations. IVRT is performed using a diffusion cell system comprised of Franz cells and a synthetic membrane designed to simulate the permeability across actual skin at normal body temperature. As stated in the FDA's SUPAC guidance for nonsterile semisolid dosage forms (http://www.fda.gov/cder/guidance.html), "In most cases, in vitro release rate is a useful test to assess product sameness between prechange and postchange products."

Mixing it up

TScale-up of a semi-solid product introduces numerous challenges, mainly related to mixing and creating a uniform, homogeneous material. The product must have the correct viscosity and the desired sensory qualities. The use of different equipment can have a major impact on the final product.

"When you transfer a customer's existing product from another site, it is very difficult to achieve the exact same texture, viscosity, and homogeneity, for example," says Ms. Laliberte. "Changing even a single piece of equipment in the production process can lead to quite a different final result. A thorough understanding of the product characteristics and the complexity around semi-solid dosage forms can help reduce the risk during a tech transfer."

State-of-the-art milling and mixing technology is essential to achieve complete dispersion or dissolution of the ingredients. Proper equipment is needed for precise control of the cooling rate to ensure optimal mixing of the oil and water phases and to obtain the correct product texture.

Cambrex understands that no detail can be overlooked on site transfer, scale-up, and testing to ensure physicochemical and bioactive comparability between a new and existing product. In partnering with a client on a tech transfer project, Cambrex takes the position that the initial development and manufacturing approach may not have sufficiently challenged all of the key parameters, including the raw materials, the product attributes, and the process. In the case described here, to avoid any knowledge gaps, Cambrex performed all of the design and development work needed to produce the customer's dermatological ointment and to demonstrate its similarity in terms of ingredients and bioequivalence. Manufacturing was scaled up to produce batches of 900kg that are packaged in 45g aluminum/laminate tubes and 2g sample packets.

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Maryse Laliberte
General Manager

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.