Case Study 6
Improving product quality by reducing segregation in a pharmaceutical application

The Problem
Particle segregation (separation) is a concern in most industries. However, it probably receives the greatest attention in the pharmaceutical industry, where only very slight variations in the concentration of active drug are permitted. Drugs that are produced in solid dosage form (i.e., tablets and capsules), contain many ingredients. If the active ingredient (possibly a very low percentage of the entire blend) is not uniformly distributed, the finished product will not fall within content uniformity specifications and the entire batch may be rejected. Rejected batches are unacceptable from both quality and financial standpoints.

A leading pharmaceutical firm was in the process of validating a new tablet product. The process begins with several ingredients being added to a tumble blender. The blended material is discharged into two portable containers, which in turn are relocated above a tableting press. Initial tests during scaleup showed high active ingredient percentages in the tablets produced from the material that discharged last from each container.

The company contacted Jenike & Johanson to assist in determining the cause of the problem and to recommend a solution. The first step in solving any problem is to gather all of the available information. Jim Prescott, a senior project engineer at Jenike & Johanson, went on-site to observe the process and equipment firsthand, and to discuss the situation with key individuals.

Typical areas of concern with such a process include the tumble blender (which may not be creating a homogeneous blend), the portable containers (which may be promoting segregation due to a funnel flow discharge pattern), the transfer chute from the portable container (which may be a nonsymmetrical Y-branch feeding two inlets to the press), and the press feed hopper below the chute (which also could provide a funnel flow discharge pattern).

Prior to the site visit, Mr. Prescott recommended that flow properties tests be conducted on four variations of the formulation to determine their handling characteristics. These tests, which included cohesive strength, wall friction, compressibility, permeability, and segregation potential, were conducted at Jenike & Johanson’s Westford, Massachusetts facility.

During the site visit, Mr. Prescott found that the material discharged significantly faster from the center of the portable containers. This was supported by flow properties tests, which indicated that the existing surface of the containers was too frictional to provide mass flow. As is typical of a funnel flow discharge pattern, the material discharging at the end of the run was initially along the hopper walls.

The flow pattern in the containers would be less of a concern if the material remained uniformly blended. However, during the filling of the container, segregation occurred which resulted in fine particles accumulating near the perimeter of the container. This was due to both fluidization and dusting segregation mechanisms. During free-fall into a container, particles tend to separate from each other, with fine particles forming dust clouds. When the falling stream impacts the pile, it can become aerated, and generate more dust. In this case, the airborne dust was carried by the airstream, causing it to settle along the walls. Aerated material, at the point of impact of the falling stream, drove fines to the surface of the pile, from where they slid down the pile towards the walls of the container. The combination of a side-to-side segregation...
pattern, during filling of the containers, with a funnel flow discharge pattern was causing the recorded trend of high assays at the end of each run.

**The Solution**

Several options were considered to solve the segregation problem, but due to restrictions on modifications that could be made to the existing equipment, only one seemed reasonable. It was determined that the best solution was to eliminate the dusting, and hence segregation, by reducing the drop height from the blender to the portable container, using a retractable let-down tube. Such dust control equipment is used on large-scale operations, such as ship loading, but no such equipment has been available for the pharmaceutical industry. Without an off-the-shelf piece of equipment available, Jenike & Johanson engineers further developed the concept, then designed and built the new PharmaSok™ filling system [see below].

**The Result**

Tests with the PharmaSok at our facility in San Luis Obispo, California showed a dramatic reduction in the observed dust, normally generated during container filling. The first unit was shipped at the end of January, and trials are currently being conducted under actual process conditions.

According to the manager of formulation development, "It is common, across the pharmaceutical industry, to address problems of this nature during scale-up of a new product, especially a direct blend. Validation requirements are stringent, and rightfully so; however, this makes it a very time consuming and costly process. The improvement anticipated in this case is significant in terms of saving both time and expense - for our company as well as the consumer. We fully anticipate that the solution provided by Jenike & Johanson will help us control this process, and we hope to try it with some of our other products."

**PharmaSok™ Filling System Eliminates Dusting**

In the production of drugs in solid dosage form (i.e., tablets, capsules), dusting and the resulting segregation can cause unacceptably high variations in the concentration of active ingredient (which is usually only a small percentage of a blend). This poor content uniformity creates product losses and safety hazards that can cost pharmaceutical manufacturers millions of dollars annually. Transferring mixed powders from a blender to a bin creates a dust cloud, which settles on top of the pile and concentrates along the bin walls. This finer material, commonly the active ingredient, often discharges at the end of a batch run, producing tablets that are not within specifications. Entire batches are failed as a result.

The PharmaSok filling system (patent pending) is a new method of preventing these problematic dust clouds from forming. It includes a rolling stand, FDA compliant tubing (the “sock”), and a PLC-operated retraction unit. The system is rolled in place beneath the blender, to which it is sealed. An empty portable container is then positioned below the system. The operator discharges the powder mixture from the blender through the PharmaSok, into the container. Because the powder is completely contained, there is no free-fall, and therefore, no dust cloud. The PharmaSok automatically retracts the tubing at a pre-set speed, filling the container gradually without dust or segregation. The used tubing is automatically rolled up for easy disposal as it retracts.

The PharmaSok filling system is supplied through ProModus, a division of Jenike & Johanson. For more information, call (978) 392-1863, or visit the ProModus website at [http://www.promodus.com](http://www.promodus.com).