# Green Particle Engineering Industry Challenges

### Problem 1: Melt Granulation Drug Product Simplification

Due to the energy and mass challenges associated with pharmaceutical manufacturing, pharma companies are striving to simplify manufacturing operations where possible. In the formulation area, this means 2 things:

1. reducing the number of unit operations in secondary manufacturing
2. using continuous processing

An area of interest for GSK is the possibility to use continuous melt granulation. Melt granulation eliminates the need for drying in wet granulation yet can yield similar granule properties. Many continuous wet granulation techniques use modified extruders which have appropriate temperature control to allow melt granulation to be sufficiently controlled.

### Expected Output of Research

It is desired to have a continuous melt granulation process developed such that controlled melt granular occurs in the first half of the barrel, then extra-granular excipients are added at the end of the granulation barrel and sufficiently mixed to allow the final output from the granulator/extruder to be suitable for direct compression tablet manufacture. The final output mixture should not be sensitive to temperatures of 55 C or below to ensure standard stability assessment conditions can be used for stability evaluation.

### Problem 2: Targetted Delivery

Most pharmaceutical new chemical entities have efficacy limitations because they do not reach the target site of action in the body to a significant extent. This results in several sustainability problems:

1. there is a high attrition rate among drugs in development due to poor target engagement, increasing R&D costs and generating large amounts of drug which are eventually not used.
2. When a drug does show efficacy and make it to market, low concentration at the target site of action requires high doses of active ingredients. Much of the active ingredient is ‘wasted’ and ends up in the environment as excreted mass.

### Exemplification of Problem

It is common for certain drugs, particularly antivirals for the treatment of HIV, to have doses well in excess of 1 g per day. Most of the drug is not used to treat the disease, but is used to ensure adequate exposure for a therapeutic benefit. This causes both a pill burden on the patient and a large amount of drug that is wasted to the environment.

Over time, drug attrition rate has increased with molecular complexity (molecular weight, chirality, functionalization). Within GSK, attrition rates from candidate selection to commercial manufacture are in excess of 95%. Certain drugs have shown some activity but have not reached exposure levels high enough to judge whether a therapeutic effect is possible, despite extremely high doses.

It is possible to overcome some dose constraints by using subcutaneous or intramuscular injections, however, this approach does not yield enhanced delivery to the target site of action.

### Expected Output of Research

We would like to develop a mechanism to achieve enhanced targeted delivery to mucosal tissues for HIV when the compound is delivered by an injection; either subcutaneous, intramuscular or intravenous.

### Problem 3: Improving efficiency of feeder mechanisms for continuous processing

There is pressure to reduce costs and increase efficiency in secondary manufacturing (e.g., preparation of drug product capsules, tablets, etc..). In addition, there is pressure to reduce environmental impact. To remain competitive in a highly competitive market, we must seek to develop more intensified, safe, yet environmentally-friendly processes.

Given a regulatory framework for continuous processing, the key question is whether it offers benefits compared to batch manufacturing. A weakness of continuous processing is the start-up and shut-down material losses that impact the batch yield. For start up, the losses can be reduced through specific start-up sequences or pre-blending key components. However, shut down losses primarily occur because input feeder can not maintain feed rates below critical levels.

It would be ideal to developed modified feeder mechanisms that minimize the shut down losses to material being left in the feed hopper compared to current equipment. This requires the feeders to operate at the target federates consistently until nearly all material has been delivered.

### Expected Output of Research

During small scale batch manufacture, the yield loss is nearly zero. However, at small “scale” continuous manufacturing, the yield losses are very high. It is expected that the output of this research will significantly reduce that amount.