SPRAY DRYING AS PART OF THE CONTINUOUS MANUFACTURING VALUE PROPOSITION AT NOVARTIS

By

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Submitted to the MIT Sloan School of Management and the Department of Materials Science & Engineering in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration
AND
Master of Science in Materials Science & Engineering

In conjunction with the Leaders for Manufacturing Program at the
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ABSTRACT

Novartis Technical Operations is considering a complete overhaul of their manufacturing processes. To date, all drugs have been made by using a batch process. In an attempt to lower costs, Novartis is evaluating moving some drug production to a continuous process. Novartis has instituted lean in their production plants and it has been very successful, but what is on the table now is a way to bring lean to the highest level, and a chance to make a seismic shift in manufacturing performance. The continuous manufacturing initiative between Novartis and MIT exists to pursue that idea. My task was to evaluate the economic impact and feasibility of spray drying on drug manufacturing. Spray drying is an advanced manufacturing technique that could allow Novartis to skip multiple steps in chemical & pharmaceutical operations. It is also a process that can be used continuously. I investigated the use of spray drying with X, one of the drugs in Novartis' product pipeline. The major results of this investigation are that drug solubility in the solvent is a critical variable and that X is stable after spray drying. All experiments in the scientific section were performed with the drug dissolved in Ethanol, and all experiments resulted in stable versions of X combined with various additives. The drug solubility directly affects the number of spray dryers necessary for production within an allocated time span. Using economic assumptions that are detailed later in this work, there is a breakeven point for most drug volumes at around 3% drug solubility, assuming additives poses no problems for dissolution. Despite economies of scale considerations and factory adjustments, this breakeven point is accurate for drug demands from 1 ton/year to 100 tons/year. Since my experiments were performed at 1.53% drug solubility (too low), I did not prove the economic viability of spray drying X in particular, but rather laid a framework for future studies.

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GLOSSARY

API: Active Pharmaceutical Ingredient
CHAD: Chemical Research & Development, part of TRD
ChemOps: Chemical Operations, part of TechOps
DS: Drug Substance; End result of Chemical Operations
DP: Drug Product; End result of Pharmaceutical Operations (the pill)
Excipient: Benign agent used to stabilize drug or provide a medium for its bio-distribution
GC: Gas Chromatography
PHAD: Pharmaceutical Research & Development, part of TRD
PharmOps: Pharmaceutical Operations, part of TechOps
Polymorph: One of many different structures of the same material. Generally related to crystal structure; solids which form chemical composition can exhibit different crystal lattice forms
TechOps: Technical Operations, division in charge of drug manufacturing
TRD: Technical Research & Development, division in charge of development and scale-up
XRD: X-ray Diffraction
INTRODUCTION

1 Problem Context

1.1 Novartis Pharmaceuticals

Novartis was founded in 1996 from the merger of Ciba-Geigy and Sandoz. It is headquartered in Basel, Switzerland and employs nearly 100,000 people. In 2007, Novartis had $38.07B in sales from operations divided between pharmaceuticals ($24.03B), Sandoz ($7.17B), consumer health ($5.43B), and vaccines & diagnostics ($1.45B). The pharmaceutical division, which accounted for 63% of sales in 2007, focuses on general medicines for arthritis, bone, cardiovascular & metabolism, dermatology, gastrointestinal, hormone replacement therapies, infectious diseases, neuroscience, respiratory, as well as special medicines for oncology & hematology, transplantation & immunology, and ophthalmics. Its most recent blockbuster drugs (> $1B in annual sales) were Diovan for hypertension, Gleevec for leukemia, Zometa for bone cancer, and Sandostatin for neuroendocrine tumors.

Please refer to the following schematic, in order to get a better understanding of Novartis’ drug development process, and to see how the divisions of Drug Discovery, Drug Development, and Technical Operations operate (note: Phase VI should read Phase IV):

![Drug development process](image)

**Drug Discovery (D0 - PoC)**

Like most bio-focused companies, research is a key part of Novartis’ pharmaceutical strategy. Most of the research is conducted at the Novartis Institutes for BioMedical Research (NIBR), which is headquartered in Cambridge, Massachusetts. In addition to this engine of organic growth, Novartis supplements its own work through collaborations with biotechnology companies and academic institutions throughout the world. Finally, Novartis also licenses drugs from other companies and
acquires those with strategic intellectual property. Drug discovery is where compounds are tested for their possible impact on the human body. The focus of this division is on determining the effectiveness of new compounds; as a result, drug synthesis can be a long arduous process.

**Technical Research & Development (PoC – SDP)**

Once the Drug Discovery division has come up with an attractive compound, Technical Research & Development (TRD) takes over. Another highly technical organization, TRD is conducted mainly in Basel, Switzerland, and is composed of scientists, pharmacists, and process engineers whose main objectives are two-fold:

1. Determine the most economical route to producing large quantities of the new compound
2. Formulate an economical dosage form for the compound that results in good bioavailability

These two distinct objectives result in the segmentation of the TRD. Chemical Development (CHAD) is assigned the first objective and Pharmaceutical Development (PHAD) is assigned the second. This is the first time where in a drug’s life throughout the approval process there is such a divergence; this dichotomy of Chemical and Pharmaceutical processes continues on to production, where there are separate Chemical Operations and Pharmaceutical Operations facilities. In order to achieve the first objective, the compound synthesis is almost always tweaked with different reagents and solvents in order to make the process suitable for large-scale manufacturing and in order to reduce costs. There are many options for dosage forms, such as inhalants, intravenous, and transdermal, but my work concerned exclusively oral dosage in the form of tablets. Dosage form is selected based upon effectiveness, cost, and patient needs.

While this development process progresses, clinical trials are ongoing.

**Technical Operations (Phase IV)**

Once TRD has vetted the drug from an economic standpoint and clinical trials have shown positive impact of the drug resulting in approval by various regulatory bodies, the drug is ready for production. Technical Operations (TechOps) is in charge of manufacturing the active ingredient at Chemical Operations (ChemOps) plants and manufacturing the drug at Pharmaceutical Operations (PharmOps) plants. These facilities are placed all around the world, both to minimize logistics costs and to satisfy country requirements. TechOps produces a wide variety of drugs with vastly different annual production amounts.
1.2 Drug Manufacturing

Chemical Operations

Chemical Operations is a subset of TechOps that produces the Drug Substance (DS), which is a modified form of the Active Pharmaceutical Ingredient (API) to make it easier to ship and use in PharmOps sites. There are multiple sites throughout the world that do this and their main customers are PharmOps sites. It is only in the ChemOps sites where compounds are actually changed chemically – solvents are added, reagents are mixed, and process conditions are changed in order to synthesize the DS. Reaction sections and separation methods are critical to the success of this endeavor – most process equipment comes in the form of reaction vessels, dryers, extraction columns, and filters.

The complexity of the processes required to synthesize various DS' within ChemOps varies widely with the type of drug. Annual production volumes are determined by weighing the complexity of the synthesis, the value of the final product, and demand. Meeting those volumes involves intermediate storage and testing between process steps, leading to additional holdup in overall drug production time.

Pharmaceutical Operations

Pharmaceutical Operations are starkly different from ChemOps. Since the DS is the main input along with specific additives (referred to as excipients), most of the unit operations are physical in nature. The output of a PharmOps plant is the Drug Product (DP), which is ready for patient use.
Like ChemOps, a large degree of versatility is required within a PharmOps plant. The ability to process the API in its solid form is directly related to the API being a “flow-able powder” – that is, a powder that is able to move easily through different pieces of process equipment. Therefore, several different types of granulation exist in order to ensure that the powder produced flows optimally. Having equipment to handle different types of granulation is only one form of versatility needed within PharmOps; different types of process steps also exist to ensure that the proper dosage of the API ends up in the dosage form. This need for quality control with respect to dosage size is significant, since for certain highly active compounds the dose can be on the order of micrograms in oral pill.

The processing steps that take place in a PharmOps plant include drying, roller compaction, coating, tabletting, and encapsulation. Some of these process steps, such as encapsulation, tabletting, and packaging, are able to operate essentially continuously. However, other process steps such as wet granulation, milling and coating are currently batch. These batch processes increase the costs of drug production by both increasing the overall throughput time and necessitating that the intermediates upstream be stored. Elimination of that intermediate storage would result in massive savings, since it is almost finished drug product that is not being sold.

Another major consideration within PharmOps is the extensive cleaning regime each piece of equipment must undergo. In order to ensure no cross contamination between API’s and to avoid microbiological contamination, each piece of process equipment needs to be shut down for several hours in order to be thoroughly cleaned whenever a new drug is to be proceeds. The downtime required for this cleaning creates several bottlenecks within the drug manufacturing process, which contributes to the overall cost of production.

**Batch Processing**

Most of the operations performed in ChemOps and PharmOps are batch and the inherent nature of a batch process results in unavoidable waste. Walking through a ChemOps facility you can observe operators carefully measuring reagents, adding them to reaction vessels, and sometimes cleaning them. There is very little in the realm of process analytical technology to monitor the progress of a reaction, but it is not as necessary since the duration of the process and variables are prescribed in the operations manual. PharmOps facilities are much the same way; you can observe operators measuring out additives, DS, and mixing them manually. Large containers are all around in order to
facilitate the transfer of intermediates from one process unit to another. The batch nature of these processes allows the use of the same equipment for the production of many different drugs—changeovers take time, but that flexibility can be helpful with the unpredictability of drug demand (especially for a new drug). It also makes production scheduling difficult and causes the lead-time for drugs to be longer than necessary.

Despite the inherent downsides of batch processing outlined above, Novartis has not remained behind the times in process improvement. Novartis' Suffern, N.Y. plant is the Swiss company’s sole pharmaceutical production facility in the U.S., and it is now a role model for the corporation. European facilities are basing some of their Lean Manufacturing objectives on the success in Suffern, and Novartis has described its vision as striving to be the “Toyota of the Pharma Industry.”

Back in 2001, the Suffern plant was the least competitive facility in Novartis’ PharmOps portfolio. Four years later, it was beating records in cycle times, back orders, and production costs. Now it is the model to follow. All of this was a result of the implementation of Lean from a process, organizational, and supply chain perspective. Rewards and recognition programs encouraged employee empowerment, Information Technology upgrades made operators more aware of their status, and SAP increased transparency throughout the organization. In two years, cycle times for
the major product were reduced 50%, back orders were cut from 19 days to 9 days, and the organization was completely redesigned into a flatter, more process-oriented organization.

**Novartis-MIT Continuous Manufacturing Initiative**

In 2007, Novartis and the Massachusetts Institute of Technology launched a 10-year partnership, known as the Novartis-MIT Center for Continuous Manufacturing. The objective of this partnership is to develop new technologies that can replace conventional batch operations in the pharmaceutical industry and result in continuous manufacturing from start to finish. In order to accomplish this objective, Novartis has pledged to invest $65 M in research activities at MIT.

According to Daniel Vasella, Chairmen and CEO of Novartis, “This partnership demonstrates our commitment to lead not only in discovering innovative treatments for patients but also in improving manufacturing processes, which are critical to ensuring a high-quality, efficient and reliable supply of medicines to patients. Our collaboration with MIT, a worldwide leader in developing cutting edge technologies, holds the promise to achieve a quantum leap in the production of pharmaceuticals, a field which has received rather little attention in the past.”

![Continuous processing schematic](image)

Novartis and MIT expect this collaboration to benefit patients and healthcare providers through increasing supply availability and the quality of medicines. This way, patients can have quicker and...
more reliable access to the medications they need. As an ancillary benefit, this methodology may also result in reducing environmental impact of manufacturing activities.

In addition to these rewards for patients, there are other expected benefits:

1. Accelerating the introduction of new drugs by designing production processes earlier
2. Using smaller production facilities with lower building and capital costs
3. Minimizing waste, energy consumption, and raw material use
4. Monitoring quality assurance on a continuous basis rather than post-production testing
5. Enhancing process reliability and flexibility to respond to market demand

1.3 Project Background

My project is an attempt to demonstrate the feasibility and economic benefit of implementing spray drying, as one milestone on the way to operating a completely continuous process. As a basis for comparison, one drug (X) was chosen out of Novartis’ pipeline; I analyzed the feasibility of spray drying with that X, as well as the economic impact of using spray drying with that X’s expected conventional manufacturing process. In order to fully cover the context required to understand how my project fits into the Continuous Manufacturing Initiative, I will discuss what parts of TechOps we are dealing with and what processes spray drying can replace. Additionally, I will provide some background on spray drying itself.

As discussed earlier, in ChemOps an intermediate product is the API and the final product is the DS, whereas for PharmOps the final product is the DP, which is consumed by the patient. Spray drying is an exceptional technique but it is not traditionally used as a reaction step. As a result, we need to have an active drug compound, the API. However, it is not necessary for this API to be fully segregated from other compounds, and so we can implement spray drying before the conventional production of the DS. This logic brings us to the conclusion that spray drying can be implemented somewhere between the tail end of ChemOps (also called the end game) and the beginning of PharmOps.

Below you can see a flowchart of the part of the conventional production process (specific to the drug studied) relevant to spray drying:
Ideally, we could use the drug solution (containing API) along with excipients as feed for the spray dryer, produce a powder, and compress the powder directly. This would entail skipping crystallization, filtering, drying, milling, and roller compaction. That sort of operation would be the Holy Grail for spray drying implementation. Unfortunately, things are not so easy.

For X, it turns out that the crystallization step is necessary for the removal of a mutagenic byproduct. Since crystallization is necessary, filtering and drying are also necessary (those steps serve to eliminate that mutagenic compound). Milling only serves one objective in this process flow: make the DS very small. This is a requirement so that when excipient is added in the next step, roller compaction, the mixture of DS and excipient is relatively homogeneous.

Spray drying can replace milling and roller compaction in the conventional production process for X. By mixing the excipient and the un-milled API in a solvent that dissolves the API, we can achieve a homogeneous mixture. Here is the proposed process flow:
Spray Drying Process & Equipment

Spray drying is a commonly used method of drying a liquid feed with a hot gas. Usually the gas is air, but sensitive materials like pharmaceuticals and solvent like ethanol require nitrogen. The liquid feed varies depending on the material being dried and may be a solution, colloid or suspension. This process of drying is very rapid and effective, and by skipping multiple steps it can result in profit maximization and process simplification.
A spray dryer is a device used in spray drying. It takes a liquid stream and separates the solute or suspension as a solid and the solvent into a vapor, so it can be thought of as a separations device. The solid is usually collected in a drum or a cyclone. The liquid feed is sprayed through a nozzle into a hot vapor stream and vaporized. Solids form as moisture quickly leaves the droplets. A nozzle is usually used to make the droplets small for a higher surface area to volume ratio.

In addition to its usefulness as a separations technique, spray drying can offer a lot of value as an encapsulation technique. With a load (in our case, the drug) and a carrier (in our case, an excipient that does not dissolve in the solvent) in a solvent we can produce homogeneous slurry. Once this slurry is fed into a spray drier at the right temperature, the atomized slurry forms micelles. The small size of these drops results in a large surface area, which dries quickly. As the solvent dries, the carrier (excipient) forms a hardened shell around the load (drug). This application of spray drying encapsulation has often been used to prepare “dehydrated” powders of substances, like instant drink mixes and skim milk. In my project, we took advantage of the fact that the slurry was originally homogeneous, and postulated that we should be able to skip milling and roller compaction, which are essentially methods of making the DS very tiny and combining it with excipients, to finally result in homogenous mixture.
2 Scientific Investigation

The objective of my scientific work was to determine the characteristics of drug X when combined with different excipients after spray drying. The ideal outcome of this exercise was evidence that drug X was stable after spray drying under specified process conditions, along with some analysis of the various structures that resulted.

Spray drying experiments were performed with drug X and four excipients at three different drug loadings (20%, 50%, 80%). Temperatures were determined by the desire to have a dry sample and reduce energy requirements; they were held constant throughout the experiments. Ethanol was chosen as the solvent because it is used often for spray drying and because it can be used to dissolve X.

After four weeks of stress testing at 40° C and 75% Humidity, X is pronounced stable when combined with Avicell (Microcrystalline Cellulose), PVP, Lactose, and Aerosil.

X forms a stable polymorph (Acetate, mod. D) with Avicell at 80% drug loading and 50% drug loading, and a stable amorphous form at 20% drug loading. X forms a stable solid dispersion with PVP at all drug loadings, a stable amorphous structure on crystalline Lactose at all drug loadings, and a stable amorphous mixture with Aerosil at all drug loadings.

2.1 Process

Initial process for setting boundary conditions

Before starting experiments with X and excipients, several baseline measurements needed to be taken and certain process variables set. Excipients were chosen both because they were compatible with drug X and also because we wanted to characterize drug X interaction with both carriers and stabilizers. Carriers do not interact with drug X and do not dissolve in the solvent, while stabilizers have the potential to do both.

1. X-ray diffraction spectra of excipients, drug X, spray dried excipients, and spray dried drug X were obtained for future comparison. Optical microscopy was also performed on the same samples.
2. Ethanol was chosen as the solvent since drug X is weakly soluble in it and Ethanol is a known solvent used for spray drying. Furthermore, drug X has documented interactions with other possible candidate solvents, so this limited our choice dramatically.

3. Temperatures for spray drying operation were set based on the desire for low moisture product and economical operation. 145° C Inlet, ~85° C Outlet.

**Spray dryer operation**

1. Turn on nitrogen flow for atomization and respiration
2. Set nozzle temperature
3. Introduce pure ethanol as preliminary feed
4. Once temperatures are equilibrated, introduce slurry containing ethanol as solvent, drug X, and/or excipient
5. Adjust slurry pump rate or nitrogen rate if necessary to maintain the same outlet temperature.

**Experimental Process**

1. Solutions were prepared of Solvent (ALANP Ethanol), Excipient, and drug X. Homogeneous solutions were achieved through ultrasonification and shear-mixing.
2. Spray drying procedure followed using prepared solutions and given temperatures (145° C inlet, ~85° C outlet)

3. Initial analysis of powder product performed using X-ray diffraction (XRD), Gas chromatography (GC), and Optical Microscopy (OM)

4. Powder product placed in dessicator for two weeks at 75% humidity and 40° C

5. Analysis of “stressed” product using same methods (XRD, GC, OM)

6. Powder product placed in dessicator for two more weeks (four weeks total)

7. Analysis of “stressed” product using same methods (XRD, GC, OM)

8. Differential Scaling Calorimetry (DSC) performed on samples for further characterization

### Experimental Data

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<tr>
<th>label</th>
<th>Drug X</th>
<th>Excipient</th>
<th>Ethanol</th>
<th>Filter P</th>
<th>inlet °C</th>
<th>outlet °C</th>
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<td>77</td>
<td>2.6 g</td>
<td>26%</td>
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</tbody>
</table>

Figure 8: Mixtures used in the analysis

#### 2.2 Laboratory Analysis

Analysis was done with X-Ray Diffraction (XRD), Gas Chromatography (GC), Optical Microscopy, and Differential Scaling Calorimetry (DSC). However, XRD was discovered to be the most valuable method in my work. The reason for this is that the crystal structure (or lack of one) gives insight on the form that drug X takes after spray drying in combination with excipients, whereas the other methods only give secondary information (like melting points, moisture content, etc.) on the drug. The structure X takes after spray drying has consequences for the bio-distribution and stability for use in an oral form. It can also impact the drug loading possible for that drug, although only
empirical analysis can be done for that factor. Originally, we expected that any amorphous structures would quickly re-crystallize, thus implying that such a structure would be unstable. This was why we did stress testing followed by more analysis. It is currently unknown just how much an amorphous structure would change bio-distribution, since almost all drug products that Novartis sells in the oral dosage form are crystalline in nature.

We found the GC data to be unhelpful since the moisture could be tuned in a pilot/production scale setup and preliminary economic work showed that the energy required to vaporize ethanol was an extremely small portion of the costs of running a spray drying (<1%). DSC was worthwhile for full characterization of the substance, but not completely necessary for my simple analysis. If the final result of my economic model showed an economic benefit for spray drying drug X, the DSC data would be useful for work downstream in the new process development product, like pressing the powder into a pill. Optical Microscopy photos are included in this analysis in order to show the color and particle size of the powders produced and to bring the analysis from the abstract realm in to the physical realm. Particle size can also be manipulated by using different operating conditions on different scale equipment, but I felt it necessary to show that powders were actually produced and analyzed.

**Drug X alone**

To begin with, we have found that upon spray drying drug X becomes amorphous. Here is a graph of micronized crystalline X, with spray dried X for comparison:

![Graph of Drug X Micronized, Drug X Spray Dried](image-url)
**Drug X and Avicell (Microcrystalline Cellulose)**

Next, we see that X is stabilized into a different, stable polymorph (acetate mod. D) at 80% and 50% drug loading (Avicell 20% and Avicell 50%) combined with Avicell. The 20% drug loading (Avicell 80%) does not exhibit this polymorph and is instead amorphous. First, we have a graph of the different drug loadings:

![Graph of Drug X and Avicell, different loadings](image)

Figure 10: Drug X and Avicell, different loadings

Second, the 50% drug loading and micronized crystalline X, to show that we have a polymorph, along with pure spray dried avicell to show that it is amorphous upon spray drying:
Third, we show how the actual polymorph was determined; the XRD for 50% drug loading is combined with appendix 5 from the drug X Salt program report (different polymorphs), and the closest match is Acetate mod. D (the pure micronized drug X is in form Acetate mod. B):
Figure 12: Documented polymorphism of Drug X

Optical Microscopy photos of 50% and 80% loading:

In order to demonstrate stability we show the 50% loading at each stage in the stress testing (initial, two weeks, and four weeks). All drug loadings were stable:
**Drug X and PVP k-30 (Polyvinylpyrrolidone)**

For our second excipient, we see evidence of a solid dispersion. First, this is a graph of the different drug loadings:

![Graph showing drug loadings for Drug X and Avicell Stability](image)
Next, we have the spectra of spray dried pure X and spray dried pure PVP along with 50% loading to show the constructive/destructive interference:
Here is optical microscopy of the 50% and 80% loading samples, showing the amorphisity (lack of structure) at various magnifications:

Finally we demonstrate stability by showing the 50% loading at each stage in the stress testing. All drug loadings were stable:

Figure 16: Drug X and PVP Stability
**Drug X and Spray Dried Lactose**

For our third excipient, we see evidence of the excipient remaining in crystalline form while the drug X deposits an amorphous phase on top of it. First, this is a graph of the different drug loadings:

![Graph of different drug loadings showing crystalline and amorphous phases.](image)

**Figure 17: Drug X and Lactose Loadings**

Next, we have the spectra of pure spray dried Lactose and 50% loading, to show that the peaks are at the same points, indicating that Lactose remains in crystalline form:
Here is optical microscopy of the 50% loading, showing a crystalline base with amorphous blobs on top:

Finally we demonstrate stability by showing the 50% loading at each stage in the stress testing:
**Drug X and Aerosil 200**

For our fourth and final excipient, we see an amorphous phase. First, this is a graph of the different drug loadings:

![Figure 19: Drug X and Lactose Stability](image)

![Figure 20: Drug X and Aerosil Loadings](image)
Next is a graph of pure spray-dried X, pure Aerosil, and 50% aerosil:

![Graph of Drug X and Aerosil analysis](image)

Figure 21: Drug X and Aerosil analysis

This is the 50% loading at different magnifications:

![50% loading at different magnifications](image)

Finally we demonstrate stability by showing the 50% loading at each stage in the stress testing:
2.3 Conclusion of Scientific Investigation

Spray drying experiments were performed with four excipients (Avicell, PVP, Lactose, Aerosil) at three different drug loadings (20%, 50%, 80%). Temperatures were determined by the desire to have a dry sample and reduce energy requirements; they were held constant throughout the experiments at 145°C inlet and ~85°C outlet. Ethanol was chosen as the solvent because it is used often for spray drying and because it can be used to dissolve drug X.

After four weeks of stress testing at 40°C and 75% Humidity, drug X is stable with Avicell, PVP, Lactose, and Aerosil.

Drug X forms a stable polymorph (Acetate, mod. D) with Avicell at 80% drug loading and 50% drug loading, and a stable amorphous form at 20% drug loading. Drug X forms a stable solid dispersion with PVP at all drug loadings, a stable amorphous structure on crystalline Lactose at all
drug loadings, and a stable amorphous mixture with Aerosil at all drug loadings. Differential Scaling Calorimetry data is in the appendix for reference.

3 Economic Investigation

My work was done by comparing spray drying to currently existing and possibly replaceable technologies used in the production of drug X: milling and roller compaction. Below is a picture representing the shift that we envision:

The most significant result of this investigation is that drug X solubility in the solvent is a critical variable. All experiments in the scientific section were performed with the drug X dissolved in Ethanol. The solvent mass directly affects the number of spray dryers necessary for production within an allocated time span. It does this in two ways: spray dryers are more effective with a lower solvent content and less total throughput is needed for a lower solvent content. Using my assumptions that are detailed later in this work, there is a break-even point for most drug volumes at around 3% drug X solubility, assuming the excipient poses no problems for dissolution (most likely a carrier that does not need to dissolve into the solution). Despite economies of scale considerations and factory adjustments, like allowing larger spray dryers and accounting for increased operating costs of high mix factories, this break-even point is accurate for drug demands from 1 ton/year to 100 tons/year. Furthermore, sensitivity analysis has shown that the second most important factor for the economic feasibility is labor costs, and that none of those variables dramatically affected the solubility break-even point. Since my experiments were done at 326 gram of solvent per 5 grams of X (1.53% solubility), I did not prove the economic viability of spray drying drug X in particular. By varying solubility and keeping all other variables at Novartis’ averages and given values, I generated both of these graphs to show the impact of solubility on drug production savings:
3.1 Data and Methods

Data used for the model that generated these results was obtained from various sources. Capital costs for milling and roller compaction were obtained from ChemOps and PharmOps production personnel. Quotes from NIRO, a widely used spray drying equipment maker, were used for spray drying capital costs – they currently sell seven designs, all of which were incorporated in the model. The two main components of operating expenses, labor and equipment, were set by variables in the
model. Equipment expenses were obtained by looking at SAP data for currently existing production, and labor estimates were obtained from ChemOps personnel. Plant uptime was calculated as an average over Novartis’ portfolio, and acts as a scalar for the economic benefit/loss of spray drying. Equipment uptime was taken directly from SAP results, so it based on historical data. Other costs (PharmOps other costs and ChemOps other costs) are included as a percentage of the total operating expense that can be changed in the model, but are currently at the Novartis accepted rates for drug X. They include charges for environmental handling and product testing. Overheads (General Factory Overhead and Process Overhead) are included on a percentage basis on the recommendation for both ChemOps and PharmOps finance personnel. Production Area Overhead accounts for costs that have a general character and cannot be allocated directly to products. This includes indirect labor, indirect space (corridors, break rooms, where manufacturing is not happening), and training of process personnel. General Factory Overhead refers to expenses incurred within a plant that are related to production, but cannot be attributed to individual production areas. This includes plant & production management, safety, health & environment, production support, engineering, and IT. The higher cost penalties of high mix facilities (instead of low mix) are added in as a factory adjustment based on historical data. Finally, discussions with ChemOps finance set the discount rate at 10%.

Novartis’ Total Production Cost (TPC) method was used to calculate yearly costs. This method combines capital costs and expenses into one single number that is the same every year for the life of the project (15 years). Essentially, the TPC is what you get when you take a net present value and turn it into an annuity for the lifetime of the project. This allows for easy comparison among production methods with varying capital costs, and for simple communication of the data.

3.2 Equipment-based, Direct, and Full Costing

The equipment for the X campaign is assumed to be used for other campaigns throughout the year

This is by far our most important assumption, and perhaps illustrates why the pharmaceutical industry is slow to implement new processes. In order to put Spray Drying and conventional processing on a level playing field, in order to compare apples to apples, it is imperative to use equipment-based costing. What this means is that capital costs are only assigned for the time the equipment is in use (whether processing material, cleaning, or in repair related to drug X). The rest of the time, another drug is assumed to be using the same equipment.
Unfortunately, there are problems with this assumption. If you are only using spray drying with one specific drug, then it is unlikely that spray dryer will be used the entire year. As such, all capital cost should be assigned to that drug (full costing). But then, as more drugs are added in spray drying the cost becomes less and less per drug.

What does this imply for someone actually planning to use spray drying? First, that the outcome of this model is appropriate in sign (positive or negative) but not in magnitude of financial benefit if the sprayer is to go in a Greenfield site and only one drug will be spray-dried (due to capacity constraints in other facilities). Second, the outcome of the model is correct if the spray dryer is used during all plant uptime in the Greenfield site. Third, the model is not appropriate for Brownfield sites. If there is excess capacity in existing mills and roller compaction machines, it is quite likely that they are the best choice to use. The reason is that they are being underutilized and thus any financial analysis should view them as a sunk cost, and only direct costs should be considered (essentially, everything but the capital cost of the equipment).

A simple question is, if this model is only appropriate if the spray dryer is up and running during all plant uptime, why even make it? Simply put, that is the model of continuous manufacturing. The idea of continuous manufacturing is to make Greenfield sites sized for the correct drug demand and to produce that drug alone. Flexibility can be added to accommodate more drugs in the same line, but the idea remains the same – to use the same sort of process equipment, all the time, with very few changes. Since my project is part of the continuous manufacturing initiative, I chose to present my model in this manner.

3.3 Model

Model Logic

In order to obtain these results, a model was formulated. The model was based on Total Production Cost and thus incorporated capital costs and operating costs. As with all models, many assumptions were taken and they are listed here:

- High mix factories are intrinsically more expensive to run than low mix factories
- Discount rates, overhead rates, labor rates, other financial variables
- Yields are assumed to be 100%
- Estimates on time needed to mill & roller compact
By far the most important and influential assumption is the last one. Run time for each process was obtained by looking at the average throughput of the average mill and average roller compaction machine in actual drug production. However, it is quite possible that the runtime would change if you could use a much larger mill or roller compaction machine.

Why are these numbers so important? They determine the total capital costs for mills, roller compaction machines and spray dryers, as well as the time those devices are used. That means that these numbers essentially carry out equipment-based costing. The total capital cost is derived from looking at the time on stream and calculating the number of machines required to match throughput for a given drug demand. Spray drying run time is assumed to be the maximum of roller compaction or mill run time.

It is critical that good data is used for the time needed to mill & roller compact because those values dramatically impact the case for spray drying.

The yield assumption may seem high, but the average yields from roller compaction and milling approach that number, as do the yields for spray drying. Furthermore, any change in overall yield for both technologies would wash out in the calculations.

**Spray drying versus conventional processing**

There are several considerations when looking at implementing spray drying:

- Less labor required: two workers required for a spray dryer whereas five workers required for milling and roller compaction combined
- More energy required: this was determined to be negligible by comparing energy cost to boil and condense solvent to the operating cost of the conventional process
- Less downtime: mills are frequently down for maintenance and cleaning, roller compactor's not as often, and we expect spray dryers to be down even less
- What is the impact on other costs like ecology and quality assurance? We assumed there was no impact, but this may not be the correct assumption

**Milling and Roller Compaction machine selection**

Selection of machine type and number of machines was based on the throughput required by operating time (variables in the model for both milling and roller compaction) and drug demand (1 ton/year, 10 tons/year, 50 tons/year, and 100 tons/year default values in the model).
Please see below for a snapshot of those calculations:

<table>
<thead>
<tr>
<th>required throughput</th>
<th>milling/micronization</th>
<th>roller compaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ton/year</td>
<td>42 kg API/hour</td>
<td>42 kg API/hour</td>
</tr>
<tr>
<td>10 tons/year</td>
<td>60 kg API/hour</td>
<td>69 kg API/hour</td>
</tr>
<tr>
<td>50 tons/year</td>
<td>174 kg API/hour</td>
<td>208 kg API/hour</td>
</tr>
<tr>
<td>100 tons/year</td>
<td>208 kg API/hour</td>
<td>321 kg API/hour</td>
</tr>
<tr>
<td># machines</td>
<td>1 ton/year: 6.6</td>
<td>10 tons/year: 9</td>
</tr>
<tr>
<td></td>
<td>50 tons/year: 28</td>
<td>100 tons/year: 33</td>
</tr>
<tr>
<td>max throughput/machine</td>
<td>6 kg API/hour</td>
<td>69 kg API/hour</td>
</tr>
<tr>
<td>capital cost/machine</td>
<td>CHF 1,200,000.00</td>
<td>CHF 2,000,000.00</td>
</tr>
</tbody>
</table>

Figure 25: Calculations for machines required

**Spray drying machine selection**

Selection of machine type and number of machines was based on the throughput required by operating time (maximum of the inputted values for milling and roller compaction) and drug demand (1 ton/year, 10 tons/year, 50 tons/year, and 100 tons/year default values in the model). In addition, the seven models of NIRO were incorporated into the model so that the user can pick and choose which spray dryers to use. The number and types of spray dryers is heavily dependent on the amount of solvent used. Although spray dryers have a rated throughput, there is also a maximum evaporation rate set by the solids content in the slurry. Higher solids content results in a higher evaporation rate.

**Model Mathematics**

In order to demonstrate the interaction of variables, let us look at how the TPC is calculated. Once all the terms have been identified, all that remains is discounting at the proper rate, developing the total production cost, and annualizing that cost to present the Novartis TPC.

Here is a section from the discounted cash flow spreadsheet, showing the various variables (and only years 0, 1, 2, and 3):
## Capital Costs

Capital costs are separate from the expenses incurred every year. Capital costs are assigned using equipment based costing, so:

\[
\text{Capital Costs} = \frac{\text{Total Capital Costs} \times \text{Days Running}}{\text{Max Utilization}}
\]
Where DaysRunning is the days the equipment needs to run to produce the required drug demand, MaxUtilization is the number of days per year the facility operates, and TotalCapitalCost is the total value of all equipment purchased. TotalCapitalCost for roller compaction & milling is determined by looking at the required drug demand, the throughput per machine, and the cost of each machine. Drug demand was varied from 1 ton/year to 100 ton/year in the model. There are provisions in the model to accommodate different sized spray dryers with different costs, but the general formula is the same:

\[
\text{TotalCapitalCost} = \frac{\text{DrugDemand}}{\text{DaysRunning} \times \text{MachineThroughput}} \times \text{MachineCost}
\]

The first term is equivalent to the number of machines used (MachinesUsed).

Direct Expenses

Direct expenses are those incurred by operating the machines. This includes labor, maintenance, and depreciation. Labor costs are calculated in this manner:

\[
\text{LaborCost} = \frac{\text{DrugDemand}}{\text{MachineThroughput}} \times \text{LaborRate} \times 24 \times \text{Operators}
\]

Since the first term is just MachinesUsed x DaysRunning, we see that the LaborCost equation is self-explanatory. The LaborRate is given in CHF/hour, 24 hours in a day, and Operators is the variable for the number of personnel to operate the equipment. This can be different for milling, roller compaction, and spray drying. Depreciation is calculated as simply the equipment-based cost (CapitalCost) divided by the number of years in operation (assumed to be 15). Maintenance is the maintenance frequency times depreciation, since it is lost time on the machine.

Indirect Expenses

Then there are the indirect expenses like the Factory Adjustment, PAO, ChemOps other costs, PharmOps other costs, and GFO.
The factory adjustment is based exclusively on direct expenses. It accounts for increased costs of operating equipment at lower volumes (to account for changeovers):

\[ \text{Factory Adjustment} = \% \text{Adjust} \times (\text{Labor} + \text{Maintenance} + \text{Depreciation}) \]

PAO is calculated in the exact same way, except it accounts for indirect labor and other costs discussed earlier, and so can remain the same no matter what volumes we are dealing with. PharmOps and ChemOps other costs are calculated in this manner, and are based upon only direct expenses:

\[ \text{Other Costs} = \frac{\text{Labor + Maintenance + Depreciation}}{1 - \% \text{Other Costs}} - 1 \]

Why such an odd formula? Because the Other Costs are defined as a percentage of the total expenses; if we rearrange the equation we get:

\[ \text{Other Costs} = \% \text{Other Costs} \times (\text{Labor} + \text{Maintenance} + \text{Depreciation} + \text{Other Costs}) \]

Finally, GFO is calculated as a percentage of all the Other Costs, for the reasons discussed earlier.

\textit{Model Operation}

Coming up with the rationale and logic behind a model is one thing, whereas operating is a different model entirely. This model was built to have quite a few variables, because many things are uncertain in this analysis. On the “Total Production Cost sheet”, the most important variables are the time on stream for milling and roller compaction.
The other variables, also highlighted in yellow, are rarely changed, but if new data becomes available about labor requirements, maintenance frequency, or other costs then changing the values will make this model more accurate. It is important to know that if the days running numbers are changed, you need to recalculate the workbook by pressing F9 in windows or “apple” and “=” at the same time on a Macintosh.

Once the “Total Production” sheet has been manipulated to reflect anticipated (or currently operating) values then it is necessary to switch to the “Spray Drying EOS” sheet. This is where you set the solubility of X in the solvent (relates directly to the mass of solvent required to dissolve X), drug loading, and select the number and types of spray dryers for the model.

The method for selecting spray dryers is as follows:

1. Set all yellow cells to zero
2. Look at throughput required (in red) and drug X kg/hour throughput (in light blue) of the different spray dryers
3. Add spray dryers by putting the number chosen in the yellow cell that corresponded with the spray dryer you want and the drug demand you are trying to accommodate.

4. The cells for match-calculated section will turn from violet to green once there are enough spray dryers to match the necessary throughput.

<table>
<thead>
<tr>
<th>throughput (kg/h)</th>
<th>PSD 1</th>
<th>PSD 2</th>
<th>PSD 3</th>
<th>PSD 4</th>
<th>PSD 5</th>
<th>PSD 6</th>
<th>PSD 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>34</td>
<td>47</td>
<td>60</td>
<td>120</td>
<td>180</td>
<td>370</td>
</tr>
<tr>
<td>cost (CHF/1,000,000)</td>
<td>CHF 1,000,000.00</td>
<td>CHF 2,750,000.00</td>
<td>CHF 3,187,500.00</td>
<td>CHF 3,625,000.00</td>
<td>CHF 4,500,000.00</td>
<td>CHF 5,250,000.00</td>
<td>CHF 8,000,000.00</td>
</tr>
<tr>
<td>API kg/h</td>
<td>0.3</td>
<td>1.1</td>
<td>1.6</td>
<td>2.0</td>
<td>4.0</td>
<td>6.0</td>
<td>12.4</td>
</tr>
</tbody>
</table>

# of each spray dryer required if we only used that type in order to achieve API kg/h requirements

<table>
<thead>
<tr>
<th>PSD 1</th>
<th>PSD 2</th>
<th>PSD 3</th>
<th>PSD 4</th>
<th>PSD 5</th>
<th>PSD 6</th>
<th>PSD 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>155.1</td>
<td>36.1</td>
<td>26.4</td>
<td>20.7</td>
<td>10.3</td>
<td>6.9</td>
<td>3.4</td>
</tr>
<tr>
<td>221.8</td>
<td>52.1</td>
<td>37.7</td>
<td>29.6</td>
<td>14.8</td>
<td>9.9</td>
<td>4.8</td>
</tr>
<tr>
<td>545.4</td>
<td>152.3</td>
<td>110.0</td>
<td>86.2</td>
<td>43.1</td>
<td>28.7</td>
<td>14.0</td>
</tr>
<tr>
<td>775.7</td>
<td>192.8</td>
<td>132.0</td>
<td>103.4</td>
<td>51.7</td>
<td>34.5</td>
<td>18.8</td>
</tr>
</tbody>
</table>

select best combination of spray dryers to meet API kg/h requirements

<table>
<thead>
<tr>
<th># spray dryers used</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>1</th>
<th>3</th>
</tr>
</thead>
</table>

remember - first clear all yellow cells until calculated kg API/hour reads 0 before adding spray dryers!

MATCH IN RED calculated kg API/hour match - calculated

| 1 ton/year | 41.1 kg API/hour | 43.3 kg API/hour |
| 10 tons/year | 395.5 kg API/hour | 621 kg API/hour |
| 50 tons/year | 3,905 kg API/hour | 1,739 kg API/hour |
| 100 tons/year | 5,903 kg API/hour | 2,112 kg API/hour |

Cells turn green when it is good. Cells remain violet when more dryers required.

Figure 29: Spray dryer selection sheet

Once the values on the “Total Production Cost” sheet and the “Spray Drying EOS” sheet have been chosen, switch back to the “Total Production Cost” sheet and you can see the total production cost for the conventional process (milling and roller compaction), proposed process (spray drying), and the difference between the two (delta).

<table>
<thead>
<tr>
<th>Total Production Cost</th>
<th>Current Process</th>
<th>Proposed Process</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ton/year</td>
<td>CHF 46,261.32</td>
<td>CHF 31,456.40</td>
<td>CHF 14,804.92</td>
</tr>
<tr>
<td>10 tons/year</td>
<td>CHF 431,950.55</td>
<td>CHF 275,884.59</td>
<td>CHF 156,065.95</td>
</tr>
<tr>
<td>50 tons/year</td>
<td>CHF 2,023,440.59</td>
<td>CHF 1,277,057.75</td>
<td>CHF 746,382.84</td>
</tr>
<tr>
<td>100 tons/year</td>
<td>CHF 3,777,159.57</td>
<td>CHF 2,461,885.58</td>
<td>CHF 1,315,273.99</td>
</tr>
</tbody>
</table>

Figure 30: Total Production Costs

Model Applicability and Suggestions

In order for this model to work, it must be used with a drug that undergoes both milling and roller compaction. These are the operations replaced by spray drying in our analysis. However, the type of solvent does not matter and the drug loading can be varied.
A way to expand the scope of this model is to allow other types of mixing techniques (other than roller compaction). This would mean getting the capital costs of all sorts of mixers and granulators and allowing the user to add them until reaching a required throughput, in a similar manner to the “Spray drying EOS” sheet. Adding this sort of capability, along with the ability to select more/different mills, would enable extension of this model to almost any sort of drug. The benefits of different (cheaper) drying techniques upstream of the spray dryer were considered, but the data was not gathered in time for rigorous analysis. Liquid/liquid extraction was also considered as an upstream operation, but once again there was not enough time for a rigorous analysis.

3.4 Sensitivity Analysis

In addition to the rigorous analysis of the impact of solubility on spray drying feasibility, several other variables were considered. First, the run length was multiplied for different campaigns; this resulted in very little difference for economic performance. This was done by doubling the run length for milling and roller compaction, halving it, and keeping it the same. I did not attempt to try disparate run lengths for milling and roller compaction because there is a low probability of that type of operation and it would never happen in a Greenfield facility (milling for 1 day and roller compaction for 5 days, or one of a million other combinations). Next, labor costs were varied; that had a profound impact on the economic viability of spray drying, since it is a much less labor intensive process compared to milling and roller compaction. Finally, drug loading (the ratio of drug to drug + excipient, or the ratio of the drug mass to the actual pill that is produced) was tweaked and very little impact was made on the economic fundamentals. The reason for this is that the sizing of the spray dryers has a lot more to do with solubility; doubling the amount of excipient has a much smaller impact than doubling the amount of solvent required, since the spray dryers need to match the throughput of the slurry, and no matter what the solvent mass is going to be greater than the excipient mass. Below is a graph showing the outcome of these tests:
<table>
<thead>
<tr>
<th>Solubility</th>
<th>5%</th>
<th>Annual TPC Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ton</td>
<td>CHF 14,101.51</td>
<td>CHF 120,794.16</td>
</tr>
<tr>
<td>2x run time</td>
<td>CHF 14,804.92</td>
<td>CHF 156,065.95</td>
</tr>
<tr>
<td>reg run time</td>
<td>CHF 15,156.63</td>
<td>CHF 156,065.95</td>
</tr>
<tr>
<td>1/2 run time</td>
<td>CHF 9,049.78</td>
<td>CHF 99,264.07</td>
</tr>
<tr>
<td>75 CHF labor</td>
<td>CHF 14,804.92</td>
<td>CHF 156,065.95</td>
</tr>
<tr>
<td>100 CHF labor</td>
<td>CHF 20,560.06</td>
<td>CHF 212,867.83</td>
</tr>
<tr>
<td>125 CHF labor</td>
<td>CHF 15,508.33</td>
<td>CHF 156,065.95</td>
</tr>
<tr>
<td>25% load</td>
<td>CHF 15,508.33</td>
<td>CHF 156,065.95</td>
</tr>
<tr>
<td>37% load</td>
<td>CHF 14,804.92</td>
<td>CHF 156,065.95</td>
</tr>
<tr>
<td>50% load</td>
<td>CHF 14,804.92</td>
<td>CHF 156,065.95</td>
</tr>
</tbody>
</table>

Figure 31: Sensitivity analysis

Although the labor costs do impact the economic benefit substantially, they have very little impact on the break-even point for solubility. Variance of solubility with labor costs and the impact on savings are shown below for 1 ton/day drug demand (and the results are similar for all drug demands); they are “jumpy” because the spray drying equipment purchasing is discrete, not continuous:
3.5 Conclusion of Economic Investigation

This model, given the proper input data, can accurately reflect the advantages and disadvantages of spray drying when compared with milling and roller compaction. It was determined that drug solubility is a crucial value, and that my experiments were all done at too high a solvent mass from an economic standpoint. What this means is that for drug X specifically we need to find a solvent that it is acceptably soluble in and check product stability. The more soluble the drug is in the solvent, the higher the economic benefit of spray drying. For a 100 ton/year drug product, there is a potential to save as much as three million dollars a year by implementing spray drying.

4 Discussion

4.1 Three Lens Analysis

In the following analysis, it is incredibly important to remember two things:
1. Spray drying will only be effective for a subset of Novartis' drugs
2. Continuous manufacturing will only be effective for a subset of Novartis' drugs
The overlap of these two is questionable. In some cases, spray drying may be a slam-dunk but continuous manufacturing will prove impossible. In other cases, cheaper methods may exist to accomplish the same tasks as spray drying, and continuous manufacturing will be the most economically viable mode to production. Despite this, where both spray drying and continuous manufacturing are applicable are where we see a lot of value created, and the most strategic and political changes. It is difficult to ascertain the cultural impact of these various scenarios, since they are confined to specific drugs and not the entire organization. However, the push for continuous manufacturing wherever possible will have definite cultural consequence.

Those two caveats may mean that the best way to achieve value is to split departments even further. Essentially, within Technical Research and Development (TRD) and Technical Operations (TechOps) dedicate personnel to continuous manufacturing. Within TRD, have some individuals determine feasibility of spray drying under the continuous manufacturing umbrella, and with TechOps have operations personnel dedicated to continuous processing that can train other operators in batch processing how to operate spray dryers.

This sort of division may lead to competition among continuous and batch TRD and TechOps, but it would result in an effective distribution of control.

**Strategic Lens**

In a vacuum, the implementation of a new manufacturing technique rarely has implications for the strategic design of an organization. The hierarchies, cross-divisional ties, and knowledge sharing should in general stay the same. However, spray drying is unique in that it serves to bridge two wholly dissimilar processes – Chemical Operations (ChemOps) and Pharmaceutical Operations (PharmOps). In one case, you have individuals focused on generating a Drug Substance (DS), and in another you have individuals focused on processing the DS in such a way that you end up with the desired Drug Product (DP). Any implementation of spray drying would require a huge shift in the ideas of where one division takes over and another relinquishes control.

In effect, spray drying would cause the boundary between ChemOps and Pharmops to be blurred. The question is, does this only impact the production, or are other parties affected? In my time at Novartis I worked with individuals from TRD and TechOps. When I gathered my data for building
the economic model I worked with scientists from Chemical Development (CHAD) and Pharmaceutical Development (PHAD), operations personnel from ChemOps and PharmOps, and financial analysts from CHAD, PHAD, ChemOps, and PharmOps. In short, the entire organization of Novartis after Drug Discovery is separated along the lines of chemical and pharmaceutical objectives, including normally centralized personnel like financial analysts. As a result, implementing spray drying would require at the very least a redrawing of the traditional lines of chemical and pharmaceutical development and operations in oral dosage forms, since those are the only forms that spray drying have been shown to be useful for.

As it stands now, control is passed from chemical personnel to pharmaceutical personnel when the DS is formed. The DS, in preparation for an oral dosage form, is a finely ground API that can easily be combined with excipient for final pressing into a tablet form of the DP. With spray drying, where would we draw this new line of control? A natural solution is to shorten the end game in ChemOps and perform spray drying under the PharmOps umbrella. Essentially, once the Active Pharmaceutical Ingredient (API) has been synthesized and separated from other compounds in ChemOps, ship the solid to PharmOps and allow them to dissolve the API in a solvent, add excipients, and commence spray drying. Although perhaps harder to identify, implications on TRD would be substantial as well, particularly in PHAD. Spray drying has the potential to replace many pharmaceutical techniques that have not been fully explored, like varying modes of granulation and compaction, all of which have their dedicated scientists and engineers. Furthermore, spray drying knowledge is only held by a small subset of scientists in PHAD, and thus their group would have to expand.

While this solution may be worthwhile for implementing spray drying alone, it does nothing to address the fact that spray drying is a step on the road to continuous manufacturing. My analysis was done on spray drying alone to show that it could be effective on its own, but in the context of continuous manufacturing it is easy to see that the strategic implications are even more drastic. All of the divisions between ChemOps and PharmOps would be dissolved, since manufacturing would be taking place in one single facility. TRD would have to be much more integrated, since it would be possible to extract much more value if processes upstream were to increase the yield and decrease the costs of processes downstream. Optimizing the system as a whole would be a possible and real goal, and thus the design of TRD would have to stress this synergy.
Cultural Lens

As discussed earlier, the implications of spray drying being implemented on one specific drug may not have cultural consequences, but just the mere fact that Novartis is considering continuous manufacturing does change the norms of the organization. Continuous manufacturing is a paradigm shift in drug manufacturing for Novartis and as a result the people who are involved are enthusiastic. However, this enthusiasm may not spill over to people who have dedicated their careers to conventional manufacturing. The symbolic meaning of this project is different for different people— in some cases, it is another example of why Novartis is doomed to fail, and in other cases, it is step toward the future that could result in huge gains for Novartis in the battle for market share.

Political Lens

My project relates directly to the politics of this organization. If spray drying is implemented on one or more drugs, different skills will start to be valued more and others may no longer matter. Experts in wet granulation, roller compaction, and milling may begin to feel marginalized since their techniques are no longer the most desirable from an economic standpoint, and they may feel like the organization is blazing a trail and leaving them behind. Individuals who are not part of the continuous manufacturing initiative may feel left out as well.

Power is distributed quite widely in this project. TechOps is managing the continuous manufacturing initiative, but has to rely on PHAD and CHAD to actually execute. Within PHAD there are experts in conventional pharmaceutical manufacturing as well as spray drying, so the experts in spray drying have more impact. The fact that TechOps is pushing this but TRD has veto power with respect to what compounds to consider can result in communication problems and slow progress. At this stage, simply identifying a compound to try this technique on is difficult because so many individuals have so many responsibilities that lie outside of the spray drying/continuous manufacturing umbrella.

Once spray drying is implemented, there will be a small shift in power from ChemOps to PharmOps. At the same time though, since more value added activities will shift to PharmOps, ChemOps plants may look better (have lower costs) and PharmOps plants may look worse. Whoever is designing incentives for the managers of these disparate facilities will need to take this into account, and any increase in ChemOps profitability should be scrutinized carefully. A very real danger is the project proposal for spray drying to pass, design and development completed, and then
PharmOps plants are perceived as slacking because they are learning how to accommodate this new type of input and implement this new process. Too often, a change is made with good intentions but then stopped because people not involved with the change see the effects and do not know how the change can have domino effects.

4.2 Summary
My project grew out of the Novartis – MIT Continuous Manufacturing Center, as a way to strengthen the case for continuous manufacturing. What I have shown is that spray drying can in some cases stand up on its own, as a new manufacturing technique implemented in currently existing PharmOps facilities. The degree of economic benefit is related most directly to the solubility of the API in a common solvent that can be used for spray drying, and can be on the order of millions of dollars per year per drug. In addition, what I have shown through my three lens analysis is that actually putting spray drying in action could have definite consequences for the strategic organization and a little less impact politically. Since my research and analysis were done with spray drying of pharmaceuticals in a nascent stage, it would be premature to demand immediate implementation of spray drying. Furthermore, the compound I worked with is not a good candidate for spray drying. However, I have laid a path for future experimentation and analysis. The next compound tested should have these characteristics:

- Low hazard (less than Category 3) to allow for quicker experimentation
- High solubility (>3%) in a common solvent
- Suitable for oral dosage form

Attributes that would increase the economic viability of spray drying this compound:

- Simple end game (crystallization serves to simply separate API from solvent, not from other potentially harmful compounds)
- Complex PharmOps processing

X-ray diffraction (XRD) will provide insight on the materials structure of spray dried drug & excipient. Stress testing should be completed for at least four weeks using sodium chloride at 40 degrees Celsius. Economic analysis can be carried out in a similar way as the model I have presented in this paper.
Once spray drying experiments are carried out with this new drug, it will be necessary to finally test if the product can be pressed into a tablet. If this step is reached, it may be possible to pilot spray drying within a PharmOps facility in conjunction with a corresponding ChemOps facility. Once the economic benefit identified, analysis should be done to measure the gap between projected benefit and actual benefit. If the actual benefit is proven to be substantial, spray drying should be spread throughout facilities producing the drug.

In the context of continuous manufacturing, where an entire plant is being produced from scratch, spray drying will be part of the process from the ground up at a Greenfield site.
BIBLIOGRAPHY

5 Bibliography


APPENDIX I

Differential Scaling Calorimetry (DSC) results:

DSC measurements were taken to further characterize the samples.

<table>
<thead>
<tr>
<th></th>
<th>Tg [°C]</th>
<th>Melting point [°C]</th>
<th>Enthalpy of melting [J/g]</th>
</tr>
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<tbody>
<tr>
<td>Avicell 20-80</td>
<td>134.92</td>
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<td>Avicell 50-50</td>
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<tr>
<td>Aerosil 50-50</td>
<td>140.64</td>
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<td>-</td>
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</tbody>
</table>

Figure 33: 20% Avicell
Figure 34: 50% Avicell

Figure 35: 80% Avicell
Figure 36: 20% PVP

Figure 37: 50% PVP
Figure 38: 80% PVP

Figure 39: 50% Lactose
Figure 40: 50% Aerosil