Optimal Handling of Highly Active Pharmaceutical Ingredients during Milling and Blending Operations

by

Prashant Setty

B.S. Chemical Engineering, Rice University, 2006

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

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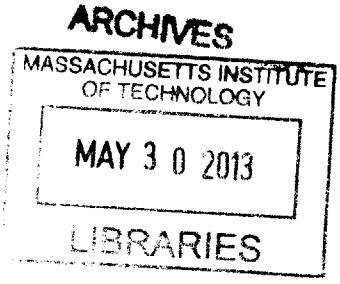

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Abstract

This thesis investigates best practices for Highly Active Pharmaceutical Ingredient (HAPI) milling and blending. We utilize a qualitative analysis centering on a benchmarking study and quantitative analyses using a probabilistic capacity simulation and tradeoff methodology. The analyses indicate that the growing number of HAPI products in a manufacturer's portfolio may result in capacity constraints. Therefore, we recommend that manufacturers pursue process improvement technologies.

Suggested process improvements include implementing online particle size measurement and Wash in Place (WIP) and Clean in Place (CIP) cleaning systems. Online particle size measurement allows for better process control and eliminates the need for HAPI blending for homogenization. Automated WIP and CIP systems decrease changeover time and allow for higher equipment availability. Additionally, the results of the analyses suggest that manufacturers consider standardizing transportation containers with the upstream vendors and downstream consumers. Lastly, from an organizational standpoint, we recommend that manufacturers include both subject matter experts and operations personnel when developing and implementing internal guidelines so as to ensure the guidelines are practical and uniformly applied.

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1 Introduction

Highly Active Pharmaceutical Ingredients (HAPIs) are a recent and expanding product offering in the drug development space [1]. Similar to normal Active Pharmaceutical Ingredients (APIs), HAPIs are the compounds in medications that provide therapeutic effects. What differentiates HAPIs from APIs is their potency [2]. Although the HAPI definition is not clear cut, in general we consider HAPIs to be compounds with therapeutic doses less than 1 mg [2], Occupational Exposure Limits (OELs) less than 10 $\mu g/m^3/8$ hr [3], or compounds that exhibit carcinogenic, mutagenic, teratogenic, or cytotoxic effects [4].

The pharmaceutical industry is searching for the best methods to produce HAPIs with respect to safety, quality, and cost. One specific area of concern is HAPI dry milling and blending, inherently dusty processes that are part of the manufacturing value stream. To date, there is no single standard for designing milling equipment specific to HAPIs. This thesis attempts to address this issue by providing an overview of some of the best practices currently in use and by applying Lean principles to a milling and blending workflow.

1.1 Problem Statement

The purpose of this thesis is to identify best practices for handling Highly Active Pharmaceutical Ingredients (HAPIs) in milling and blending operations. We propose that a HAPI manufacturer should utilize the specific best practices for which the benefits outweigh the costs. With this in mind, we provide a tradeoff analysis for opportunities and methodologies that can add value to a pharmaceutical milling operation.

1.2 Company Background

Novartis International AG is a large pharmaceutical developer and manufacturer with products in the brand name, generic, vaccine and diagnostic spaces [5]. This thesis utilizes the author's internship analyses for Novartis' Active Pharmaceutical Ingredient (API) Milling and Blending functions.

Organizationally, the internship took place in the chemical operations group, a unit inside the technical operations group of Novartis' brand name division, Pharmaceuticals (see Figure 1).

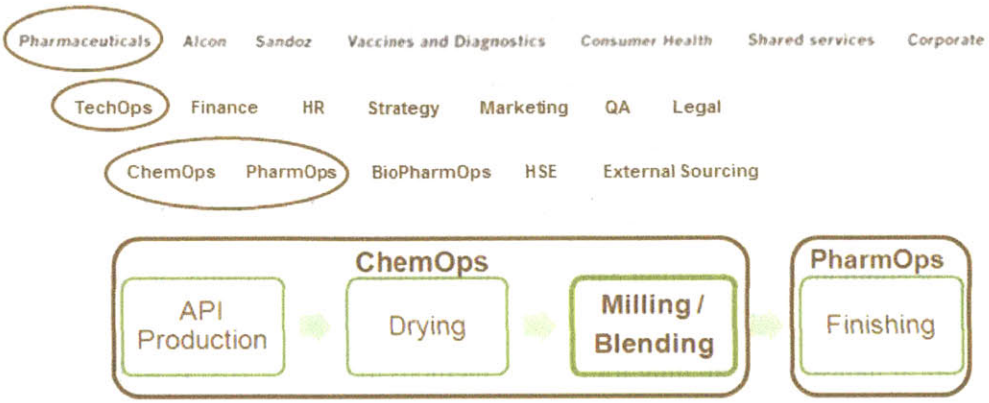

Figure 1. Project Organizational Structure

Geographically, the internship took place at one of Novartis' Milling and Blending Centers (MBCs) in Stein, Switzerland. Novartis plans to adopt industry best practices in the facility's design of any future expansion or new Milling and Blending plant. This new center will consist of multiple multi-purpose production suites, a subset of which is dedicated to HAPI products.

1.3 Thesis Overview

We organize this thesis in the following chapters:

- Chapter 1 provides an introduction to the problem of handling HAPIs in milling and blending operations
- Chapter 2 provides more detail on the milling process, health and safety containment, and product quality
- Chapter 3 details the qualitative and quantitative methodologies utilized in this thesis
- Chapter 4 identifies the results of the analysis

- Chapter 5 provides recommendations specific to pharmaceutical milling and blending and more general recommendations regarding organizational best practices in applying new safety and quality standards

2 Review of Current Equipment and Processes

2.1 Motivation for Processes

At the Novartis Milling and Blending Center, the current HAPI milling process follows the path we outline in Figure 2[1].

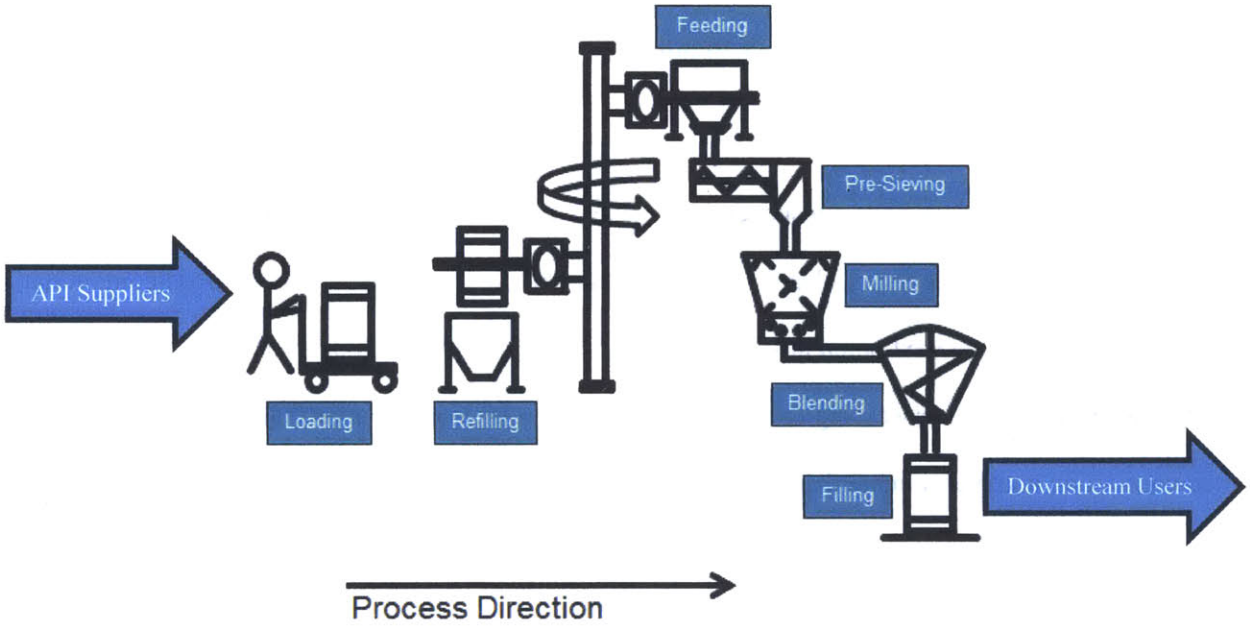

Figure 2. Milling and Blending Process at Milling and Blending Center (Current State)

The process begins with un-milled HAPI powder arriving at the Milling and Blending Center. The powder comes mainly from local suppliers. An operator transports the un-milled product to a production suite that contains the necessary milling and blending equipment. The operator repeats this "Loading" step until she has enough un-milled powder for a batch. The operator then performs the "Refilling" step

[1] An additional cleaning step between batches is not shown in process map

which consists of transferring (via gravity) HAPI powder from the original container(s) into an Intermediate Bulk Container (IBC). The IBC has two split butterfly valves – one on the top of the vessel and the other on the bottom. During the "Refilling" step, Un-milled HAPI powder is transferred through the top valve. Following the "Refilling" step, the operator utilizes an automated lifting arm to raise the IBC to the docking station located one floor above. The operator docks the IBC's bottom split butterfly valve to the docking station. The next step, "Feeding", consists of dosing powder through the system using screw pumps. The powder proceeds through a "Pre-Sieving" stage where it runs through a sieve to remove foreign debris. Following the "Pre-Sieving" stage, the powder is milled (the "Milling" stage) and then blended (the "Blending" stage). After "Blending", the operator fills empty drums with milled product and then transfers the drums to a holding area for distribution to downstream users. These downstream users combine small amounts of milled HAPI powder with excipients to create finished goods.

A cleaning step takes place between successive batches. If the next batch utilizes the same HAPI, the operator might perform a cursory cleaning step since he will not have to worry about cross-contamination. On the other hand, if the next batch utilizes a different HAPI, then the operator performs a thorough, verifiable, cleanse of the processing equipment to prevent cross-contamination. This process is quite time-consuming and we estimate that in the current process setup it can take seven to ten days for cleaning and verification.

2.1.1 Milling

Milling is the process of mechanically reducing the size of solids. It is also often referred to as comminution, grinding, disintegration, pulverizing, and dispersion [6]. Milling is an important step in the process of turning active pharmaceutical ingredients into viable drug products. Specifically, by reducing particle size, milling increases an API's rate of *in vivo* dissolution and/or increases its bioavailability [7]. Indeed, the industry trend is towards smaller particle size in order to increase API effectiveness [8]. Currently, only a few drugs utilize submicron particle sizes (100-200nm) but more are expected to do so

in the near future [9]. In addition to decreasing particle size, another important aspect of milling is its effect on particle size distribution. Particle size distributions impact powder mechanical properties, compression characteristics and dissolution performance [10]. The industry trend is towards narrower particle distributions to make products more uniform and effective.

There are many different commercially available mills. They vary based on the milling process they use. Milling processes may be subdivided into groups based on the medium in which milling occurs and the comminution method. Milling can take place either in gas (dry milling) or in liquid (wet milling). This thesis only considers dry milling as this is the sole type of milling used by Novartis at their Milling and Blending center. Comminution methods include impact, attrition and media. Examples of impact mills are hammer or pin-type. An example of an attrition mill is a jet mill. And, an example of a media mill is a ball mill [7]. This thesis considers the aforementioned comminution methods.

2.1.2 HAPI Blending

Subsequent to milling, we blend the HAPI powder. The purpose of blending is to homogenize the batch. Batch homogenization serves two related purposes. First, it means fewer samples have to be taken to obtain a representative sample of the powder population. Second, it helps ensure final product consistency. HAPI therapeutic doses are quite small (often less than 1 mg). Given that a batch size is often in the kilogram range, a batch might consist of millions of therapeutic doses. Homogenized powder means that each dose contains a similar HAPI particle size distribution.

2.1.3 Containment (Health, Safety and Environment)

Due to their high potency, working with HAPIs requires special safety considerations. These considerations fall under the category containment. With respect to milling, containment focuses on methods and equipment that prevent operator exposure to HAPI powder. For the purposes of this thesis, we consider engineered equipment solutions, administrative controls, and personal protective equipment (PPE) as ways to prevent operator exposure to HAPIs. Additionally, this thesis assumes that engineered

equipment solutions and administrative controls are more preferred solutions than PPE for addressing operator safety.

When considering which types of safety equipment to install, pharmaceutical manufacturers take in account the toxicity of their products. They face the option of creating bespoke solutions for each drug they manufacture, or creating different solution sets to address a broad swath of products. From a cost perspective, the latter option is preferable. One method of segregating products is to use an Occupational Exposure Banding (OEB) method [11]. We provide an example in Figure 3.

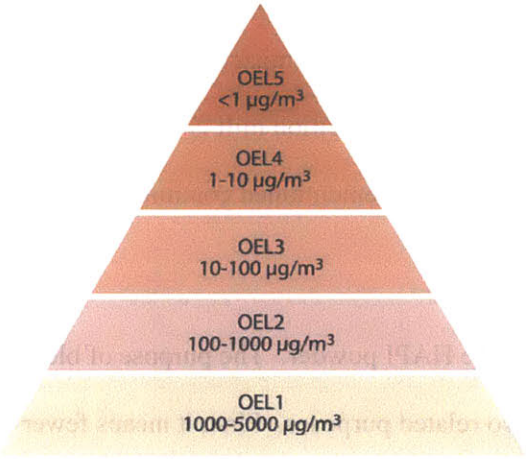

Figure 3. Sample Occupational Exposure Limit (Banding) Hierarchy [12]

Figure 3 shows five bands of products based on their Occupational Exposure Limit (OEL). Under this classification system HAPIs would fall under bands 4 and 5. A manufacturer might use this hierarchy to design processing suites and to define the PPE that its operators should wear. For example, a manufacturer might design a milling suite for band 4 and 5 that includes an isolator around the processing equipment. Furthermore, the manufacturer might stipulate that its operators wear full safety-suits with assisted air to prevent exposure to HAPI powder.

There are many different types of engineered containment solutions available. We refer the reader to "Handling Highly Potent Active Pharmaceutical Ingredients" by Axon et al and the ISPE's "Good

Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment" for a more detailed description of the available solutions [1] [13].

2.1.4 Good Manufacturing Practices

Good Manufacturing Practices (GMPs) govern pharmaceutical product quality. Within the US, the Food and Drug Administration (FDA) enforces product quality standards using its version of GMPs termed current Good Manufacturing Practices (cGMPs). For the purposes of this thesis, we will utilize cGMPs when discussing quality. cGMPs require that manufacturers utilize quality management systems and operating procedures to prevent adverse incidents such as product contamination and incorrect formulations [14].

With respect to multi-purpose machinery for HAPIs, cross-contamination is a major concern [2]. As we further describe in Section 3, manufacturers address this issue by verifiably cleaning equipment between different products. For milling equipment, verifiable cleaning is often done manually, making cleaning a time-consuming step in the manufacturing process.

Another aspect of cGMP is the requirement for consistent product. With respect to milling, this verification step consists of measuring the HAPI powder's particle size distribution.

3 Evaluation Methodology

In order to provide recommendations for handling HAPIs during the milling and blending processes, we want to know what alternatives are available and what their respective pros and cons are. We utilize both qualitative and quantitative methods for identifying and comparing alternatives.

3.1 Qualitative Benchmarking Study

To develop a set of best practices and understand the types of solutions that are available and feasible we perform a benchmarking study with pharmaceutical manufacturers, industry manufacturers and industry contractors. We aggregate the responses and order them based on effort.

3.2 Quantitative Capacity Modeling

As new highly active pharmaceutical ingredients enter the pipeline, we need to determine if the current processes and equipment are sufficient to handle expected demand. We utilize a Monte Carlo simulation methodology to quantify qualitative production forecasts. The results from the simulation illustrate the likelihood of capacity constraints. Insufficient capacity provides the impetus for investing in more processing facilities or for investing in improvements that decrease processing time or increase processing throughput. For the purposes of this thesis, we utilize the qualitative production forecast given in Figure 4.

Figure 4. Sample HAPI Production Forecast[2]

As we illustrate in Figure 4, the production forecast consists of different products that vary in production likelihood, quantity produced and production timing. For the Monte Carlo analysis, we assign probability profiles to each combination of production likelihood and quantity produced. To account for production timing, we assume that we are in a future state (in the case of Figure 4 we assume it is 2023). This

[2] This production forecast is meant to be representative only. Individual HAPIs are designated by letter.

assumption provides us with a "worst-case" capacity scenario since products that come online from 2014 through 2022 are still assumed to be in production.

We couple the production forecast (Figure 4) with the quantitative probability ranges and profiles given in Table 1.

Table 1. Probability Ranges and Distribution Type[3]

Variable Description			
Production Likelihood	**Definition**		**Distribution Type**
High	Produced 75% of the time		Binary
Medium	Produced 50% of the time		Binary
Low	Produced 25% of the time		Binary
Quantity Produced	**Low Value (tonnes/yr)**	**High Value (tonnes/yr)**	**Distribution Type**
High	5	10	Uniform
Medium	0.5	5	Uniform
Low	0	0.5	Uniform
Processing Times	**Low Value (hr)**	**High Value (hr)**	**Distribution Type**
Batch Time (20 kg)	4	10	Uniform
Setup Time	72	240	Uniform

The values in Table 1 are inputs in the capacity analysis. The Production Likelihood values are base case values. As part of a sensitivity analysis, we also perform the capacity analysis assuming ±15 percentage points from the base case. Batch Time refers to the total time to run a 20 kg batch of a single HAPI through the milling and blending facility. Without any assisted lifting devices, 20 kg provides a rough estimate for the heaviest amount of HAPI powder an operator can handle inside an isolator. Batch Time includes the time required to change containers for the same HAPI but does not include cleaning time. Batch Time may be different for each substance due to the mill type and substance properties. Setup Time refers to the time required to changeover from processing one HAPI to processing a different HAPI. Setup Time includes cleaning time and equipment change-out time. Note that by only considering processing times with respect to equipment, we inherently assume labor is not a limiting factor. This makes sense since capital expenditures for processing suites are significantly higher than operational

[3] The values in Table 1 are meant to be representative only.

expenditures for additional labor. Additionally, we assume that there are two HAPI production suites, which means that there are a total of 17,520 equipment hours available for use.

The last input in the capacity analysis is the number of changeovers per product per year. We term this value the number of campaigns. The number of campaigns reflects the number of times production shifts between different products. It provides an indication of the relative importance production planning plays in determining capacity constraints. We expect that a larger number of campaigns results in more required processing time and potentially less available capacity. We run the Monte Carlo simulation assuming between one and six campaigns per HAPI.

3.3 Discussion of Factors and Tradeoffs

We suggest proceeding with an alternative if we believe the benefits from its implementation outweigh its costs. We value the benefits and costs specifically for the Novartis Stein scenario utilizing the hypothetical production forecast from Chapter 3.2. We also identify the tradeoffs that lead to the decision in order to provide a more general solution.

3.4 Process Improvement Suggestions

3.4.1 Eliminate the refill step by transporting un-milled HAPIs in IBCs

The first tradeoff study examines whether it is better to transport un-milled HAPIs in intermediate bulk containers (IBCs) versus the current process of transporting un-milled HAPIs in drums and other small containers (see Chapter 1.3). The existing process is a holdover from open handling of less potent substances. Different suppliers ship un-milled APIs to the MBC and the MBC combines the drums and small containers into batches. This refilling step is time-consuming and a source of exposure opportunity. From a duration standpoint, refilling takes approximately six minutes per drum and a normal batch might consist of three to ten drums. From an exposure opportunity standpoint, additional containment equipment must be installed to prevent open handling if HAPIs arrive in drums or small containers. This

option lessens the exposure opportunity by removing the requirement to transfer powder from drums to a container.

The cost of using IBCs to transport un-milled HAPIs is a function of the number of IBCs and their associated split butterfly valves, and the cost of retrofitting the upstream producer's filling facilities to fill into IBCs.

The benefits of this option are the removal of an exposure opportunity, a decrease in labor time, a decrease in the number of drums, and less waste due to eliminating the refill step.

3.4.2 Ease an exposure opportunity by unloading milled HAPIs into IBCs

This option is similar to the preceding option, except that it takes place at a different step in the process. After milling is complete, the operator fills the milled product into drums (see Chapter 1.3). For HAPIs, we utilize additional containment to prevent open handling of the milled powder. One alternative is to use a split butterfly valve, with one half attached downstream of the blender and the other half attached to an IBC. However, this alternative precludes the use of drums. If we want to unload into drums, an alternative is to use a continuous liner system.

The costs of using IBCs for unloading milled HAPIs are a function of the number of IBCs and their associated valves and the cost of retrofitting the downstream consumers' facilities to accept IBCs.

The benefits of this option are a decrease in waste, less opportunity for operator exposure and quicker unloading.

3.4.3 Install online particle size measurement for each HAPI production suite

Online particle size measurement consists of sampling the process stream during milling activities and determining the particle size distribution. Since the purpose of milling is to obtain particles that fit a specific size profile, online measurement is a quick way to evaluate the milling process. Further, online particle size measurement analyzes far more samples than other offline methods, thereby providing more

confidence that an accurate particle size distribution is estimated. Multiple analysis and collection methods exist commercially.

3.4.4 Prevent future powder flow issues by empirically and quantitatively testing powder flowability during the research and development phase

In the past, the MBC has had to deal with powders with poor "flowability". These powders often arch [15] inside the container requiring additional operator intervention and physical stimulation to exit the IBC during the "Feeding" step. For HAPIs, operator intervention will be severely limited since the powder is inside production equipment which is in turn inside an isolator. Therefore, understanding which HAPI drug substances might exhibit poor flowability is important to ensure processing capability.

As it turns out, this information is relatively time-consuming to assess from first principles. One recent method utilizes Atomic Force Microscopy to measure inter-particle forces [16]. A powder's flowability depends on the cohesive and frictional forces between its particles [17]. These forces in turn depend not only on chemical composition and physical particle size, but also on idiosyncratic measures like the amount of compression force applied to the powder while it is transported in an IBC.

This option looks into the viability of empirically testing powder flowability prior to the production phase.

4 Results

4.1 Qualitative Benchmarking Study

The qualitative benchmarking study provides insight into both best practices and adoption of process improvement technologies. We tabulate the results of the benchmarking study in Table 2.

Table 2. Benchmarking Study Results

Topic	Low Effort	High Effort
Applying New Internal Standards or Guidelines	1. Roll out standard to project sites and let them apply them 2. Little interaction between central HSE/Quality organizations and site teams	1. After rollout, assign a site-led team to perform a gap analysis 2. Review gap analysis with both site management and central HSE/Quality organizations. 3a. With site management, define a timeline for fixing gaps or mitigation measures for addressing gaps 3b. With both site management and HSE/Quality organization, identify gaps that will not be addressed 3c. With HSE/Quality organizations update the standard if it is either too onerous or too lax 4. Build new projects to meet the newest guidelines
Capacity	Limit batch sizes to the maximum an operator can handle inside an isolator (20kg).	Assisted lifting devices are used inside isolators in order to handle batch sizes in excess of 20kg.
Flexible Solutions/Disposables	Do not consider waste minimization	Consider the holistic process and seek to minimize waste. The tradeoff is often between disposable plastics and cleanable permanent solutions. Also, consider any psychological effects associated with using flexible solutions
Cleaning	Operator cleaning	Wash in Place (WIP) followed by operator cleaning and verifiable Clean in Place (CIP)
Online Particle Size Measurement	Not utilized	Used for process control and release
Containment level to Utilize	Only utilizes OELs or OEBs	Process specific and includes the likelihood of exposure

We provide further discussion of the results from Table 2 below.

4.1.1 Best Practice for Implementing New Standards

As we illustrate in Table 2, companies have different ways of implementing internal containment and quality standards. The goals of these directives are that their implementation be uniform across an organization, that they be doable, and that their intent be met. What separates a highly effective organization from a less effective one is how these guidelines are implemented on site and how they are updated. From a site implementation standpoint, effective organizations rely on on-the-ground representatives to identify gaps in the existing operation. These representatives interact with the

HSE/Quality functional organization in case the standard's requirements are too restrictive or difficult to interpret. After the gaps are identified, the team, in conjunction with site management, develops a timeline for addressing the gaps. If the team chooses to not fix specific discrepancies, this information should be shared with the HSE/Quality function. This cycling back will allow the HSE/Quality group to adjust the standard if necessary and to ensure that the directive is uniformly applied throughout the organization. Finally, new projects should be designed to meet the standard. In general, we should recognize that guidelines are evergreen and that it is important that we achieve their intent rather than their prescriptions.

4.1.2 Expected Maximum Batch Capacity

From a capacity standpoint, top firms are able to handle large (>20 kg) batch sizes in rigid isolators. These sizes are larger than what one individual can manage in an isolator. Therefore, if batch size is a capacity constraint, firms can utilize assisted lifting devices or arrange isolators so that more than one operator can work on a batch.

4.1.3 Best Practices for Flexible/Disposable Containment Solutions

Most manufacturers utilize both flexible and disposable containment solutions. Two aspects of using these solutions that world-class organizations take into account are:

1. Waste Lifecycle Costs
2. Psychological Effects

When comparing disposable alternatives to non-disposable options, the additional costs associated with additional waste should be applied to the disposable options. From a psychological perspective, manufacturers should consider how their operators view powders in flexible containment solutions. Flexible isolators, for example, tend to look more flimsy than their rigid counterparts. An operator handling HAPIs in a flexible isolator may infer that they are less dangerous than HAPIs handled in a rigid isolator.

4.1.4 Best Practices for GMP Cleaning

To eliminate exposure routes, cleaning process equipment that has been in touch with HAPIs is best performed using automated devices instead of manually by operators. As it turns out, however, mills are difficult to verifiably clean using automated devices. The alternative that best protects operators is to first utilize a Wash in Place (WIP) system to remove bulk powders and lower the dustiness potential. Then, operators can dismantle the equipment that is difficult to verify clean and replace it with dummy spools. Finally, while the operator hand cleans the difficult equipment, a verifiable Clean in Place (CIP) system can clean the rest of the process train. One additional benefit of this cleaning concept is that it should be faster than cleaning everything manually. Assuming a 20% decrease in changeover time and utilizing the quantitative capacity model, we find that the likelihood of having insufficient capacity decreases by 12%.

4.1.5 Best Practices for Online Particle Size Measurement

Some manufacturers utilize online particle size measurement. They use it both for process control and for release. Methods used include Focused Beam Reflectance Measurement (FBRM) and laser diffraction.

4.1.6 Best Practices for Determining Containment Levels

The final topic we list in Table 2 involves defining which factors should influence the containment strategy. Top firms look at more than just Occupational Exposure Levels (OELs) and Occupational Exposure Bands (OEBs). They also consider exposure potential by understanding process-specific factors such as dustiness potential, quantity handled and exposure duration. They tailor containment solutions based on all of these factors.

When it comes to deciding the number of technical barriers to use for a given compound, different companies will not always utilize the same number. This is because each company utilizes different cut-offs to determine which containment strategies or equipment to use. Thus, an API that might require two technical barriers at Novartis might not require the same type of containment at a different company because the cut-off is different.

4.2 Quantitative Capacity Modeling

As we discuss in the Methodology section of this thesis, the decision to adopt HAPI process improvement technologies is in part driven by whether there is enough capacity in the system to handle expected HAPI production. If there is sufficient capacity, then a milling organization may not require (or elect to pay for) process improvements. On the other hand, insufficient capacity may drive a milling organization to implement process improvements. We provide the results of the capacity analysis below.

The capacity models indicate that two production suites may be insufficient for the production profiles we define in Figure 4 and Table 1. We provide the output from one of the 100 Monte Carlo runs in Figure 5.

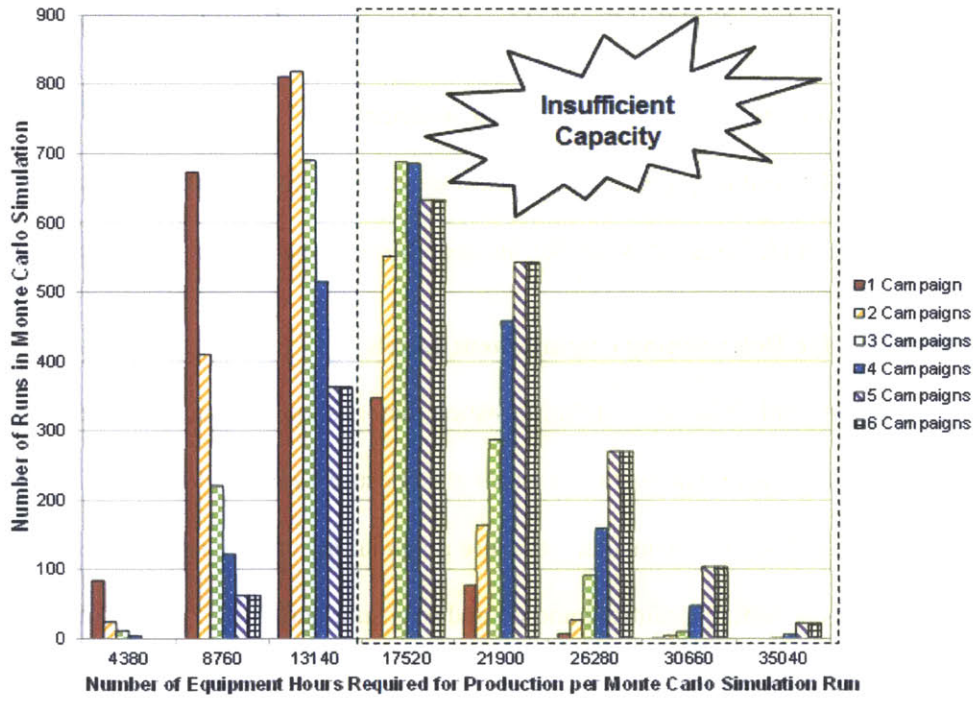

Figure 5. Sample Monte Carlo Simulation Output

Figure 5 shows the distribution of required processing hours for one Monte Carlo capacity simulation. We bucket the number of equipment hours and count up the number of simulation runs for each group. For example, for 1 campaign, we notice that 342 runs have required equipment hours between 17,520 and 21,900 hours. Since we assume that there are only two HAPI production suites, the maximum available

equipment hours is 17,520. Therefore, any runs that indicate required equipment hours in excess of 17,520 also imply that there is insufficient capacity. Each Monte Carlo simulation consists of 2,000 individual runs per number of campaigns. Results on the left hand side of the graph occur either due to fewer projected HAPIs making it to production or due to lower HAPI production volumes. The percentage of runs that highlight insufficient capacity are given in **Error! Reference source not found.**.

Table 3. Monte Carlo Simulation Output

Number of Campaigns per HAPI	Simulation Runs Identifying Insufficient Capacity (% of Total Runs, $\mu \pm 2\sigma$)
1	5.1% ± 1.0%
2	11.3% ± 1.2%
3	21.3% ± 1.8%
4	34.1% ± 1.8%
5	47.7% ± 2.2%
6	59.7% ± 2.2%

As we note in Table 3, the number of campaigns (i.e. changeovers) strongly affects the likelihood of having insufficient milling capacity. Additionally, even if there is only one campaign per HAPI per year, there is still a possibility of having insufficient milling capacity.

Since the Likelihood of Production inputs are best guesses, we also perform a sensitivity analysis by bookending their values by ±15 percentage points. Table 4 provides the results for the one campaign scenario.

Table 4. Sensitivity Analysis on Capacity Model (1 Campaign Scenario)

Likelihood of Production		Output		
Description	Base Case with Bookends	Lower	Base	Upper
Low	25% +/- 15%	2.1%	5.7%	10.3%
Medium	50% +/- 15%	3.9%	5.7%	7.1%
High	75% +/- 15%	3.2%	5.7%	7.5%

As Table 4 indicates, adjusting the Likelihood of Production value for the "Low" products results in the greatest change in likelihood of insufficient capacity (2.1%-10.3%). We note that despite decreasing the

Likelihood of Production values by a significant amount, the simulation still points to a non-zero chance of having insufficient milling capacity.

4.3 Process Improvement Suggestions

4.3.1 Standardize Loading and Filling Containers to IBCs

We find that the main tradeoff between standardizing "Loading" and "Filling" containers to IBCs and the status quo is that IBC standardization requires a significant upfront capital investment but provides a breakeven labor savings. We estimate that standardizing the "Loading" containers requires 75 one m^3 IBCs. The number of containers is a function of the MBC's distance from the upstream facilities' locations and the number of expected products. The cost for 75 IBCs with two large-diameter split butterfly valves and completing the necessary upstream facility modifications is roughly $2.4M. We compare this cost to the estimated labor savings associated with quicker loading and determine the payback period is fifteen years at a discount rate of 10%.

On the other hand, we estimate the number of "Filling" containers to be approximately one order of magnitude higher than the number of "Loading" containers. The number of "Filling" containers is a function of the number of downstream facilities, their locations and the number of expected products. Using labor savings alone, standardizing filling containers is not cost effective.

However, there are other benefits that we do not quantify. For example, we do not consider the value of decreasing the likelihood of operator exposure in monetary terms. Instead, given the current process steps, we note that utilizing IBCs in the "Loading" step reduces overall exposure likelihood more than utilizing IBCs in the "Filling" step.

4.3.2 Install online particle size measurement for each HAPI production suite

The qualitative benchmarking study indicates that online particle size measurement is already in place for process monitoring, process control and particle size distribution verification. In the current process these

tasks are performed by the "Blending" step and operator sampling. Therefore, utilizing online particle size measurement may obviate the need for blending equipment and operator verification of particle size distribution.

4.3.3 Prevent future powder flow issues by empirically and quantitatively testing powder flowability during the research and development phase

We find that one of the biggest concerns with empirically measuring powder flowability in the R&D phase is that pharmaceutical developers believe that testing consumes a large amount of product [18]. Through our research we found that recent product offerings in shear cell technology require only small amounts (~30ml) of powder [19]. Early measurements of powder friction and cohesion will provide insight into the likelihood of poor flowability and should allow steps to be taken, such as increasing outlet sizes or purchasing containers with steeper interior angles, to ensure these issues are addressed.

5 Recommendations

5.1 Specific Recommendations for Milling and Blending

Specific to milling we recommend utilizing process improvements that either increase throughput or decrease processing time. In addition to providing better performance, we believe that these improvements will decrease the likelihood of running out of milling capacity. Options for enhancing efficiency include utilizing online particle size measurement, measuring HAPI powder flowability prior to the production phase, and utilizing WIP and CIP cleaning processes. Online particle size measurement enables process control and particle size distribution verification. It may also remove the need for blending. Measuring powder flowability early in the development process ensures that design alterations can be made prior to the production phase for products exhibiting poor flowability. WIP and CIP cleaning systems allow for quicker changeovers between products.

Standardizing loading and filling containers is another process improvement area that may be beneficial for HAPI milling. Rather than provide a blanket recommendation, we believe the choice is idiosyncratic to the manufacturer. The tradeoff decision is between the upfront costs for containers and the benefits of lower labor costs and fewer exposure opportunities. The factors to consider when standardizing are the distance between the milling center and the upstream/downstream facilities, the number of different upstream/downstream facilities, and the number of different products. Larger distances, more facilities and more products make container standardization less appealing.

Finally, the choice to use disposable containment equipment is also idiosyncratic to the pharmaceutical manufacturer. The tradeoff is between lower upfront capital costs incurred from utilizing disposable containment equipment and extra costs associated with waste disposal. Additionally, there is a psychological component that pharmaceutical manufacturers should be aware of. Specifically, manufacturers who utilize disposable containment equipment should train their operators to understand that despite the containment equipment seeming less sturdy, the powder it contains is still dangerous.

5.2 General Conclusions and Recommendations for Handling HAPIs

Trends indicate that particle size will continue to decrease and that API potency will increase over time [20]. Manufacturers will need to have the right equipment in place to handle the smaller particle sizes and higher potency compounds. Moreover, they will probably continue to update their internal standards around quality and safety. Through the benchmarking study we note that certain companies have better methods of cascading standards through their organization.

The key to effective implementation is to engage both the group responsible for producing the standard and the groups responsible for implementing it in the production environment. This helps ensure that the standard implementation is doable and uniform throughout the organization.

Lastly, we suggest that companies investigate the tradeoff between API holding costs and capital costs. As this analysis indicates, an increase in the number of production campaigns may result in insufficient

capacity. Therefore, as part of an internal effort or future LGO internship, manufacturers should include holding costs and likelihood of insufficient capacity in the production planning model.

6 References

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