Framework for the Determination of Yield Limits

In Pharmaceutical Operations

By

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ABSTRACT

The manufacturing production of active pharmaceutical ingredients often involve a series of processing stages in which yield limits are prescribed to ensure that the target yield has been achieved for a batch and that the workers may proceed to the next batch of materials. Such yield limits is comprised of a maximum value for yields above 100% and a minimum value for yields of lower than 100%. These yield limits for each of the processing steps are conventionally prescribed based on accumulated experiences with production after an extended period of time. This paper is based on an internship project at a major pharmaceutical firm in Singapore, and it discusses the sources of yield losses and the reasons behind yield excursions which have not been well documented within the production facility. In doing so, the paper attempts to provide insights into the possible explanations for the current maximum and minimum yield limits application. Furthermore, using the yield limit values as applied for certain products, a preliminary framework is developed to provide a set of recommendations for the adjustment of conventional yield limit values to suit similar processing stages for the manufacturing of a novel drug product. This framework should prove to be useful in meeting the uncertainties inherent in the production of new products and in making initial recommendations for yield limits since there is usually limited experience from drug developments and clinical manufacture.

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CHAPTER 1 INTRODUCTION

1.1. COMPANY BACKGROUND

Established in 1891 as a subsidiary in the United States, Andrew & Co, Inc, located in Whitehouse Station, New Jersey, represents one of the largest pharmaceutical companies in the world today both in terms of market capitalization and revenue, alongside competing companies such as Novartis, Pfizer, Bayer, and GlaxoSmithKline. The company currently hires more than 60,000 employees worldwide, and has reported revenues amounting to $27,428 million and a net income of $13,024 million in fiscal year 2009.

Construction of the manufacturing division of the company (Figure 1) in Singapore began as early as October 1998, and involved an investment of more than US$300 million for the manufacturing of a variety of bulk active pharmaceutical ingredients, such as those for the control of asthma and the treatment of osteoarthritis and the relief of pain [1].

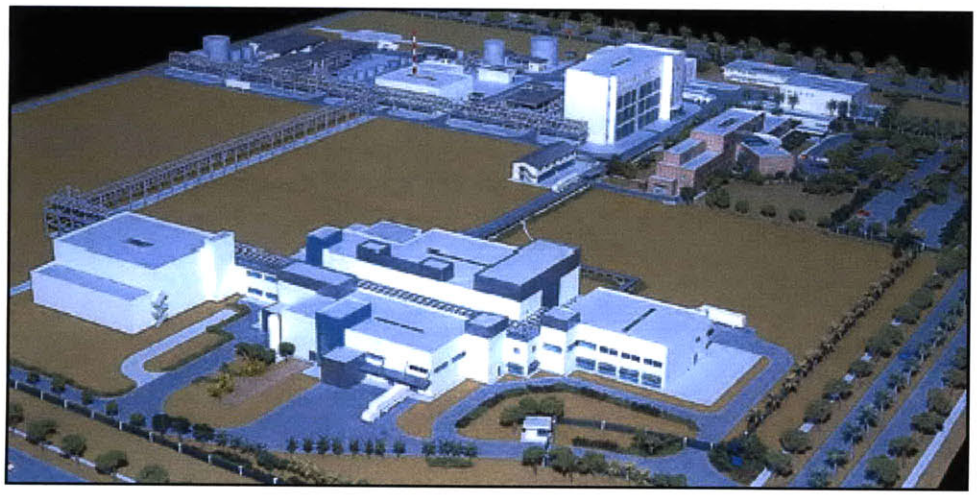


Figure 1 The manufacturing division of the company is located in Tuas Biomedical Park, Singapore

Located on approximately 50 acres of reclaimed land in Tuas Biomedical Park [2], the manufacturing division underwent further expansion to include a second and third facility in the next twenty years, bringing the company's total investment in Singapore to over US$780 billion. The Tuas Biomedical Park, developed by the Jurong Town Corporation (JTC), is primarily designed for production operations at major biomedical companies, and is based on the cluster

development strategy that seeks to bring about collective benefits through the sharing of key infrastructural provisions such as power, water, telecommunications, and gas and sewer requirements.

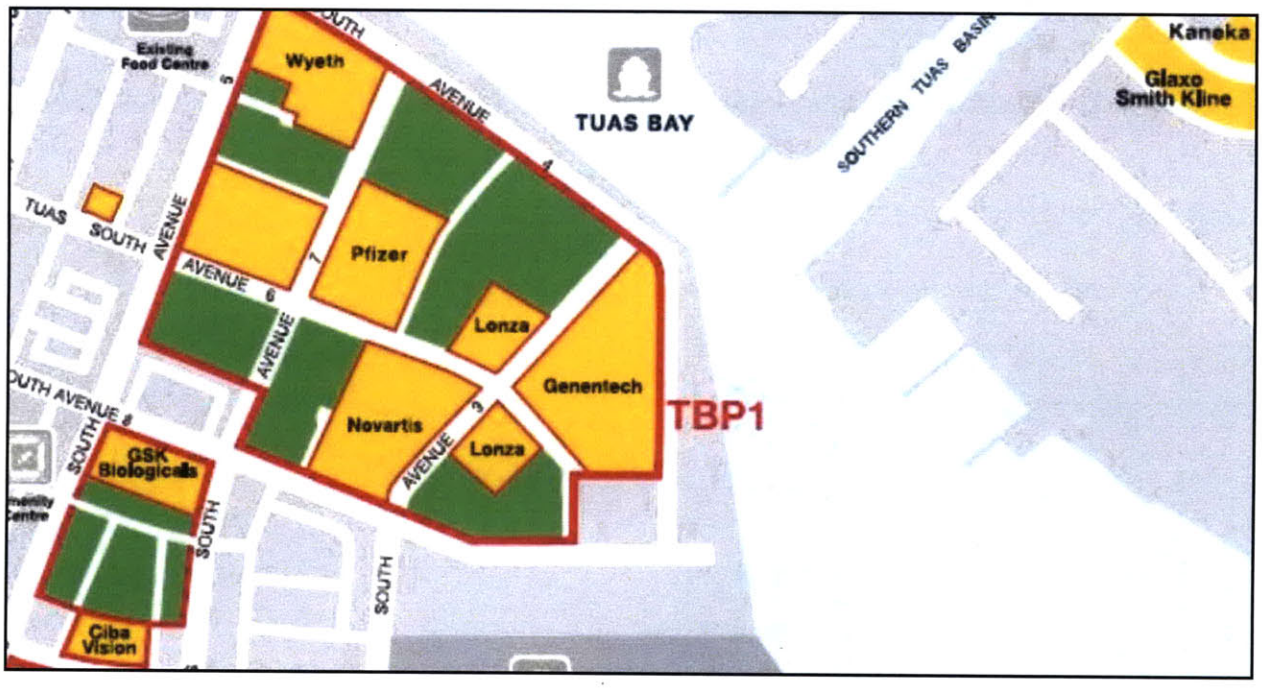


Figure 2 Map of Tuas Biomedical Park, Singapore

In a reverse merger completed in November 2009, Andrew & Co merged with another major pharmaceutical company in a deal worth $41 billion. Although the overseas rights to some blockbuster drugs still remains in dispute, the newly formed company has acquired the rights to the production of a number of valuable drug products. As of now, the manufacturing facility of the company in Singapore is comprised of an additional bulk active pharmaceutical ingredient (API) plant on top of the existing pharmaceutical formulation plant.

1.2. MANUFACTURING CAPABILITY

The manufacturing division of the company is comprised of the Active Pharmaceutical Ingredient (API) Facility at the west campus and the Pharmaceutical Facility at the south campus.

For the west campus, the API facility contains several dedicated lines for the production of steroidal drugs and the synthesis of finished drug substances which are incorporated into drug dosage forms (i.e. tablets, capsules, parenterals, etc). Figure 3 shows the manufacturing facilities available at the west campus, and a list of manufacturing capabilities at the API facility.

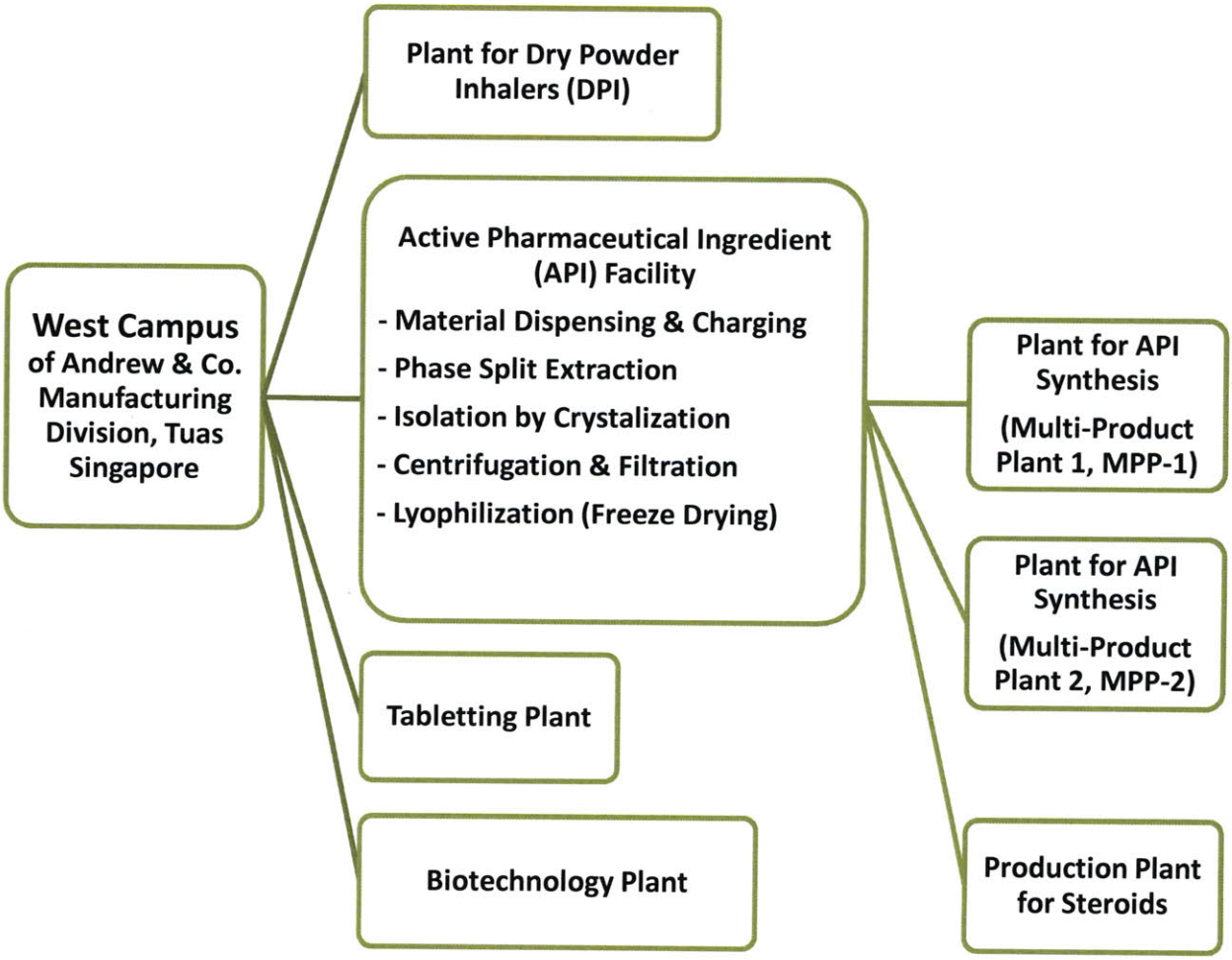


Figure 3 Manufacturing facilities at West Campus

For the south campus, there are a total of 4 pharmaceutical facilities, which are respectively referred to as Pharmaceutical Facility 1 (PF-1), PF-2, PF-3, and PF-4. During the course of the internship project, on the job training has been provided for some of the major processing capabilities at PF-1 and PF-3. This includes assembly and disassembly of process equipment, online process measurements and control actions, standard operating procedures for maintenance and cleaning. As will be discussed in later sections of this paper, in order to identify the critical operating parameters, sources of yield losses and yield excursions, it is necessary to first obtain a thorough understanding of the inner workings of each of the individual processing stages.

Figure 4 shows the pharmaceutical manufacturing facilities available at the south campus, and a list of the manufacturing capabilities at PF-1 and PF-3 which are of particular concern in this paper.

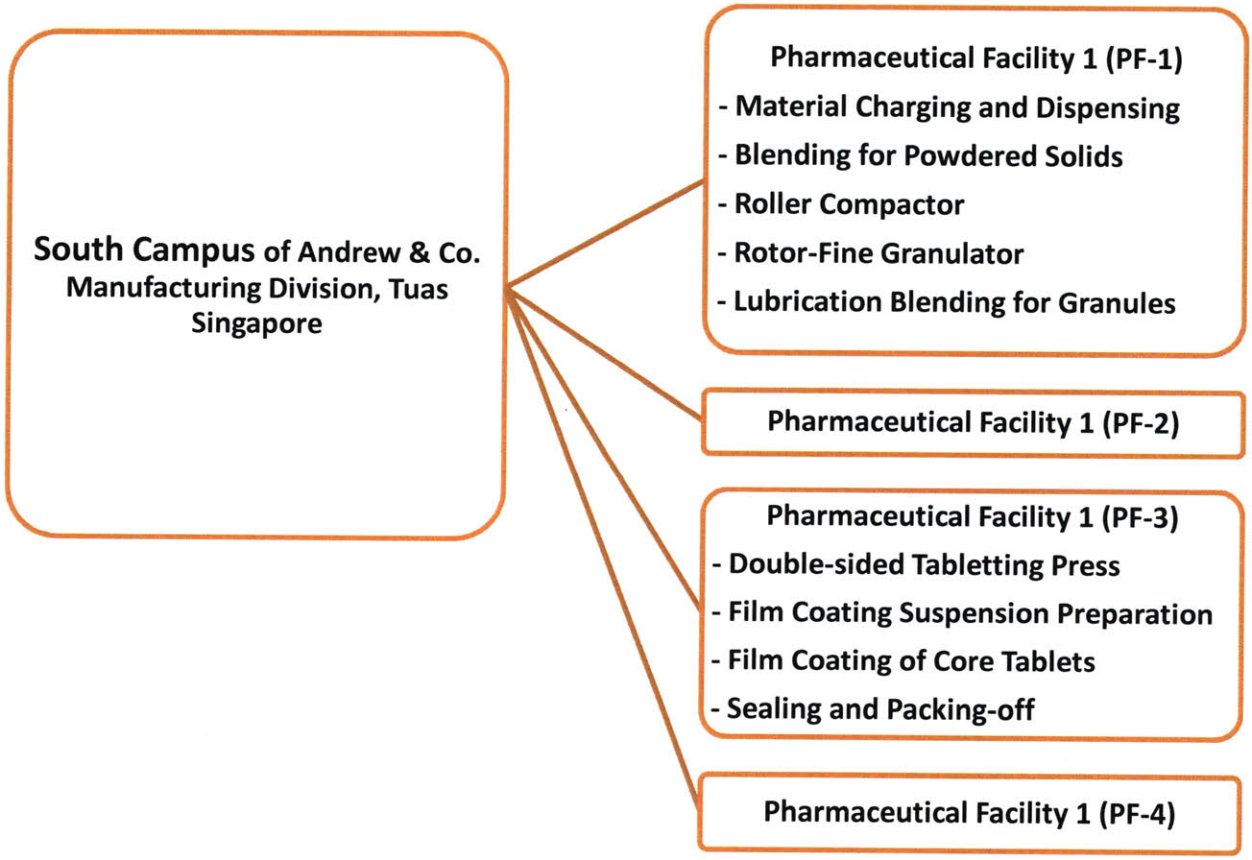


Figure 4 Manufacturing facilities at South Campus

1.3. COMPANY PRODUCT (PRESCRIPTION) OFFERING

According to the Department of Logistics & Planning, the core business of Andrew & Co lies in the discovery and development of products ranging from vaccines, prescription drugs, and consumer products to veterinary medicines.

For prescription drugs, there are a total of 12 categories as shown in the table below (Table 1). The products of particular manufacturing concern in the discussions that follow in the later sections for the various comparable processing stages have been described in greater detail in the table. These products include products 'V', 'ZA', and 'ZR', from the cardiovascular category, product 'R' from the infectious diseases category, and products 'N', and 'S', from the respiratory category.

Table 1 Major Prescription Products by Andrew & Co, Inc

Major Prescription Products by Andrew & Co, Inc		
Category	**No. of Products**	**Description of Certain Products**
Cardiovascular	9	**Product 'V'** ▪ Contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin) ▪ Medication is indicated as adjunctive therapy to diet to: i. reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia ii. reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid lowering treatments **Product 'ZA'** ▪ Contains an inhibitor of intestinal cholesterol (and related phytosterol) absorption ▪ Medication is indicated as an adjunct to diet to: i. Reduce elevated total-C, LDL-C, and Apo B in patients with primary hyperlipidemia, alone or in combination

		with an HMG-CoA reductase inhibitor (statin) ii. Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate iii. Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin iv. • Reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)
		Product 'ZR' ▪ Contains an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to: i. Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events ii. Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia iii. Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia iv. Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia v. Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy
Endocrinology	4 Products	
Gastroenterology	1 Product	

Immunology	2 Products	
Infectious Diseases	12	**Product 'R'** ▪ Indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients ▪ Inhibits the catalytic activity of HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication ▪ Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus.
Neuroscience	4 Products	
Oncology	5 Products	
Opthalmics	5 Products	
Respiratory	7	**Product 'N'** ▪ Nasal Spray for the treatment of: i. nasal symptoms of seasonal allergic and perennial allergic rhinitis, in adults and pediatric patients 2 years of age and older ii. nasal polyps in patients 18 years of age and older **Product 'S'** ▪ Contains a leukotriene receptor antagonist for the following: i. Prophylaxis and chronic treatment of asthma in patients 12 months of age and older ii. Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 15 years of age and older iii. Relief of symptoms of allergic rhinitis (AR): seasonal allergic rhinitis (SAR) in patients 2 years of age and older, and perennial allergic rhinitis (PAR) in patients 6 months of age and older
Urology	2 Products	
Women's Health	4 Products	
Others	2 Products	

CHAPTER 2 PROJECT DESCRIPTION

2.1. YIELD DEFINITIONS

The manufacturing production of active pharmaceutical ingredients often involves a series of processing stages. At each processing stage, yield limits are prescribed to ensure that the target yield has been achieved for a given batch so that the process engineers may proceed to the next batch of materials.

The yield limits for a certain *processing stage k* is generally represented as a range of acceptable batch yield values which is bounded by a maximum value for excursions and a minimum value for losses (i.e. $Y_{k,min}$ to $Y_{k,max}$). Before continuing further, it is necessary to define the following terms:

Batch Yield — The Yield for a batch of materials being processed at *processing stage k*, denoted as $Y_{k,actual}$, is defined as the mass ratio of the processed materials exiting the processing step to the total amount of material entering the process.

Maximum Yield Limit — The Maximum Yield Limit, denoted as $Y_{k,max}$, represents the upper bound for the acceptable batch yield values for yield excursions in which a yield of more than 100% is obtained.

Minimum Yield Limit — The Minimum Yield Limit, denoted as $Y_{k,min}$, represents the lower bound for the acceptable batch yield values for yield excursions in which a yield of more than 100% is obtained.

While it is straight-forward that the actual achievable yield is generally a value that is lower than a 100%, and that 100% represents the ideal batch yield to be achieved, it may be less obvious to the reader as to how a yield of more than a 100% is achieved. At this point, it is worthwhile to offer a general explanation to appreciate the need to define a Maximum Yield Limit term.

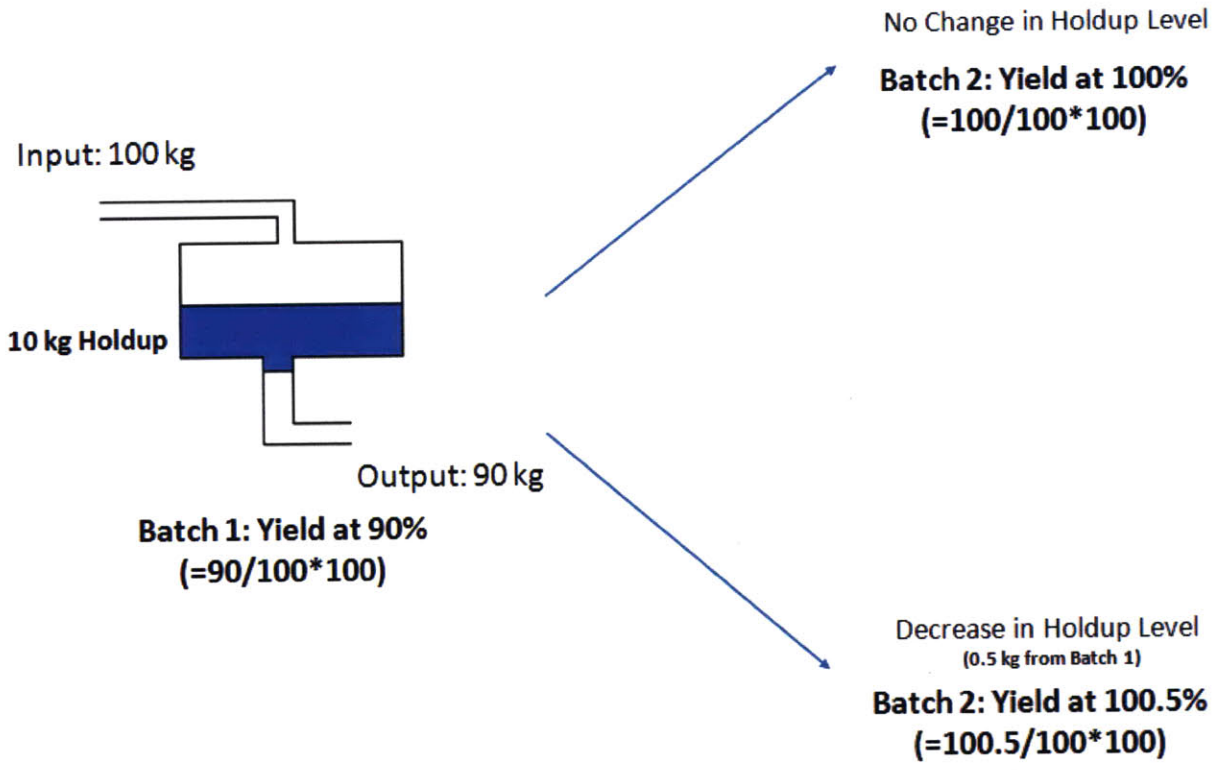


Figure 5 Example scenario in which a yield of more than 100% is obtained

Referring to Figure 5 for a given production process, one of the many reasons for a batch yield of more than 100% (or rather, a yield excursion) is that there is a decrease in the holdup level within the equipment. We can think of the holdup level as a form of buffer in which the accumulated amounts of materials within the equipment varies continuously. Assuming that 10kg of material is retained as holdups within the equipment during the processing of Batch 1 in which a standard batch total of 100kg of material is being fed, the yield obtained for Batch 1 is calculated to be 90% according to the definition as discussed earlier. In the next batch, three scenarios are possible.

In the first instance, a yield of less than 100%, as is normally the case, is obtained due to further retention with equipment or losses due to spillage and other reasons.

A second possible scenario involves a yield of exactly 100% during processing in which there is no change in the holdup level and no loss of material.

The third possible scenario, according to the example (although there are many reasons other than holdups), is that a yield excursion in which a yield of more than 100% is being obtained as a result of a decrement in the amount of holdup beyond than that of being lost. Assuming that 0.5kg of material from the holdup from the previous batch exits the process together with the current 100kg batch, the calculated yield of 100.5% is obtained as follows:

$$Y_{k,actual} = \frac{output\ mass\ of\ process\ material\ +\ gain\ from\ holdup}{mass\ of\ each\ batch\ size} \times 100\% = \frac{100 + 0.5}{100} \times 100\% = 100.5\%$$

As mentioned, there are several reasons for yield excursions at each processing stage, just as there are various sources of material loss. Variation in the material holdup level within the equipment is only one of many.

In a later section, the reasons for yield excursions and sources of material loss at each processing stage will be addressed in greater detail for a more complete discussion.

2.2. MOTIVATING EXAMPLE

These yield limits for each of the processing steps are conventionally prescribed based on accumulated experiences with production after a period of time. There is generally neither a scientific basis nor statistical analysis being performed when yield limits are prescribed using only some of many historical data.

According to an internal company memo for a certain Product 'N/L', the justification for prescribing a yield range of 94.9% to 99.0% at the high shear granulation process step is reported as follows:

"[Table 2] shows the accountable yield observed ... Based on the data collected thus far, it is recommended to set the initial accountable yield range at 94.9% to 99.0%. It should be noted, however, that this initial range is determined from the batches that were manufactured in the High Shear Module (HSM) that had not undergone full equipment train major cleaning or minor cleaning preceding the batch."

Table 2 Tabulated values of batch yield obtained at the high shear granulation process for Product 'N/L'

Batch ID	Accountable Yield	Rx Type	ID of Fluid Bed Dryer used	Notes
1009440	90.8%	Single-part	FB320	First batch to be processed in the HSM after equipment major cleaning.
1009450	94.9%	Single-part	FB320	--
1009460	95.5%	Single-part	FB320	--
1009470	93.3%	Single-part	FB320	Minor cleaning performed on full equipment train prior to this batch
1009480	89.8%	Single-part	FB310	First batch to be processed in FB310 after its major cleaning
1009490	96.0%	Single-part	FB320	--
1009500	95.8%	Single-part	FB310	--
1009650	98.2%	Four-part	FB310/FB320	--
1009660	99.0%	Four-part	FB310/FB320	--

The rationale behind the use of 94.9% as the minimum yield limit and 99.0% is relatively simple in this example. Using information on the batch yield for several batches of material processed at the high shear granulation stage, the lowest value for yield that was achieved is being prescribed as the minimum yield limit while the highest value for yield that was achieved is being prescribed as the maximum yield limit. The yield values obtained from the first batches are not considered since it is at the first stage in which material is generally observed to coat onto the walls of equipment, thereby giving a poor indication of the yield that is achievable at the processing stage.

As unsophisticated as the above described method may be in determining the maximum and minimum yield limits, the pharmaceutical manufacturing facilities of the company worldwide have been using this very method and have enjoyed a considerable amount of success in it operations in the last few years.

It should be further noted that more than often, the yield values achieved for most processing steps are usually close to 100% and far from the maximum and minimum yield limits, and that when such yield limits are applied, the values are seldom changed even after several years of operation.

Nevertheless, there exists an area for work that has been of interest to the pharmaceutical firm for a long time. Rather than an investigation into the basis behind the prescribing of yield limits, there is a need to consolidate a list of yield limits for the major processing stages together with

their critical operating parameters, and to document all sources of material loss and reasons for yield excursions for the major processing stages. With the gathered information, adjustments may be made to the yield limits for the various processing stages in the pharmaceutical manufacturing of novel products. This will be what this paper is generally about.

2.3. SCOPE OF PROJECT

Several major processing stages are common to the manufacturing of certain high-value products at the manufacturing division. They include processing stages such as blending of powdered substances, roller compaction, both high-shear granulation and wet granulation, tableting, etc.

Above everything else, it is crucial that a detailed hands-on understanding of these processing stages is obtained first. As such, this project involves a weekly basic practical training in equipment handling, operation, assembly and disassembly, maintenance, and cleaning at the pharmaceutical firm under the guidance of process engineers at each site during the summer period of the internship. Among the products being manufactured, the primary focus of the project will be on processing stages which are common to Products 'V', 'ZA', and 'ZR', from the cardiovascular category, product 'R' from the infectious diseases category, and products 'N', and 'S', from the respiratory category.

As mentioned in the previous section, there is a need for a comprehensive memo which documents the following information:

- Critical Operating Parameters of Major Processing Stages
- Currently Prescribed Maximum and Minimum Yield Limits
- Sources for Loss of Material at Each Processing Stage
- Reasons for Yield Excursions

Based on the collected information, a preliminary framework consisting of a set of recommendations will be developed for the adjustment of currently prescribed yield limits for use in processing stages of new products.

2.4. PROBLEM STATEMENT

Prior to commencing work on the project, a problem statement has been prepared and submitted to the internship company for approval. It is included in this thesis as follows:

The manufacturing production of high-value pharmaceutical products at the facility often involve a series of processing stages, such as the dispensing and charging of raw materials, roller compaction into ribbons, granulation, blending, compression into tablets, film coating, and bulk packaging. At each processing stage, yield limits have been prescribed to ensure that the target yield is achieved for a batch before the process engineers proceed to handle the next batch of materials. Such yield limits is comprised of a maximum value for excursions above 100% and a minimum value for yields of lower than 100%. These yield limits for each of the processing steps are conventionally prescribed based on accumulated experiences with production after an extended period of time. Working within the scope of yield loss and yield excursions during manufacturing, this project looks into the various parameters which are critical to equipment operations during the processing of materials, the sources of yield loss and the reasons for yield excursions at each of the major processing stages.

Furthermore, a preliminary framework that provides a set of guidelines for the use of yield limits in the production of novel products will be developed. Using the yield limit values as applied for major products, the framework will provide recommendations for the adjustment of conventional yield limit values to suit similar processing stages for the manufacturing of a novel drug product. This framework should prove to be especially useful in meeting the uncertainties inherent in the production of new products and in making initial recommendations for yield limits since there is usually limited experience from drug developments and clinical manufacture.

The proposed project will be sponsored by a process engineering Continuous-Improvement (CI) team at the Global Technical Operations (GTO) department of the Andrew & Co. Manufacturing Division in Tuas Biomedical Park, Singapore.

CHAPTER 3 LITERATURE REVIEW

A review on existing literature and previous work has been conducted in order to find out more about information pertaining to the process description of major products, equipment information on assembly, disassembly, maintenance, and cleaning. This initial step will provide the basic theoretical knowledge necessary for an inexperienced individual to engage in meaningful discussions with the management and the process engineers at the factory floor in later stages of the project.

The literature sources are comprised of the internal database of the company, worker's manuals and checklists, and training information pertaining to current good manufacturing practices (cGMPs).

3.1. ANALYSIS OF MAJOR PRODUCTS FOR PROCESSING STAGES

In order to identify the relevant processing stages for analysis, literature search on the company database has been conducted for products 'V', 'ZA', and 'ZR', from the cardiovascular category, product 'R' from the infectious diseases category, and products 'N', and 'S', from the respiratory category, based on recommendations by personnel at the Global Technical Office and the Department of Logistics and Planning.

As will be discussed in Section 6, the major processing stages include the dispensing and charging of raw materials, pre-blending of raw materials prior to roller compaction, dry granulation using roller compaction, post roller compaction blending and lubrication, compression into tablets, preparation of film coating suspension, film coating of core tablets, and the transfer and packing of coated tablets.

Bi-weekly walk-downs with members of the process engineering team at PF-1 and PF-3 also help to further clarify matters pertaining to the information within the literature.

3.2. WORKER'S CHECKLIST AND cGMP MANUALS

Worksheets available at the factory ground are made available for the workers to generate reports for individual processing stages on a daily or weekly basis. The following shows a list of such handouts which were referred:

i. Bilayer compression processing stage checklist
ii. Granulation processing stage checklist
iii. Blending processing stage checklist
iv. Compression processing stage checklist
v. Individual drum checklist for bilayer tablets
vi. Azo-charging checklist pharm-facility 3 (PF-3)
vii. Split process FIBC charging processing stage checklist
viii. Roller compactor & blending processing stage checklist
ix. Film coating processing stage checklist
x. PF-3 charging processing stage checklist
xi. Packaging of coated tablets processing stage checklist

Apart from the handouts stated above, cGMP manuals are referred to as well. Some of the more comprehensive ones are as follows:

i. Manual for performing tablet in-process testing and adjustment for compression parameters (Two-sided Tableting)
ii. Manual for providing product elegance evaluation (for Film Coating)
iii. Manual for management of finished products (for Packing-off and Sealing)

CHAPTER 4 METHODOLOGY & APPROACH

4.1. SCHEDULE FOR ON-THE-JOB TRAINING

Having identified the major processing stages for analysis, an on-the-job training schedule is proposed with the supervisor at the company for weekly rotations on each of the 8 major processing stages at PF-1 and PF-3. In doing so, the co-supervisors for each processing stage are determined, and the timings for morning walk-downs at the factory floor are scheduled. Additional provisions are made for basic training in the assembly and disassembly of process equipment in order to further understand the possible sources of loss of material and how holdups within the machinery can occur.

4.2. CONTINUOUS IMPROVEMENT TEAM

The continuous improvement (CI) team at the West Campus is the personnel who are mainly responsible for the management of this internship project so that the results and findings may be applied for the improvement of operations at the company. For the purpose of this internship, the CI team reviewed the proposed problem statement, and using it prepared an internal statement to the management to explain the following key points:

- Performance gaps and targets
- Potential benefits for value capture
- Follow-up issues
- List of related activities, tasks, and personnel
- Analysis and justification

Using the findings from this report on the sources of material loss and reasons for yield excursions for the processing stages, an internal memo was also prepared for submission to the company database.

4.3. SURVEY WITH ONSITE PERSONNEL

A survey is conducted with process engineers in the form of a focus group to better understand the inner workings of processing stages. During fort-nightly meetings which are set up for this

purpose, personnel are given a brief interview which is based on their respective description of how parts of the equipment function (such as the pre-compression, main compression step in tableting, or the rotor-fine-granulation step in granulation of sheet ribbons), the sources of yield losses and yield excursions, their individual suggestions on areas for improvement, and how satisfactory the yield values are according to yield limits which are in place.

4.3. THE AS/400 INFORMATION HANDLING SYSTEM

The AS/400 platform is used for the storing of large amounts of data at both the South and West Campuses of the company. Related information include planning of raw materials, costing, theoretical yields per batch, and location, time, and reasons for the transfer of finished goods and disposal of unused materials. In the initial stages of the internship, extra training has been provided for the plotting of product yield for several campaigns across multiple time periods. The AS/400 information handling system also in turn allows the identification of the major products produced at the Singapore facility.

CHAPTER 5 MANUFACTURING PROCESSES

5.1. MAJOR MANUFACTURING PROCESSES

The production of products 'V', 'ZA', and 'ZR', from the cardiovascular category, product 'R' from the infectious diseases category, and products 'N', and 'S', from the respiratory category at the manufacturing division in Singapore is generally comprised of a total of 8 distinct major pharmaceutical manufacturing processes that take place across Pharmaceutical Facility 1, PF-1, and Pharmaceutical Facility 3, PF-3. These processing stages are namely:

(i) Dispensing and charging of raw materials

(ii) Pre-blending of raw materials prior to roller compaction

(iii) Dry granulation using roller compaction

(iv) Post roller compaction blending and lubrication

(v) Compression into tablets

(vi) Preparation of film coating suspension

(vii) Film coating of core tablets

(viii) Transfer and packing of coated tablets

5.2. DISPENSING AND CHARGING OF RAW MATERIALS

The dispensing of raw materials takes place in the dispensing area where air flow is carefully monitor to ensure that the raw materials, in the form of fine powders, do no escape into the general manufacturing environment. In line with standard company operating procedures, this operation involves the sequential manual weighing of each raw material at the weighing stations and their transfer to a charge hopper for gravity discharge through a charge chute. A sieve fitted with a vibratory device is sometimes used for certain raw materials at this stage to achieve a particular desired powder fineness. In order to effectively carry out the dispensing and charging operation, the location of the dispensing area is strategically placed at a level directly above the next pre-blending operation. After exiting the charge chute, the released raw material enters an intermediate bulk carrier (IBC) which serves a temporary storage space that facilitates handling and transportation in later stages.

5.3. PRE-BLENDING OF RAW MATERIALS PRIOR TO ROLLER COMPACTION

The sequential release of raw materials in the previous processing operation usually leads to the formation of several powdered layers within the IBC after gravity discharge. In the pre-blending step, the objective is to prepare a homogeneous mixture of raw materials for roller compaction through mechanical mixing. After the IBC containing the materials are weighed to confirm the quantity of materials, the IBC is docked and secured to the blending station. Here, the IBC is rotated at approximately 10 revolutions per minute for a total of 100 revolutions, with a change in direction every 10 revolutions to ensure even blending.

5.4. DRY GRANULATION USING ROLLER COMPACTION

The entire dry granulation process consists of 3 separate sections, namely the charging area, roller compaction room, and the collection area, each of which is located at a floor below the other.

From the previous pre-blending operation, the IBC is transported to the charging area where the IBC is docked to the feed hopper leading to the roller compaction room located at the floor below. At this step, the pre-blended raw materials in the IBC are released to the feed hopper to maintain a prescribed level of feed material to the roller compactor downstream.

At the roller compactor, the pre-blended raw materials are handled via a twin screw feeder for gravity feeding. These powdered solids are then compacted between two cantilevered rollers at a fixed gap under a prescribed hydraulic force setpoint and roll speed setpoint. After compaction at the rollers, a material ribbon is formed. In order to form granules of a certain size, the ribbon is first allowed to pass through a sheet breaker and a series of inline Rotor-Fine Granulators (RFGs). The rotor-fine granulation process [3] is a continuous one that allows the processing of both dry agglomerates and slightly moist materials to granules via size reduction. During rotor-fine granulation, the rotor is operated in a diagonally positioned screen, with crushing effected by the rotor bars and compression. Different granule sizes may be obtained through the use of screens of different mesh sizes (Figure 6).

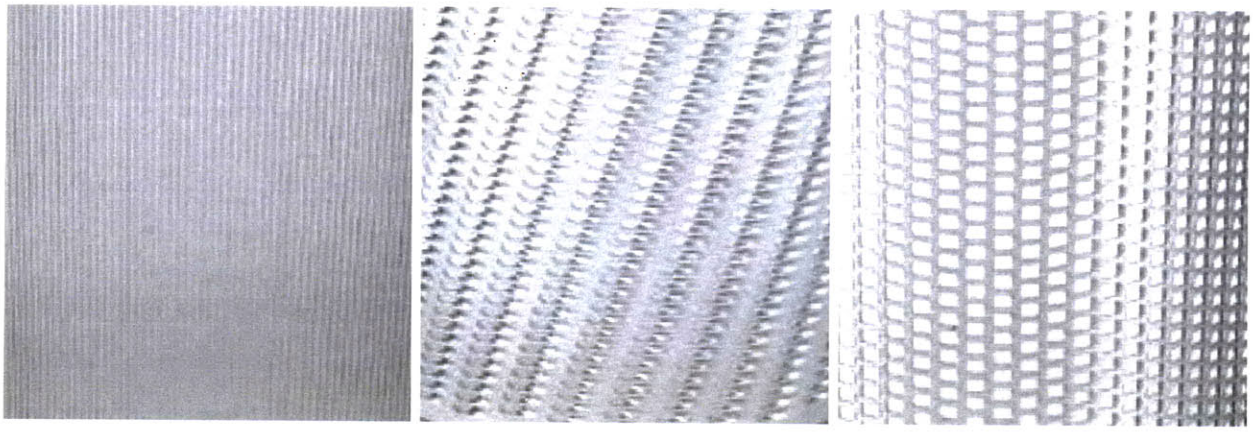


Figure 6 The use of different mesh sizes in rotor-fine granulation determines the quality of granules being produced

During rotor-fine granulation, the material is drawn into the working gap by the rotor before being crushed to further push the material through the mesh. Depending on the desired particle size and particles-size distribution, the granulator is adjusted for the mesh size or plate geometry, the working gap, the rotor speed, and the geometry and angle of attack of the rotor bars. As an illustrative example, the following figures show the inner layout of the granulator (Figure 7), the arrangement when linearly integrated with one another (Figure 8), and the tilted arrangement of the screen (Figure 9) which represents an improvement over the conventional U-shaped arrangement.

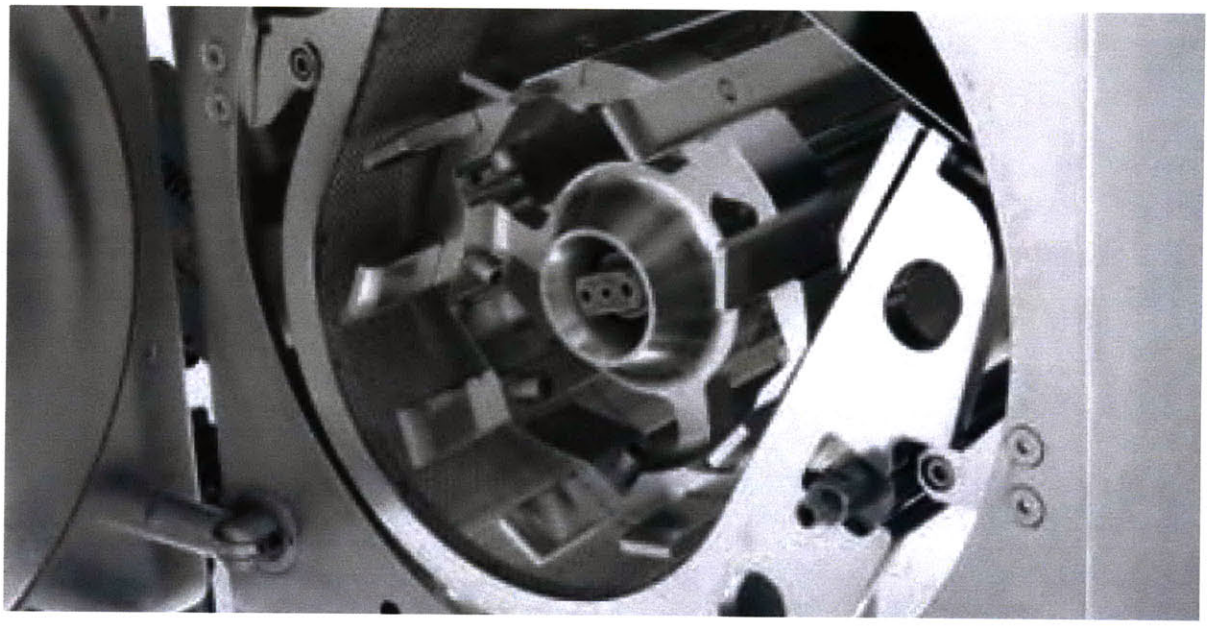


Figure 7 Inner layout of a rotor-fine granulator showing the tilted diagonal arrangement

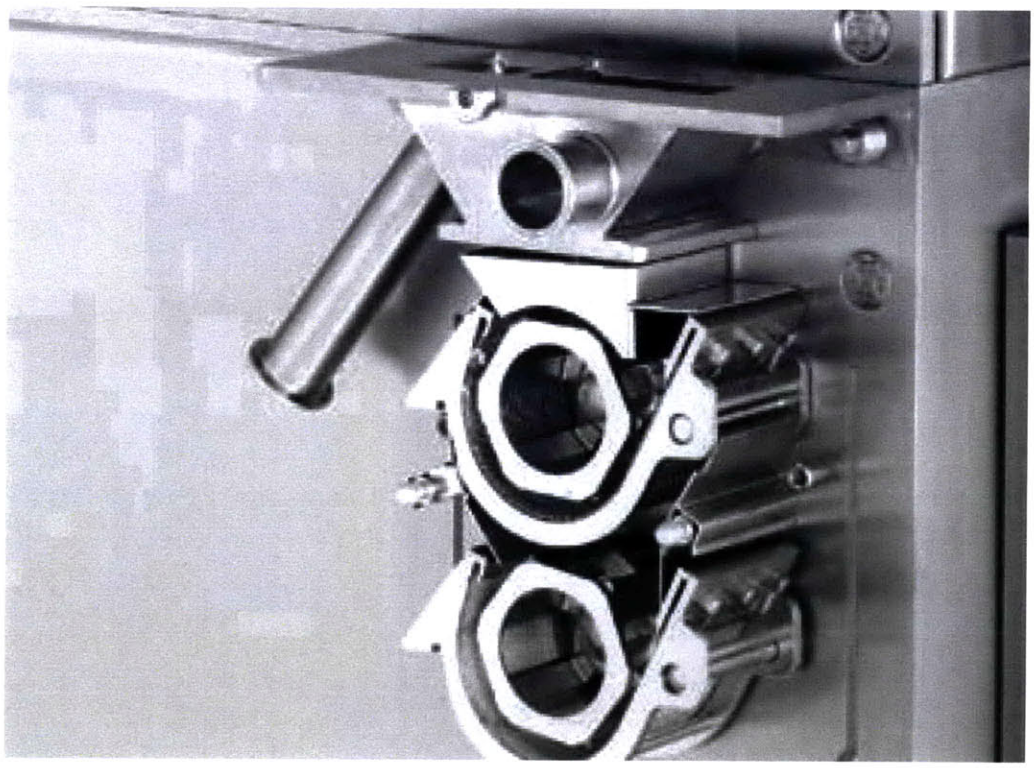
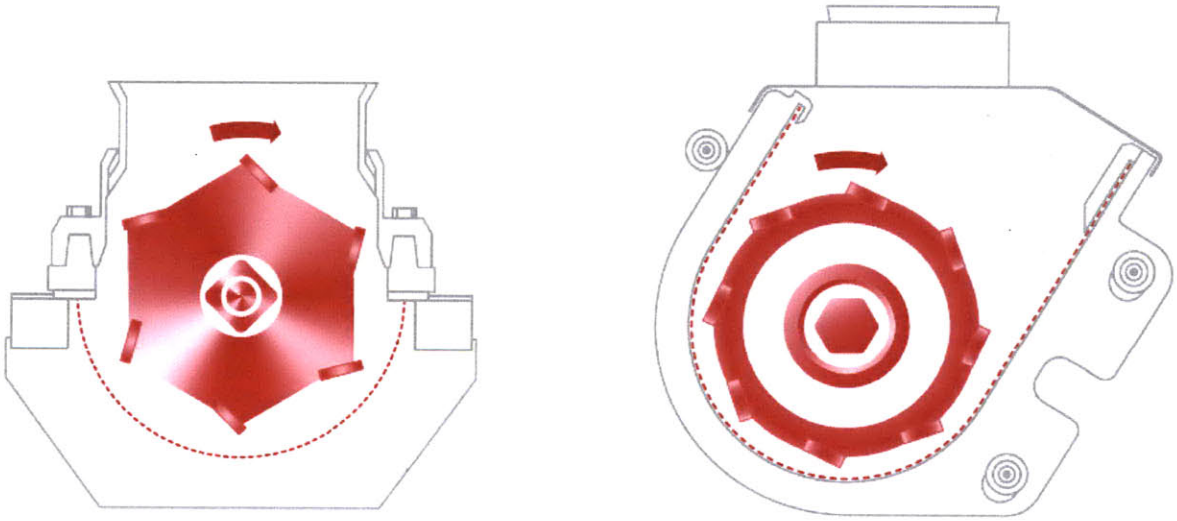


Figure 8 Two or more rotor-fine granulators may be linearly integrated to achieve a desired performance



Conventional U-shaped arrangement of the revolving screen.

Tilted arrangement of the revolving screen in the D Design.

Figure 9 (Left) Conventional U design with the revolving screen arranged symmetrically relative to machine center line, (Right) Tilted D design by the Alexanderwerk Company that considerably increases the effective area in the 3rd quadrant of rotation that in turn results in a higher throughput

Upon the completion of the granulation process, the granulated material is then discharged into a drop chute into the collection IBC for storage. This IBC is transported to another room for post roller compaction blending and lubrication.

5.5. POST ROLLER COMPACTION BLENDING AND LUBRICATION

The blending step in this process is different from that in the described previously in the second operation where powdered forms of different materials are mixed for homogeneity. In this step, the materials are in the form of granules of uniform composition and the primary aim is to lubricate each granule in order to facilitate compression during tableting at a later stage. A commonly-used lubricant is magnesium stearate which is added through a mesh sieve. The use of magnesium stearate serves three fundamental purposes of decreasing frictional forces at the interface between granules, improving anti-adherence properties in preventing deposits on the walls of machineries, and enhancing flow as a form of glidant. Since magnesium stearate exists in the form of lamellae crystals, layers of the crystal are sheared away as the blending process continues, thereby forming a layer of lubricant coating on the granules. The IBC is rotated at approximately 5 revolutions per minute for a total of 50 revolutions, with a change in direction every 5 revolutions to ensure even blending.

5.6. COMPRESSION INTO TABLETS

The tableting process involves the compression of the lubricated granules in a double sided rotary press using feed from a rotary valve through a connecting chute which delivers granules from the IBC. As an illustrative example, the Double Rotary Press developed by Fette America, Inc can be used in a typical tableting process for the handling of large batches of materials for tablet production via compressions from both sides. To further improve the production rate, the rotary press may be fitted with 2 filling devices on opposite sides of the circular rotary table, each with a set of pre-compression and main compression stations, and a tablet discharge chute. When the tableting process is completed on the rotary press for every half revolution, a total of 2 tablets are produced at each side. In this way, it is possible to produce more than 1 million tablets per hour under conditions of moderate performance and flexibility. It is appropriate to note that the Double Rotary Press is also operated in conjunction with a de-duster for the removal of dust and for the gentle deburring of tablets, a metal-detector for

tablets, and a device to ensure that tablets produced are within acceptable weight standards, thickness and hardness. The following figures (Figures 10, 11, and 12) show the suggested floor layout for double-sided compression tableting by Fette America, Inc that is available from the company website [4].

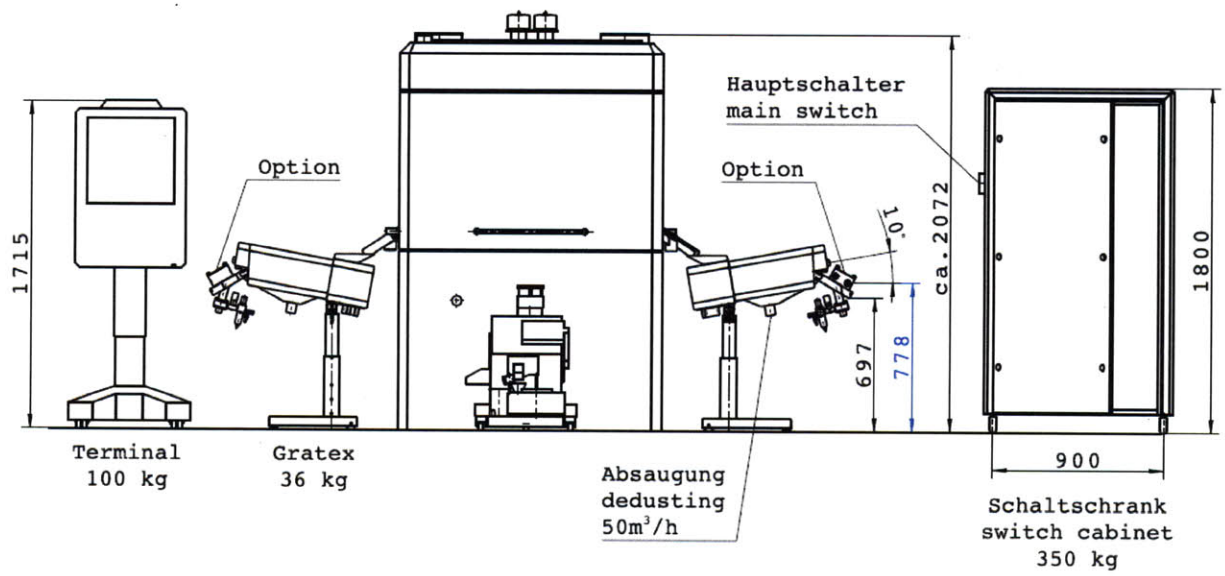


Figure 10 Front view of the double-sided compression tableting setup

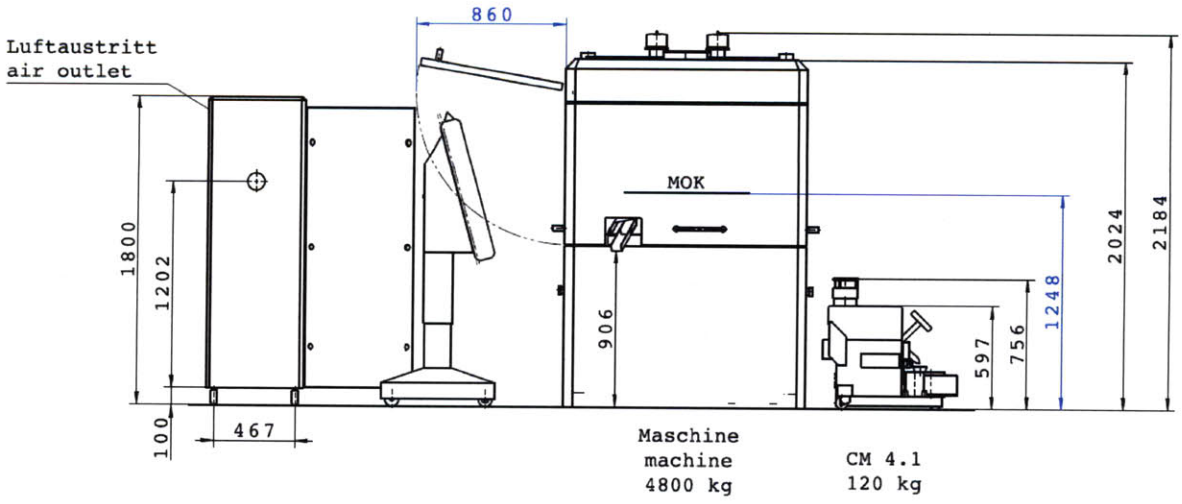


Figure 11 Side view of the double-sided compression tableting setup

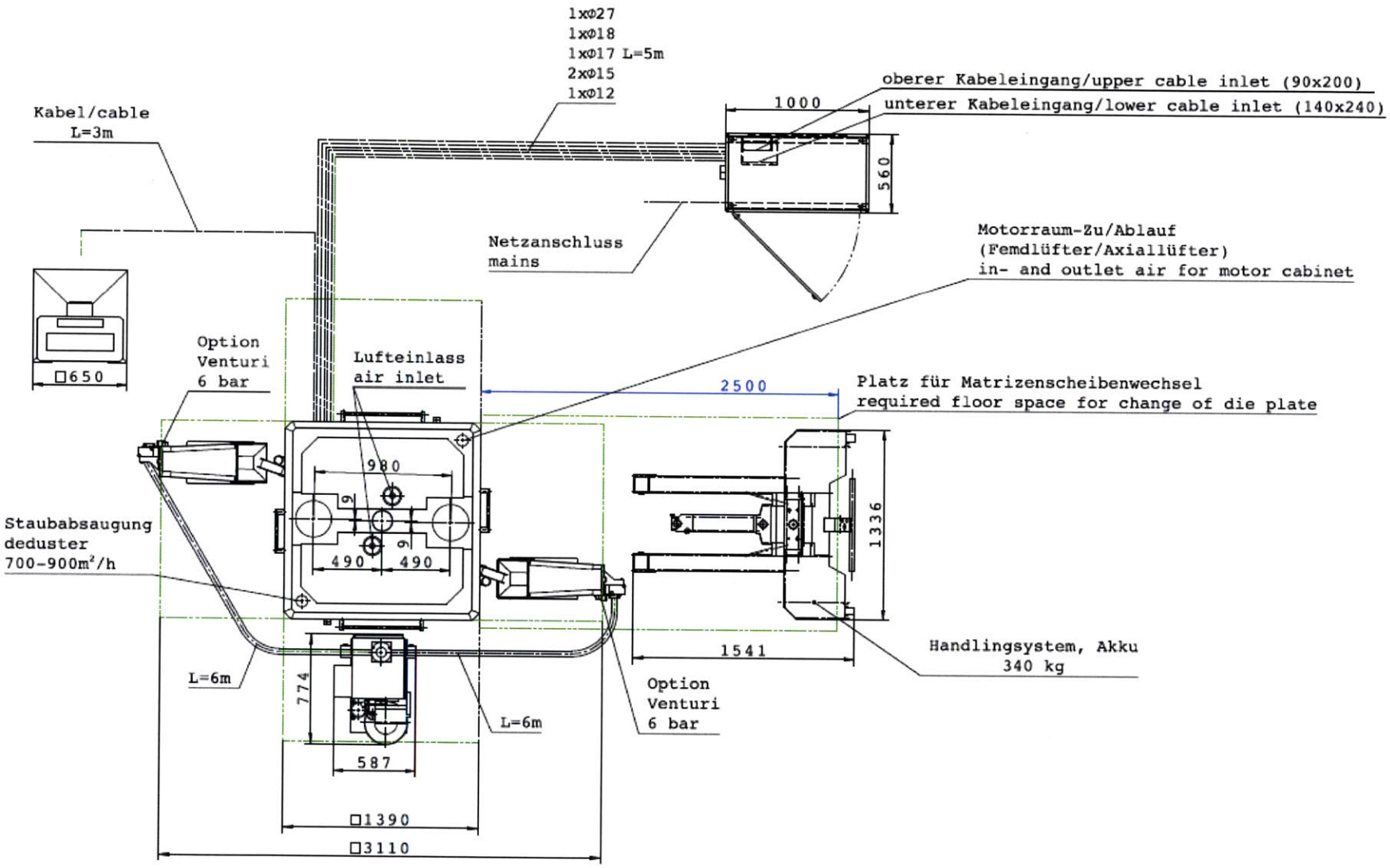


Figure 12 Aerial view of the double-sided compression tableting setup

With these peripheral devices in-place, the entire process of tableting via double compression can take place smoothly with in-process detection for acceptable physical properties, dedusting and deburring followed by checks for traces of metal within tablets prior to their eventual collection within tablet intermediate bulk carriers (t-IBC).

5.7. PREPARATION OF FILM COATING SUSPENSION

A stainless steel suspension preparation tank is used for the preparation of the film coating suspension. The preparation tank is fitted with an agitator that facilitates the dissolving of the film coating solids in water. As the film coating suspension is being prepared, the preparation tank is being positioned on a weighing scale in order to monitor the net weight of the preparation tank at any time, and to control the amount of purified water and colorants added. Prior to preparation, cleaning and sanitization is performed on all equipment parts (such as the hoses, spray nozzles, pump, spray gun tubings, recirculation return line) that come into contact with the film coating suspension. During preparation of the suspension, the agitator in the tank is set to rotate at a certain set point speed as purified water is added at room temperature. When the set point speed has been reached, the next step involves the controlled addition of the film coating solids in two batches. After the first batch is loaded, the agitator speed is increased to a higher set point before loading of the second batch is done. For Product 'R', possible film coating solids that may be used included those from Opadry II by the Colorcon Company. In choosing a film coating solid for use, points for consideration involves the coating process times, end-product appearance and elegance, moisture protection from the environment for sensitive tablet cores, and processing capacity for use with various coating equipments and substrates. The following table (Table 3) shows a list of desirable properties for the Opadry II film coating system obtained from a product brochure at the company website of Colorcon [5]. It is worthwhile to note that the list represents the characteristics that are important in the decision making framework for a desirable film coating solid to be used.

Table 3 Representative example of the desirable characteristics in the choice of a film coating system

Opadry®II Film Coating Systems
Superior Film Finish
• Higher film adhesion overcomes tablet edge defects
• Optimized film mechanics allow successful coating of difficult shapes and brittle or friable tablet cores, even at low application levels
• Improved light stability of pigmented formulas compared with traditional HPMC systems, reducing batch-to-batch or tablet-to-tablet color variation
• Enables excellent logo definition even with challenging designs
• Provides lower level of water permeation and superior oxygen barrier protection
Process Advantages
• Solutions can be applied at solids levels ≥ 25% for maximum film coating productivity
• Wide processing range simplifies use on all types of coating equipment, including continuous film coating machinery
• Improved bulk tablet flow properties on even non-standard shapes increases packaging speeds, resulting in time savings
• Equipment cleaning with water enables faster equipment turnaround
Available in Clear or Pigmented Formulas
• Ready-to-use dry mix contains polymer, plastisizer and pigments color-matched to product specifications
• Clear formulas available, which can also provide superior oxygen barrier protection or a natural core appearance (eg: bi-layer tablets or naturals)
Regulatory Acceptance
• Non BSE (Bovine Spongiform Encephalopathy) and TSE (Transmissible Spongiform Encephalopathy) implicated
• All formulations are specifically designed to meet the regulatory requirements of the user, regionally or globally, for either pharmaceutical or dietary/food supplement applications
• Aqueous-based for enhanced operator safety and reduced regulatory issues

Upon addition of all materials, i.e. purified water and the two batches of film coating solids, the preparation tank is left to stand with the agitator still in operation for a further 2 to 3 hours for compete mixing and de-aeration to take place. The film coating suspension tank is then transported from the suspension preparation room to the film coating room for the coating of core tablets.

5.8. FILM COATING OF CORE TABLETS

The film coating suspension tank (Figure 13) which has been moved from the suspension preparation room to the film coating room is positioned on a weighing scale to monitor the available remaining suspension during film coating [6]. The suspension tank is next connected to the suspension delivery system that facilitates the circulation of suspension using a set of peristaltic pumps through the spray nozzles into the film coater. At any instant, the suspension is kept at a certain prescribed agitation speed while being in continuous recirculation to and fro the film coater via the suspension delivery lines.

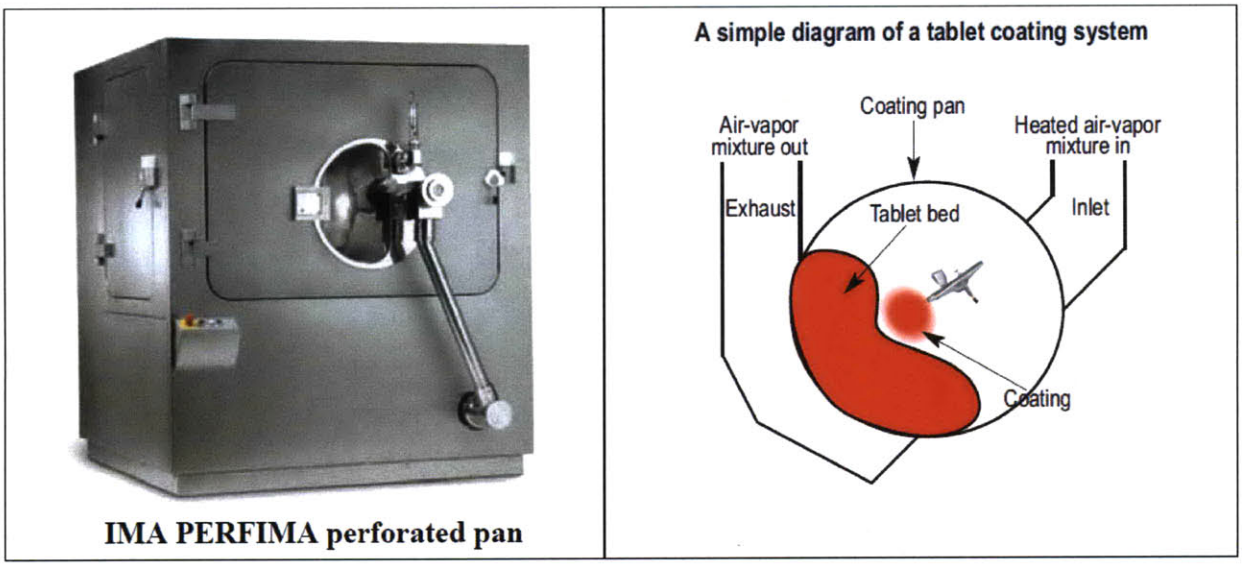


Figure 13 (Left) The PERFIMA pan coater produced by IMA Company for the film coating of core tablets (Right) the internal layout of a pan coater in clock-wise rotation

Before the release of the tablets, which are being held within the t-IBC, for film coating, the pan coater is pre-warmed to an exhaust temperature of approximately 45°C for the conditioning the internal environment using an internal air handling unit that is comprised of a blower and an exhaust fan which collectively control the temperature and dew point of the inlet air. As soon as the pre-warming step is completed, the uncoated tablets within the t-IBC are gravity discharged into the pan coater using a post hoist and a loading chute. The drum of the coater is jogged at appropriate intervals and a sufficiently low speed in order to distribute the tablets uniformly and to prevent the mounding of tablets. After all the tablets are discharged into the drum, the next step involves an elevation of the coater exhaust temperature to a slightly higher

value. This procedure involves the rotating of the pan at 5 RPM in cyclic mode, and it represents the second pre-conditioning step prior to the release of the coating suspension.

After the first and second pre-conditioning steps, film coating is initiated through the release of the coating suspension via the spray nozzles through a network of tubings (Figure 14).

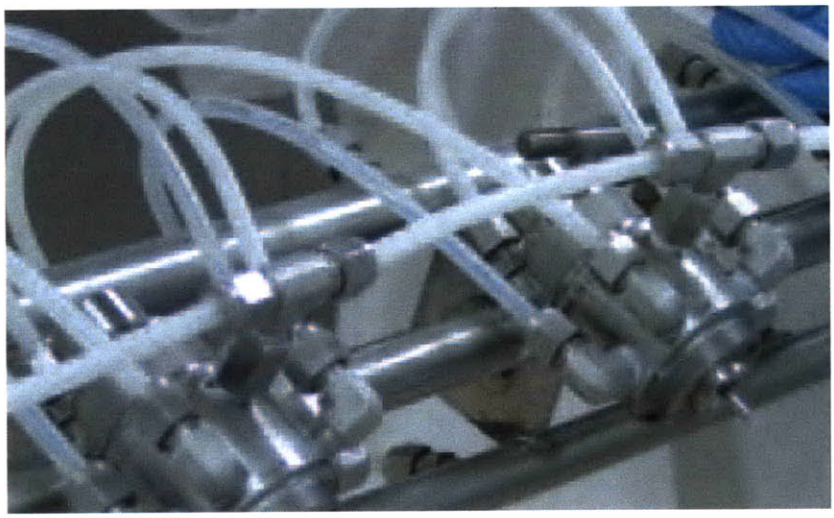
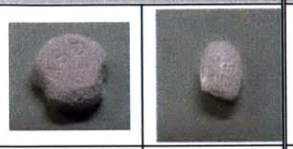
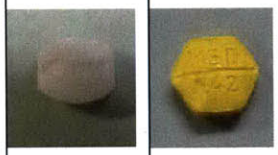
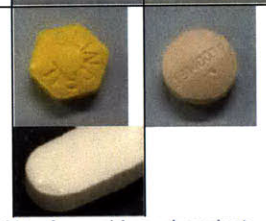


Figure 14 Network of tubings that connects the suspension tank and the film coater

There are a total of 2 phases in film coating. The first phase involves the pre-coating of the tablets at a relatively low suspension delivery flow rate of approximately 800mL/min and a target delivery weight set point of 15 kg. The second phase involves the actual coating of the tablets at a higher suspension delivery flow rate of 900mL/min and a target delivery weight set point of 40 kg. The overall effect of these two phases is to eventually coat the tablets to a target 3% weight gain. In order to ensure that the coated film on the tablets is completely dried, the pan coater is kept in operation for several minutes at the completion of the second phase. Having completed the film coating step, the tablets are then transferred into a t-IBC via gravity discharged for storage before use in the packing-off operation.

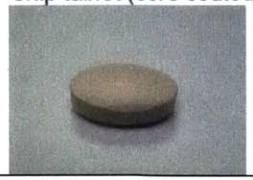
The process of tableting film coating usually leads to defects when certain critical operating parameters are not well-controlled. The following table (Table 4) shows some of the possible tablet defects that can occur during production.

Table 4 Tablet defects during production

CRITICAL	MAJOR	MINOR	ELEGANCE VARIATION
Wrong product code, embossing, shape or colour	Malformed tablets eg. tablets formed by broken punch, etc 	Grease spots 	Grease spots with ≤1mm^2 area impacted and does not affect any part of name or code 
	Product contamination or extraneous matter pending analysis 	Broken or eroded tablets (5 to 15% loss of tablet surface) 	Chipping and picking less than 5% loss from the main body of the tablet and does not affect any part of name or code 
	Broken or eroded tablets (>15% loss of tablet surface) 	Sticking or picking on face of tablet, <15% of surface 	Erosion affecting <10% of one side and product code & name is legible with no manipulation. Product code & name embossed on tablet is slightly difficult to read without manipulation but not illegible
	Capping 		
	Chipping and picking affects any part of the name or code 	Illegible product code or name on one side of tablet (double side embossing). Product code & name embossed on tablet is only legible with manipulation.	
	Illegible product code or name on both sides of tablet (double side embossing). Illegible product code or name on tablet (single side embossing).		

CRITICAL	MAJOR		MINOR		ELEGANCE VARIATION
Sticking – tablets stick together and come apart, leaving pieces of coating on one of the tablets	Picking - Rough pitted surface due to over wetting		Scuffing		Not Applicable
	Peeling of film coat (>10% of surface area)		Peeling of film coat (<10% of surface area)		

CLASSIFICATION SPECIFIC TO FILM COATED TABLETS ONLY

SPECIAL MINOR	
For film coated tablets, chips on the tablet surface (with or without core tablet exposed) may be observed after film coating. As long the defect observed is (a) is characterized by a small amount of core and/or film coating missing from the edge of the tablet (long side or short side) – such as one of the reference tablets on the right and (b) does not exceed the criteria as established for Minor defects in Appendix A, the defect will be classified and assessed as a Special Minor.	Chip tablet (core exposed)  Chip tablet (core coated) 

5.9. TRANSFER AND PACKING OF COATED TABLETS

Film coated tablets from the previous film coating operation are packed and sealed in specially designed HDPE drums in this step. The t-IBC containing the coated tablets is lifted to a height of approximately 2m before connecting the t-IBC at its bottom opening with a discharge chute. The bottom discharge valve of the t-IBC is then opened to allow the transfer of the coated tablets into an empty HDPE drum which has been positioned on a weighing scale. When the set-point weight of the drum has been reached the bottom discharge valve is closed to prevent further transfer of tablets. The pack-off procedure is then initiated for the sealing of the drum for shipping. During transfer and weighing, a heel drum is used for the removal and storage of any excess amount of tablets. After all drums have been filled, the heel drum will represent the final drum to be sealed and packed -off.

CHAPTER 6 RESULTS & DISCUSSION

The key findings of this internship project are addressed in this chapter. They have been organized according to the list of objectives as set out in the problem statement and will be discussed in detail in the following three sections:

i. Critical Operating Parameters

During the course of rotations at the various material processing areas such as the dispensing and charging rooms, blending chambers, tableting stations, packing and holding areas, the parameters which affect the batch yield at each processing stage are being identified. These parameters are the controllable attributes of the processing stages, and there are generally a set of recommended operating set-points although it is at the discretion of the process engineer to change these set-points during the course of operation.

ii. Sources of Yield Losses

Yield losses in the form of material losses to the vacuum system, at the sides of belts, spillages, or even unrealized film coating on tablets can occur during operation. These represent sources of material loss which are of concern to the management since materials and intermediates are costly, and are regarded to be more expensive towards the end of the series of processing stages.

iii. Reasons for Yield Excursions

As discussed in an earlier section, yield excursions beyond 100% at batches after the first can occur for a variety of reasons, the most common of which is hold-ups of powder and granules within machinery from the previous batches. Other reasons including the retention of uncoated tablets within coating pans and totes for storage will be discussed further in this section.

The preliminary guidelines for yield limits recommendation in the production of new products are presented later in Chapter 5.

6.1. CRITICAL OPERATING PARAMETERS

The quality of the intermediates and end product is determined by the set-points for the operating parameters which are critical to the process. Such parameters are referred to as critical operating parameters, and can vary from temperature at points of entry and compression pressure during tableting to the sizes of mesh use in granulation and rotational speeds of bulk carriers. In this section, the critical operating parameters for each of the major processing stages presented previously are discussed in greater detail.

Table 5 shows a summary of the critical operating parameters at each of the major processing stages.

6.1.1. DISPENSING AND CHARGING OF RAW MATERIALS

The chief concern during the dispensing and charging of materials is that there are usually several different kinds of raw materials of varying cost per unit mass to be transferred in different quantities into the IBC. In this case, the sequence of input of raw materials from the HDPE drums into the IBC becomes important, since a mistake such as that of a spillage which is unaccountable can become less expensive when transferred is performed in order of increasing cost of material per unit mass. However, it is appropriate to also note that there are other considerations involved apart from costs. There are cases in which the particle size and surface properties of the raw material are considered as well such as during the adding of a lubricant which requires an extra step in fixing a vibratory sieve to remove powder clumps.

6.1.2. PRE-BLENDING OF RAW MATERIALS PRIOR TO ROLLER COMPACTION

During blending operation, the aim to obtain a homogeneous powder mix in which the powdered form of all raw materials being charged in the previous step are distributed uniformly across one another. Since all the raw materials are present in powder layers within the IBC, the number of times in which the IBC is being rotated must be appropriate to achieve homogeneity. Furthermore, the speed of rotation must be high enough to encourage mixing, but not too high such that centrifugal forces cause the powders to remain relatively static

during rotation. In addition, the number of revolutions between changes in direction of rotation helps to improve mixing.

6.1.3. ROLLER COMPACTION

At the roller compactor, the feed is being compressed between two cantilevered rollers to form sheet ribbons to be processed in a later stage by the rotor-fine granulators. The thickness of the sheet ribbon that emerges from compaction is determined by both the applied hydraulic force and the amount of clearance between the two rollers. The strength of the sheet ribbons that are formed are in turn controlled by the collective contributions from both the rotational speed of the rollers and the applied hydraulic force. Finally, the size of the fragments formed from the sheet ribbons upon contact with the sheet breaker is dependent on the speed of the belts at the device; a higher speed results in smaller fragments, vice versa.

6.1.4. DRY GRANULATION

The objective of dry granulation is to obtain granules of a particular diameter by compressing ribbon fragments within a series of rotor-fine granulators. The size and geometry of the mesh plates to be used to form such granule thus affects the granules which are produced in this processing stage. Considering that most of the materials are located at the third quadrant of the granulators during operation, the working gap must be sufficiently large for a given volume of material. The choice of an appropriate rotor speed, and geometry and angle of attack of the rotor bars are also critical operating parameters to be determined.

6.1.5. POST ROLLER COMPACTION BLENDING AND LUBRICATION

In a similar fashion to the blending of powdered raw materials, the operating parameters of importance include the total number of revolutions, the rotational speed, and the number of revolutions before a change in direction. However, there is a need to also consider the type of lubricant to be used since the objective at this processing stage is to lubricate each granule for compression later-on. As discussed, the type of lubricant to be used will depend on the desired properties as a glidant and an anti-adherent.

6.1.6. COMPRESSION INTO TABLETS

The tableting process is generally regarded as an automatic processing stage in which little user involvement is expected. The average tablet hardness set-point, speed of rotation, and the set-point for the mean weight of 10 tablets are the only critical operating parameters that need to be inputted into the system before tableting commences. The average tablet hardness set-point ensures that the right pressures are applied at the pre-compressor and the main compressor. The set-point for the mean weight of 10 tablets allows real-time checks to be performed on the mass of tablets produced. The speed of rotation is based on a set of guidelines provided by the tableting machine manufacturer, and it determines the rate of tablet production.

6.1.7. PREPARATION OF FILM COATING SUSPENSION

The control of the agitator speed at different points in time during the preparation of the film coating suspension is the most important operating parameter at this step. The three set-points to be used for the agitator is determined by considerations for the ease of dissolution of the film coating solids, the extent of bubble formation, the setting rate of the film coating solids, and the amount of solids added relative to the amount of purified water used. It is worthwhile to note here that a strategy to achieve desirable dissolution is to release the film coating solids in several batches. This is usually done at the discretion of the process engineer and represents a departure from usual standard operating procedures.

6.1.8. FILM COATING OF COATED TABLETS

The coater pan environment within the film coater equipment is closely monitored during pan warm-up, tablet warm-up, spray phases 1 and 2, and the tablet drying phase. In order to prevent tablet defects such as peeling of coated films, chipping of tablet, and twinning (in which two or more tablets stick to each other after drying), the inlet air-flow rate, air temperature, and air dewpoint, suspension delivery flow rate must be carefully chosen. The integrity of the coated tablets produced at this processing stage is also determined by the speed of drum rotation and length of time allocated for drying. While a longer period of time may help

improve the drying of the film coating suspension on the core tablets, temperature unevenness within the tablets may ultimately lead to loss of strength and brittleness.

6.1.9. TRANSFER AND PACKING OF TABLETS

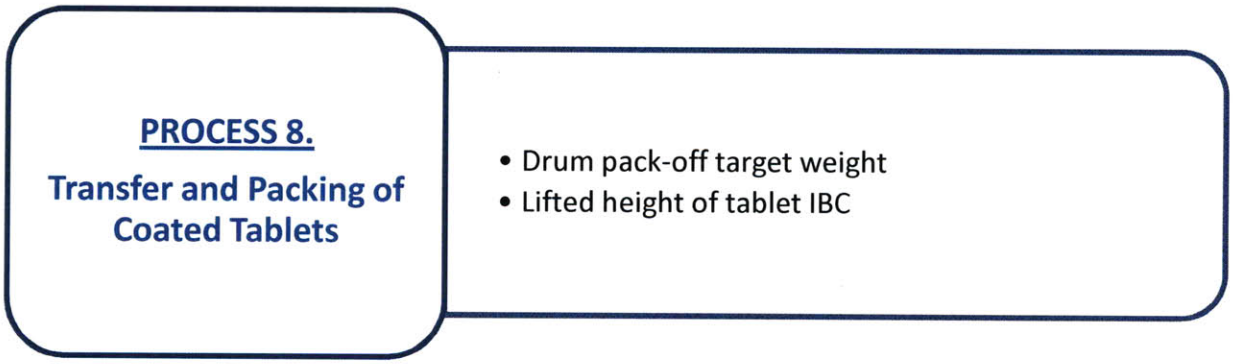
At this processing stage in which the finished tablets are transferred and sealed in HDPE drums for shipping, there are relatively few operating parameters that are of importance. In order to ensure that each drum conforms to quality standards for equal weight, it is necessary to impose a strict pack-off target weight. The lifted height of the tablet IBC may be of concern too for ease of access by the process engineers.

Table 5 Critical operating parameters for major processing stages

PROCESS 1. **Dispensing and Charging of Raw Materials**	• Sequence of material addition according to cost per unit mass,quantity, particle size, and surface properties • Allowance given for weighing of different raw materials
PROCESS 2. **Pre-Blending Of Raw Materials Prior to Roller Compaction**	• Number of revolutions per minute • Total number of revolutions • Revolutions before a change in direction
PROCESS 3A. **Roller Compaction**	• Hydraulic force set-point for cantilevered rollers • Gap between rollers • Roller speed • Sheet breaker speed
PROCESS 3B. **Dry Granulation**	• Mesh size • Plate geometry • Working gap • Rotor speed • Geometry and angle of attack of the rotor bars
PROCESS 4. **Post Roller Compaction Blending & Lubrication**	• Angle of inclination • Number of revolutions per minute • Total number of revolutions • Revolutions before a change in direction • Types of lubricant used

PROCESS 5. **Compression into Tablets**	• Rotational speed of double-sided rotary press • Mean weight of 10 tablets target set-point • Average hardness target set-point
PROCESS 6. **Preparation of Film Coating Suspension**	• Purified water charge target quantity • Film coating solids charge target quantity • Agitator speed set-point after charging with purified water • Agitator speed set-point after first charging of film coating solids • Agitator speed set-point during suspension mixing and deaeration

PROCESS 7.
Film Coating of Core Tablets
	• **Empty Pan Warmup**
	  • Inlet air flow rate
	  • Inlet air temperature
	  • Inlet air dewpoint
	• **Tablet Warmup**
	  • Inlet air flow rate
	  • Inlet air temperature
	  • Inlet air dewpoint
	• **Spray Phase 1**
	  • Inlet air flow rate
	  • Exhaust air temperature
	  • Inlet air dewpoint
	  • Rotational speed of pan
	  • Suspension delivery flowrate
	• **Spray Phase 2**
	  • Inlet air flow rate
	  • Exhaust air temperature
	  • Inlet air dewpoint
	  • Rotational speed of pan
	  • Suspension delivery flowrate
	• **Tablet Drying Phase**
	  • Inlet air flow rate
	  • Exhaust air temperature setpoint
	  • inlet air dewpoint
	  • Time for drying



6.2. PRESCRIBED YIELD LIMITS

For almost all of the major processing stages at the manufacturing division, the prescribed maximum and minimum yield limits are obtained based on a small sample from the second batch onwards.

The first batch is not used in the sampling since the materials generally forms a coating on the newly maintained and clean machinery, thereby resulting in a yield value which is not indicative. Using the small sample from the first few operations, the maximum and minimum actual yield values are noted for use as the maximum and minimum yield limits for a given processing stage.

It must be emphasized here that the above described approach to defining the maximum and minimum yield limits is certainly not one which is based on much scientific basis, as is previously discussed in Chapter 2. Neither is it an approach in which statistical analysis has being performed satisfactorily. Nevertheless, the prescribed yield limits serve a role in helping process engineers identify situations in which the yield for a given batch are way off limits. In most cases, the batch yield for the various major processing stages are at values that are very close to a 100%, and the maximum and minimum yield limits are generally only used as guidelines.

During the course of the internship, a list of the yield limits of various major processing steps is being compiled for the first time as shown in Table 6. The values given in the table is based on several helpful discussions with on-site engineers.

It may come as a surprise to the reader that the values shown in Table 6 have actually been already in use for at least 3 years (some as old as 7 years) without adjustments. Furthermore, the actual batch yield (with the exception of the first batch) for all the mentioned major processing stages have historically been reported to be in the range of 99.9 to 100.1%.

Table 6 Prescribed yield limits for major processing stages

Processing Steps	Yield Range	
	Min. Yield Limit	Max. Yield Limit
Dispensing/Charging and Pre-Blending	99.0	101.0
Roller Compaction & Post-RC Blending	98.0	101.0
Compression	97.0	100.0
Film Coating	99.0	101.0
Bulk Packaging	99.5	100.5
High Shear Granulation	94.9	99.0
Blending	99.8	100.2
Bilayer Compression	95.7	99.1

6.3. SOURCES OF YIELD LOSSES & REASONS FOR YIELD EXCURSIONS

6.3.1. ACCOUNTABLE YIELD LIMITS FOR DISPENSING/CHARGING AND PRE-BLENDING

Based on an internal Memo Ref. No. PTO-2010-0XX[1] prepared during the course of the internship from discussions with onsite process engineering teams, it was observed that the accountable yield range for the dispensing and charging of raw materials and the subsequent pre-blending operation prior to compaction for the production of products 'V', 'ZA', and 'ZR', from the cardiovascular category, product 'R' from the infectious diseases category, and products 'N', and 'S' from the respiratory category have been collectively taken to be **99.0 to 101.0%** at AMD Singapore. Here, the sources of yield loss and yield excursions at each batch are documented.

[1] The accountable yield range as discussed in section 6.3 and after will continue to be based on Memo Ref. No. PTO-2010-0XX for AMD Singapore

Sources of Yield Losses

- **Powder residues in the drum tipper charge port and vibratory sieve**

  After the raw material powder are transferred into the charge port and vibratory sieve (for Magnesium Stearate), layers of residual powder are found scattered to the sides and periphery of the equipment. Such residual powder is usually left for removal during cleaning, and they generally are vacuumed away as unaccounted material losses.

- **Powder residues in the drums and liners of raw materials**

  After returning back to its original position after reclining at an angle during charging, the drums generally still contain residual powder within themselves and at the sides. While every effort by process engineers is made to shake the drums during charging, residual powder in this form is retained. They are generally destroyed together with the HDPE drums which were designed for single time use after sealing off.

- **Unaccounted spillages during the charging of raw materials**

  Spillages almost seldom occur, but they represent a large loss in raw material per batch when workers accidentally topple the HDPE drums containing them. Recorded cases include spillages due to extrusions on drum crates which does not facilitate transfer onto the floor but instead act as an obstacle to the sliding of drums of the crates.

Sources of Yield Excursion

- **'Over-charging' of majority of the materials to be added**

  There is usually a tolerance of ±0.5% (kg of material) during the weighing of each material; charging beyond the total final weight occurs when most of the constituent materials are charged in the positive tolerance range of +0 to +0.5%

- **Differences in weighing stations**

  There are a total of 4 electronic weighing stations at the dispensing and charging area and each of these stations have been pre-calibrated at the end of each

month for accuracy. Due to the massive load that each station has to handle, the readings obtained from the weighing stations sometimes differ by approximately 100g after some time into operation. This presents a possible source of yield excursions when process engineers 'overweigh' the raw materials for charging.

- **Powder hold-ups within the equipments used for charging**

  Residual powders generally form a thick layer by adhesion onto the surfaces of the charging equipment. As such, residual powders from the previous batch within the same campaign may be retained only to be dislodged again in another batch.

6.3.2. ACCOUNTABLE YIELD LIMITS FOR ROLLER COMPACTION & POST-ROLLER COMPACTION BLENDING

The accountable yield range for the processing steps involving roller compaction, dry granulation, followed by lubrication and blending, has been generally accepted to be **98.0 to 101.0%**.

Sources of Yield Losses

- **Losses at the roller compactor**

  The roller compactor is primarily used for the formation of material ribbons through the hydraulic compressive forces of two cantilevered rollers. At this part of the machinery, powdered material that is not pressed to form ribbons are either recycled or scattered to the sides of the rollers. For those powder which remain at the sides, they are generally removed by vacuum during cleaning and maintenance at the end of a campaign.

- **Losses at the series of inline roto-fine granulators (RFGs)**

  While the series of RFGs are connected with one another without any spacings in between, materials generally become easily lodged to the inner sides of the

mesh and rotors. This is especially true towards the end of a batch when the amount accumulated becomes sufficiently large that mechanical vibrations cannot dislodge the material for processing. Similar to losses at the roller compactor, these retained materials are removed during maintenance cleaning at the end of a campaign and they represent a major loss of inline materials.

Sources of Yield Excursion

- **Retention of granules produced in the previous batch at the RFGs**
  Due to the spaces within the RFGs, granules produced in the previous batch may be retained but later enter the second batch of processed material. This is a form of "carry-over" that contributes to yield excursions at this processing step.

- **'Over-charging' of magnesium stearate lubricant**
  Approximately 50kg of magnesium stearate is being added at the blending stage after granulation. As mentioned, there is usually a tolerance of ±0.5% (kg of material) during the weighing of materials. Lubricants may be overcharged here as a result of considerations made in accounting for losses during the use of a vibratory sieve during charging.

6.3.3. ACCOUNTABLE YIELD LIMITS FOR TABLETING

According to process engineers at the tableting chambers, the accountable yield range for tablet compression is **97.0 to 100.0%**. In this processing step involving double sided compression using the rotary press, several sources of yield losses have been identified while no yield excursions are expected.

Sources of Yield Losses

- **Spillage around the periphery of the rotary press table**
  As the rotary table rotates rapidly to product approximately 250 tablets per second, powdered material is generally collected at the periphery of the circular

table. These residual powders are vacuumed during cleaning that is performed at end of every batch.

- **Spillage that were vacuumed without accurate records**

  In order to ensure occupational safety, a vacuum system has been incorporated as part of the tableting station. Although the rotary table has been contained within the station with the side glass panes sealed at their lengths, a vacuum system is used to remove air-borne powders to reduce the risk of inhalation. Some powdered material is lost to the system as a result.

- **Tablets that do not meet specifications for hardness & weight**

  Tablets that do not meet the requirements for target hardness and weight are removed for disposal at the end of batch processing

- **Tablets that are removed by the metal checker**

  Tablets that are found to contain traces of metal from machinery equipment are removed for disposal by the metal checker

6.3.4. ACCOUNTABLE YIELD LIMITS FOR FILM COATING SUSPENSION PREPARATION AND FILM COATING OF CORE TABLETS

The accountable yield range for film coating of core tablets using the prepared film coating suspension is generally placed at **99.0 to 101.0%**. The primary consideration here in the determination of a yield loss or yield excursion is the percentage weight gain of each core tablet. Generally, a 3% weight gain is expected for each core tablet.

Sources of Yield Losses

- **Less than 3% weight gain is achieved during film coating of core tablets**

  Here, the yield loss is a result of "undercoating" instead of a loss of material. Less than 3 kg of film coating is achieved for every 100 kg of core tablets.

- **Tablet hold-up in tote for uncoated tablets**

  During the gravity discharge of uncoated tablets into the pan coating for warming up, some tablets may be retained within the t-IBCs.

- **Tablet hold-up in folding of iris valve**

  The iris valve is comprised of a cloth that spreads out to form a barrier during closing but folds upon itself during opening. Uncoated tablets may be caught in the folding when the valve is open to release tablets.

- **Loss from tablet defects**

  Tablet defects such as cracking, twinning, and chipping can occur as a result of various reasons arising from non-uniformity of conditions within the pan coater. These tablets are sorted out in this processing step for batch disposal.

Sources of Yield Excursion

- **More than 3% weight gain is achieved during film coating of core tablets**

  The only means by which there can be a yield excursion in the film coating processing stage is that there is further tablet enrichment beyond 3%. This is generally a result of a time extension given for the drying of the tablets.

6.3.5. ACCOUNTABLE YIELD LIMITS FOR TRANSFER AND PACKING OF COATED TABLETS

The accountable yield range recommendation during the transfer and packaging is **99.5 to 100.5%** at AMD Singapore. Minimum yield losses and yield excursion are expected for this final step in the packing off and sealing of the drums containing the final coated tablets.

Sources of Yield Losses

- **Tablet hold-ups in tote containing coated tablets**

In this step, the coated tablets are transferred from the tote via gravity discharge. While it may be relatively to manually access the interior of the tote via a valve at the bottom, it is not possible to visually inspect if there are any tablets remaining within the tote.

- **Spillages during transfer**

  The transfer from the tote to the HDPE drums for packing and sealing-off can involve accidental spillages. This involves a loss in the total amount of coated tablets that are packed but is generally regarded as a rare event.

Sources of Yield Excursion

- **'Over-charging' of the HDPE drums**

  The standard size of each HDPE drum is 30kg regardless of the batch size for the product. Transferring beyond the total final weight of 30 kg (but still remaining within acceptable tolerances during weighing) is possible for most drums since the drums are handled by different persons and that the excess tablets at the last drum are usually distributed across all drums.

CHAPTER 7 RECOMMENDATIONS

The major findings of this internship project have been discussed in detail in Chapter 6. In this chapter, recommendations for improvements are made for the following.

i. **Scientific basis for use of yield limits**

   While the critical operating parameters, sources of yield losses, and reasons for yield excursions have been identified in this project, there appears a need to provide a link between these information and the yield limits being used. Furthermore, there is a also a need to further provide a more quantitative basis for the determination of yield limits to be applied.

ii. **Recommendation for new products**

   Despite the various shortcomings of the currently applied yield limits, an attempt is made for the development of a preliminary framework for the adjustments of currently applied yield limits for use in new products which requires similar processing stages.

7.1. NEED FOR A BASIS TO JUSTIFY USE OF YIELD LIMITS

The main focus of this internship project has been about the identification of key operating parameters that affect the operation output of processing stages, and the identification of sources of yield losses and reasons for yield excursions. This information has been included in an internal company memo for approval for use in the training of new workers or interns. While they provide a quick review of the essential elements of each process, it is seemingly difficult to explain the rationale behind the use of yield limits which are already in place.

Furthermore, there is a need to address the potential manufacturing impacts in the event that a wider or narrower range is being prescribed. In these cases, questions should be raised on the mechanisms by which an adjustment to the yield limits affects a processing stage. If the range of a set of yield limit values for a given processing stage is made wider, what are the related consequences? Similarly, if the range is made narrower, what will be its effects on operation? In

the event that there are no real consequences, an immediately obvious question to ask will be what is the use of yield limits then?

In Section 2.2, an explanation (based on an internal memo several years ago) was offered on the methodology in the choice of yield limits to use for the high shear granulation process. The observant reader would realize that the approach is really nothing more than choosing the highest and lowest actual yield values from a small sample size of processed batches initially. In this case, there lies an opportunity for improvement in the approach through the use of statistical methods that can help to quantitatively determine the yield limits and to provide a basis for their eventual application in operations.

7.2. RECOMMENDATION FOR NEW PRODUCTS

Despite the many shortcoming of the current use and determination of yield limits presented in the previous section, a preliminary framework will be presented for the adjustment of currently prescribed yield limits for use in the pharmaceutical manufacturing of a novel product. It is appropriate to note here that the real benefits of such a framework must be addressed so that its use can be justifiable.

7.2.1. ACCOUNTABLE YIELD LIMITS FOR DISPENSING/CHARGING AND PRE-BLENDING

The recommended yield range for new products remains at **99.0 to 101.0%**. The rationale for this choice is based on the development work design space, initial control space which is documented in regulatory documents pertaining to new drug application (NDA) filing procedure by the company [7]. As such, no adjustments need to be made at this processing stage.

7.2.2. ACCOUNTABLE YIELD LIMITS FOR ROLLER COMPACTION AND POST-ROLLER COMPACTION BLENDING

The recommended yield range for new products at this processing step depends on the ratio of the total capacity of the roller compactor and RFGs to the total volume of batch material being processed. This ratio can vary across manufacturing divisions in different countries.

It is highly likely that a large ratio contributes to a larger yield loss due to retention, and a larger yield excursion due to carry-over. As such, a larger accountable yield range relative to **98.0 to 101.0%**. is recommended in this case.

In the event that there is a small ratio of capacity to volume of processed material, lower yield loss and yield excursions are expected, in which case a smaller accountable yield range relative to **98.0 to 101.0%** is recommended.

7.2.3. ACCOUNTABLE YIELD LIMITS FOR TABLETING

The recommended upper yield limit for new products at this processing step will remain at **100%**, while the lower yield limit depends on the volume and nature of material being processed. The currently used lower yield limit of **97%** is decreased further if additional losses are anticipated, and vice versa.

7.2.4. ACCOUNTABLE YIELD LIMITS FOR FILM COATING SUSPENSION PREPARATION AND FILM COATING OF CORE TABLETS

The primary consideration here in the determination of a yield loss or yield excursion is the percentage weight gain of each core tablet. Since a 3% weight gain is generally expected for each core tablet, the recommended yield range for new products for this processing step should remain at **99.0 to 101.0%**. While losses are expected from hold-ups among many other considerations, the concern is about having a weight gain of less than 3% or a weight gain of more than 3%. As such, an appropriate range of between 99.0 to 101.0% must be selected such that the deviation term in the calculation of the yield, $Y = \frac{103 \pm \delta}{103} \times 100\%$, is not too large for a mass basis of 100kg of uncoated tablets.

7.2.5. ACCOUNTABLE YIELD LIMITS FOR TRANSFER AND PACKING OF COATED TABLETS

At this processing stage, minimum yield losses and yield excursion are expected =in the packing off and sealing of the drums containing the final coated tablets. The recommended yield range for new products should remain at **99.5 to 100.5%** in order to ensure that weight standards for final coated tablets during shipment are maintained.

CHAPTER 8 CONCLUDING REMARKS

This paper summarizes the findings of an internship project that took place at a pharmaceutical manufacturing facility in Tuas Biomedical Park, Singapore. During the course of the project, a substantial effort has been devoted to the study of the major processing stages in the manufacturing of pharmaceutical products. The critical operating parameters of each processing stage have been studied in detail and documented in an internal memo together with a description of the losses of material loss and the reasons for yield excursions. The use of yield limits have been investigated in parallel through discussions with on-site engineers to compile, for the first time, a list of generally accepted yield limits for the major processing stages. A preliminary framework has also been developed for the adjustments of yield limits for application in the production of new products. As a final remark, it must be emphasized, however, that the use of yield limits has been poorly justified and further work in investigating the basis for the choice of such yield limits is necessary.

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