Structured Approach for Compliance Determination of FDA Regulated Tablet Compression Process

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***Abstract* —** *Tablets are the most popular unit dosage form used by the Pharmaceutical Industry to provide health treatment to patients in the United States. It is important to control process critical parameters (variables) such as weight, thickness and hardness of the unit dosage form to provide the patient with the same drug levels obtained during clinical studies. There are also quality attributes that are inherent to product quality such as shape, color, texture, and general appearance. Without robust in-process controls, it is very likely to have undesired effects such as manufacturing yield issues, rework or re-processing, customer complaints, and possible observations from regulatory agencies that may affect not only economically but also the company quality reputation. For this reason it was developed a comprehensive method, structured to help as a guideline to understand the current level of compliance for pharmaceutical tablet compression facilities regulated by the FDA.*

***Key Terms* —** *cGMP, process controls, recall, tablet compression.*

INTRODUCTION

The meaning of the “c” in the cGMPs represent the FDA expectations for the industry to continuously improve its control assuring drug products to be “safe, and has the identity and the strength and meets the quality and purity characteristics that it purports or is represented to possess” [1].

There are many proposed definitions of what Quality means for business purposes. Some are: Joseph M. Juran - "Fitness for use as defined by the customer" [2], Philip B. Crosby "Conformance to requirements" [3], W. Edwards Deming "the efficient production of the quality that the market expects" [4], American Society for Quality "The characteristics of a product or service that bear on its ability to satisfy stated or implied needs” and “A product or service free of deficiencies" [2], Genichi Taguchi: "Uniformity around a target value" [5].

After studying these definitions and many others, it can be established in a very simplistic way, that Quality is about knowing the customer needs and supply goods or services, consistent with those customer needs.

The Food and Drug Administration in its role of public health protector, is called to set the requirements and the industry is mandated to maintain adequate controls to supply patients with drugs and devices that comply with the quality needs defined by the agency in the Good Manufacturing Practices (cGMPs). It is evident that the FDA has the authority to enforce compliance with the law regarding the manufacture, processing, packing or holding of drug products and represents in the United States the customers for the purpose of setting Quality requirements.

During the last two decades many companies have adopted continuous improvements initiatives (Six Sigma, Lean Manufacturing or Operational Excellence) that consider as a key element for success the need to “listen to the voice of the customer”. This is the principle to focus and control what it is really important to the internal and external customers.

Having established the importance of listening carefully to our customers as a basic principle to supply quality products and after stressing the fact that the FDA may be considered as the

Pharmaceutical Industry primary customer, it is very important to understand the new tendencies of what the FDA is expecting from the pharmaceutical industry community. They are looking to provide the industry with guidelines focused in risk analysis that may be considered more open to promote the implementation of up to date technology to improve the product life cycle as an alternative to make available for public health, new safer, effective and affordable drug products.

Probably the most commented is the "Process Analytical Technology (PAT)" guideline in which the FDA is showing its commitment to provide the mechanism in which the pharmaceutical companies may feel confident to implement effectively scientific and engineering principles that will result in better manufacturing and regulatory processes. I am using this guideline just with the intention of stressing the importance of having robust in-process controls, not only for the current traditional process, but also for the upcoming tendencies like the ones here described. It is not intended to discuss in detail the content of the guideline.

One pillar of PAT guideline is an old principle well known by Industrial and Quality Engineers: "quality can not be tested into products; needs to be built into the product", needs to be part of the product design. For this reason it is emphasized that the term "analytical" in PAT needs to be considered in a broad way including: chemical, physical, microbiological, mathematical, and risk analysis aspects; all conducted in an integrated manner (refer to Figure 1). Figure 1 was created using the categories described under PAT Guideline, however the same structure approach can be obtained using the 5m's (Man, Machine, Method, Material and Mother Nature), which is the typical Industrial Engineering approach.

The tendency when assessing this guideline is to focus in Process Analyzers tools as the innovation to generate real time data that may help to prove product quality with reduced or no testing. It is very appealing to have a manufacturing system that may not require laboratory testing for finish products because it will significantly reduce cycle and throughput time for the majority of the applications. However, this advantage will only be possible if companies maintain in place robust controls to assure the safety, identity, strength, quality and purity of drug products.

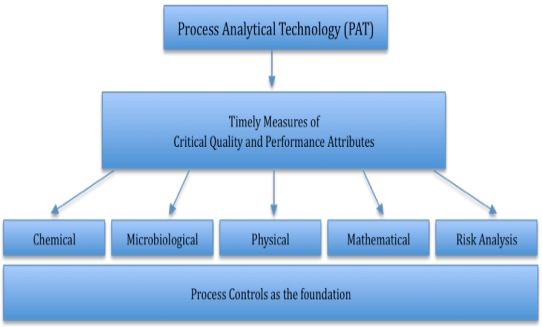

Figure 1
Pat Relationship with Process Controls

There are many examples of companies that face regulatory actions for not having adequate in-process controls resulting in market Product Recalls or Product Seizure. It is estimated that a recall of any particular drug may cost a company from $500K to $1M for the handling of the communication campaign and product pickup. These amounts do not include other expenses such as product handling and storage, safe disposition and destruction, material and labor cost of the product recalled and its replacement, the opportunity cost of not having the product available in the market and others. Also it is necessary to consider the adverse impact to the company image for the patients and regulatory agencies.

In summary, it is important having robust in-process controls because it is what the costumer expects from drug manufacturers and is what can guarantee the investment of the share stockholders.

This design project is intended to provide a comprehensive tool that may allow others to understand the controls that are necessary to bring a tablet compression area to the highest standard in order to avoid regulatory observations and to set the foundation for the new tendencies of providing up to date technology.

COMPRESSION PROCESS

The Pharmaceutical Compression Process is a significant processing step because it is where the unit dosage is formed. A unit dosage (single dose) is by definition the amount of drug product that a patient needs to initiate and maintain a therapy to eliminate or mitigate a disease or medical condition. The typical manufacturing process begins with the dispensing of active and non-active ingredients and is combined and blended together to obtain a homogenous (uniformed) distributed bulk drug mix.

To assure reproducibility of the product quality characteristics, compression process controls are necessary. CGMP's (21CFR211) includes in each subpart a general description of the controls that a pharmaceutical manufacturing company may have in place and in use to assure product is not adulterated, and the process is reproducible for consistent results. This article is intended to provide a structure approach to determine the compliance level, of a tablet compression area based on the current quality standards for the industry. To facilitate the discussion, controls will be classified as per the general categories included in Figure 1.

Chemical

This category includes the controls necessary to reduce Product Quality risks due to chemical substances or agents. Tablets by nature are made of chemical substance and are processed in compression machines that require being cleaned and maintained using cleaning agents and lubricants.

The first risk of contamination or opportunity to incur in process errors is by using wrong incoming materials from the previous stage. 21CFR211.101 establishes Material Verification controls to avoid this type of error.

Install a bin or a drum on top of a compression machine is no different in terms of material addition as to adding any component during the mixing or granulation process. Opening the bin or drum valve most be define as the event of adding the material to the compression process. Material Verification for this step must include confirmation that the material was approved for use, the quantities are as per the previous stage records, and all containers are properly labeled.

Another source of chemical contamination is due to product contact with lubricants. As per 21CFR211.65 lubricants shall not be in contact with components, drug product containers, closures, in process materials, or drug products. Lubricants for any moving part over the product filling level must be Food Grade Approved, as preventive measure for any unnoticed accidental contact.

Microbiological

Here it is included the controls necessary to reduce product quality risks due to microbiological contamination as per 21CFR211.113 (a). Inadequate cleaning methods, housekeeping and aseptic practices are some of the most common contributors of microbiological contamination. Other sources of microbial growths come from plant utilities such as Room Air Conditioning, Compressed Air, Purified and Potable Water.

Pharmaceutical companies maintain under the Quality organization a unit for Microbiological monitoring, responsible for sampling all equipments and utilities that may be in contact with drug products, in process materials or components. However, for the operational standpoint it is more relevant having validated cleaning procedures.

Cleaning by definition is the process of removing contaminants from process equipment and maintaining the condition of the equipment such that the equipment can be safely used for subsequent product manufacture. The cleaning validation is the generation of documented evidence that demonstrates that the cleaning operation is consistently capable of cleaning to establish levels of cleanliness. CGMP's contains various statements related to cleaning of equipments and facilities: 21CFR 211.42, 211.56, 211.67, 211.180 and 211.182."

A robust cleaning validation should define "level of cleanliness" considering the following:

- Residues of Active Pharmaceutical Ingredient (API)
- Excipients Residues
- Cleaning Agents Residues
- Sanitizing Agents Residues
- Microbial Bioburden
- Clean Equipment Holding Time
- Dirty Equipment Holding Time
- Campaign Size or Duration

Cleaning Standard Operating Procedures shall exist for compression equipments and facilities. In combination with training the manufacturing operators can obtain consistent results consonant with the validation acceptance criteria. The tendency is to provide in addition to the SOPs, a form where the cleaning critical process parameters can be recorded as validated.

Another source of possible microbiological contamination is due to material handling and containers for drug product, in-process materials and raw materials. Material handling should be clearly defined in terms of material, waste, equipment and people flow. Material Flow should be defined in a floor plan providing a predetermined route from the processing rooms to the storage or staging areas. This is good practice to avoid cross contamination, but also for safety and productivity reasons.

It is highly recommended to use plastic or stainless steel containers as the preferred reusable options. However, fiberboard drums exist with a plastic liner that reduces the risk of losing particles that may contaminate drug product or materials.

Tablets compression process is classified as a non-sterile manufacturing area that permits less rigorous environmental monitoring controls. However, the possibility of cross contamination always exists and it is necessary to maintain adequate in-process controls to avoid possible microbial contamination.

As the result of a risk analysis, solid dosage manufacturing areas can be classified in two major groups based on water activity level (Wet or Dry processes). Compression may be considered a dry process area that represent less risk of microbiological growth when compared with coating and granulation processing areas that requires the use of water for the preparation of coating and granulation solutions or suspensions. A good environmental monitoring program for dry (non-sterile) manufacturing areas should provide a sampling schedule considering sampling of ambient air, compressed air, product contact surfaces and non-product contact surfaces

Housekeeping is generally used to describe the activities to maintain a house or building neat and clean. For our purposes, housekeeping will be used more to describe the neat, since the importance of cleaning was covered previously. Neat by definition refers to a place or thing that is arranged in an orderly, tidy way. 21CFR211.42 emphasize the importance of a well-organized facility. An area well organized in addition to being a regulatory requirement, is also a best practice to improve productivity. From the seven types of waste, "Waiting" normally is produced due to poor organization of the working areas. 5S is a methodology for creating and maintaining an organized, clean, high performance workplace. This is obtained by following 5 steps: SORT, STORAGE, SHINE, STANDARDISE and SUSTAIN that combined with the use of visual displays provides a work place environment that promotes reduction of errors and wastes. Standard Visual displays and controls enable individuals to immediately recognize the desired working method and any deviation from it.

Physical

This category includes the controls related to the Physical attributes of the product, the equipment and instruments used for the tablet compression process. These controls are designed to assure product quality by using adequate and reliable equipments, instruments and procedures (methods).

The first things to consider is that the equipment in the compression facilities are made for its purpose and are suitable for use. This can be only obtained by conducting a Qualification and Validation exercise for the compression equipments.

Compression machines (rotary presses) are considered precision equipment and to avoid metal-to-metal friction it is very important to have setup procedures and qualified personnel to perform the equipment changeovers and setup.

"Changeover" refers to the activities to change the equipment to a different product and "Setup" refers to the critical adjustments to assure the equipment works smoothly and is capable to produce tablets within the process parameters. A good criterion to establish the borderline of these two activities is to consider changeover as the task to set the machine and no product is necessary to complete these tasks. "Setup" refers to the activities where product is necessary to make the process adjustments to obtain tablets within weight, thickness and hardness.

Experience has demonstrated that compression process where the assembly and setup activities are well structured and people are well trained achieves higher first time quality indicators than areas with fewer controls.

Compression machines are not capable to measure or weigh the tablets produced. Process parameters (weight, thickness and hardness) are obtained by controlling other indirect variables.

There exists two main process principles for the control of compression process: The first and most popular is by measuring the compression force with a Strain Gauge, and the second is by measuring displacement with a Linear Variable-Differential Transformer (LVDT) [6].

After understanding that tablet weight is obtained by controlling the volume formed by the punches and dies, it is also important to mention that the tooling difference in dimensions must be controlled and maintained to a level of tolerance where those differences can be considered non-significant to the process. Otherwise significant deviations from the tolerance will result in significant weight variation for the tablets that will result in significant differences in the intended proposed dosage of any particular product. In addition to the criticality of the tooling dimensions, there are other security controls required to prevent product tampering. The following controls are necessary for tooling used in the compression process:

- Approved Drawings
- Unique ID Number (Hub Number)
- Shape
- Dimensions
- Tolerances
- Calibrated Measuring Instruments
- Certified Tooling Personnel
- Secure Area with access control
- Cleaning and Inspection SOPs
- Cleaning Method and Frequency
- Inspection Method and Frequency
- History Logbooks

Material handling is a subject highly discussed within the logistics environment and for process improvement initiatives because it is recognized as a waste source by the lean manufacturing methods. However, for the manufacture of pharmaceutical solid dosage forms, material handling is something that needs serious considerations. Inadequate handling may produce broken tablets what will produce lower yields and process downtime at the packaging stage.

Many people tend to believe that metal detectors during the compression process serve as an inspection device to detect and reject tablets with metal particles. That concept, even when it is very common is far from the real intention for using metal detection devices. Typical metal detectors can detect metal particles (Ferrous, Non-Ferrous and Stainless Steel) as small as 0.4 mm in size. It is incorrect to think that smaller particles can be accepted as good in terms of product quality. Metal detectors are intended to serve as a monitoring device to detect atypical process behavior. This type of equipment produces false detection and

rejection of tablets due to radiofrequencies or the proximity of metal objects to the equipment body. A baseline needs to be conducted to determine the average rejection rate when the process is in control.

Regulatory agencies expect to see documentation of the challenges in the manufacturing batch record as the evidence that the equipment was challenged.

Exist three main categories of instruments used within a compression operation for the manufacture of pharmaceutical solid dosage forms:

- In-process Control
- Equipment Process Control
- Tooling Maintenance

As mentioned before, compression machines are not capable to measure weight, thickness and hardness of tablets produced, therefore it is necessary to have in-process control instrumentation to directly measure these tablet variables to confirm the machine is producing tablets within the in-process limits. For in-process control there exist two main approaches: Manual and Automatic testing. Manual applications require the operator to document individual values for each variable in order to determine if the process continues in control. The automatic alternative uses a multi-tester that is capable to analyze a sample of tablets and provide online statistics and feedback for any individual or average value out of the in-process limits. A benefit of multi-testers is that the raw data and its statistics are electronically stored that is very helpful for trend analysis, process investigations and improvements.

In addition to in-process instrumentation, compression machines include instruments that are used by the programmable logic controller (PLC) to measure independent variables to maintain the process in control and to provide feedback to process operator about process parameters such as machine revolutions (rpm), feeders speed, cams displacement, etc. Other instruments are also necessary to measure tooling according to the dimensions and tolerance specified in the approved drawings. Independently of the nature of the instrument, its is expected to determine the criticality during the validation activities and those considered critical instruments must be included in the Calibration and Maintenance program to assure the reproducibility and accuracy by conducting frequent challenges with approved and traceable standards.

In all cases where the instrument result may be affected by the technique used by the process operator, it is expected to conduct Gage R&R to establish the repeatability (operator variation) and reproducibility (instrument variation) to reduce risk of incurring in Type I or II errors.

Mathematical

There are considerations for the compression process that requires making quality decisions, based on mathematical calculations, therefore it is important to use accurate and precise methods to make these decisions. Major mathematical calculations includes:

- Process Yields
- Reconciliation Limits
- Sampling Plans
- Process Robustness

Yield calculations are typically conceived as a cost or financial tool, and are used to monitor and maintain visibility of the scrap produce and the amount of goods produced. 21CFR211.103 establishes yield as a critical step to be completed after each appropriate manufacturing phase, requiring a second verification of the calculations, because the batch yield is an indirect method to determine that the process ran without discrepancies.

By definition the “Percent of Theoretical Yield” is the ratio of actual yield to theoretical yield, expressed as a percentage and “Actual Yield” is the quantity that is actually produced at any appropriate phase of manufacture, processing or packaging of a particular drug product”. Any deviation from the limits established in the Master Batch Record should be investigated and a complete assessment of the discrepancy should be

performed before compromising the equipment and facilities with the next batches.

Compression is a continuous process (where units are being produced during the process length) where the equipment, environment, materials and method, may introduce variation that may affect product quality; it is expected to provide sampling plans to periodically assess in-process material status according to parameter values obtained in the initial setup as previously described.

Sampling Plans require specifying: sampling location, sample size (quantity), test method and the acceptance criteria for each variable or attribute that is intended to maintain in control according to the product specifications.

Regulatory agencies expect from the pharmaceutical companies to provide sampling plans based on a scientific (statistical) rationale. Custom sampling plans for variable and attributes may be designed, however many organizations opt to use recognized standards such as the current versions of ANSI/ASQ Z1.4 "Sampling Procedures and Tables for Inspection by Attributes" and ANSI/ASQ Z1.9 "Sampling Procedures and Tables for Inspection by Variables for Percent Nonconforming". The use for these standards are accepted by regulatory agencies only if they are used as designed. The most common observation regarding the use of these standards is because the Quality Control unit does not verify results and switching rules are no applied as per the standard definitions. These standards are intended to be used with process that are demonstrated to be in control and without monitoring tools and the application of the switching rules it is not acceptable to use these standards.

It is highly desirable to use Statistical Process Control (SPC) as the process control method in a compression area. However, it is very important to consider that modern compression machines are controlled by a PLC that continuously monitor compression forces and continuously make adjustments to maintain tablets within the desired target value. Experience has demonstrated that compression machines control systems are accurate and reliable and the use of SPC may be considered redundant and cannot be used to detect small shifts in the mean value.

The ability of the process to meet specifications is inherent to the process development and validation in the earliest stages of the product life cycle. Although process capability is not typically included as acceptance criteria in the validation plan, it is a good practice to understand the ability of the process to meet the specification. As a rule of thumb a healthful process should have a Cpk greater than 1.33 to provide assurance that expected changes in the mean value stays within the process specification to avoid producing defective units. Ideally the Cpk should be calculated as a quality parameter for each batch. This value is easy calculated using the following formula:

$$Cpk = \min\left[\frac{USL - \overline{X}}{3\sigma}, \frac{\overline{X} - LSL}{3\sigma}\right]$$

All these values are difficult to obtain when manual in-process testing is used because it is necessary to enter individual values in a validated spreadsheet that requires a second check verification to assure each entry is correct. However, most digital instruments used for in-process testing provide the capability to print the values and statistics for each sample and a summary for the end of batch.

Risk Analysis

People dependant processes are more susceptible to errors than non-people dependant process. When considering the five (5) M's (Man, Machine, Material, Methods and Mother Nature or Environment) it can be said that Man (human factor) interacts with all others factors in a high or low degree. Those factors where human intervention takes a higher grade of participation are normally the ones with higher incidence of discrepancies from the expected results. Figure 2 represents that relationship.

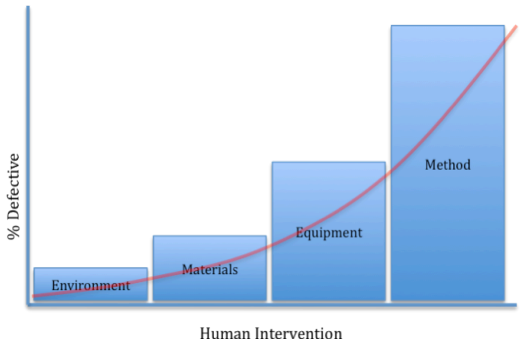

Figure 2
Human Intervention vs. % Defective

Controls that are more related to reduce the risk of errors due to human interventions with the process are: Master Batch Records (MBRs), Standard Operation Procedures (SOPs), Training, Metrics, Supervision and Internal Audits.

The Batch Production Record (also known as Manufacturing Batch Record) is the document provided to the manufacturing personnel that includes the instructions (what to do) and parameters to assure uniformity from batch to batch. The GMPs in section 211.186 and 211.188 clearly defines the requirements for the Master Batch Records and the Production Batch Records.

In addition to the requirements described in the previous GMP sections, it is highly recommended to include specific instructions and sections that are unique to compression Master Production Records such as:

- Critical Parameters Identifier
- Tablet physical description
- List of qualified equipments
- Tooling set number and description
- Recipe Selection and Verification
- Sampling plans for variables and attributes (Setup and Continuous Run)
- Instructions to maintain segregated the tablets produced during setup
- Setup approval
- Metal detectors waste segregation and evaluation
- Metal Detectors sensitivity checks
- Mechanical interventions history log

The Standard Operating Procedures are documents designed to provide instruction to end users assuring an uniform and consistent way of working, so the identity, strength, quality, and purity of the drug product is not affected.

There is a general understanding that SOPs should provide a high level of details, allowing that any reasonable person can execute the task only by reading the instructions. Be careful because experience has demonstrated that high level detailed SOPs promote a higher level of process deviations because the SOP was not fully followed. SOPs should provide enough level of detailed information to provide guidance to highly trained personnel on how to perform a task. A simple way to understand the nature of the SOP vs. PBR is that the PBR provides the "what to do" and the SOP provides the "how to do it". The GMPs mention "written procedures" in seventeen different sections, but our interest, for the purpose of the discussion, is section 211.100 "Production and Process Controls" because this section is specific for production and process controls, where compression operation is implicitly contained.

It is very difficult to establish a list of the SOPs required for a compression area because that may vary depending on the amount and variety of equipments used by each company and the SOP structure adopted. Figure 3 represents a typical compression equipment setup with the recommended SOPs boundaries definition.

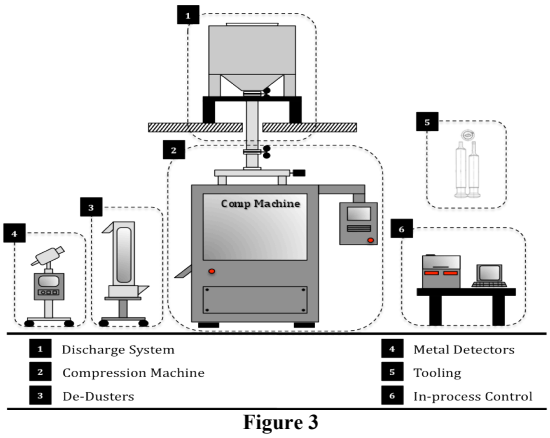

Figure 3
SOP Boundaries Definition

Additional general manufacturing SOPs should be available such as: Waste and Spills Management, Computer Systems Access and Recipe Control, Gowning, Material Handling, Scales and Balances Daily Checks, Use of Hoses, Rework and Reprocessing, Use and Control of Labels and Placards, Use and Control of Logbooks, Use and Cleaning of Production Utensils, and Statistical Inspection among others.

Training is such an important part of maintaining a GMP compliance environment, that 21 CFR 211.25 and 211.34 makes reference to it as a requirement with the same importance as the education and experience. As mentioned earlier, error opportunities increase with the human intervention for repetitive tasks. Therefore having a well-structured training program is key to maintain high performance quality standards.

The combination of education, training and experience is what makes a resource apt to be engaged in the manufacturing, processing, packaging or holding of drug products and that requires that pharmaceuticals companies maintain training structures to periodically provides training not only in GMP regulations, but also in all kind of activities required to handle drug products.

"If you don't measure; you can't control". This statement is absolutely true for the pharmaceutical manufacturing environment. Process performance is measured Audits and Process Indicators or Metrics. Audits are used to assure adherence to procedures and policies with observations of the process or by reviewing historical data. Metrics are used for processing aspects that can be measured and displayed to observe patterns or progress.

The validity of metrics and the internal audits as compliance instruments, is only obtained if the metrics and audits are captured in a approved SOPs or Policies and it can be demonstrated that are frequently discussed in the quality meetings, are posted and available for the users and actions for improvements are identified, when necessary.

In the pharmaceutical environment rework and reprocessing cannot be taken as a light topic because there are regulatory implications that do not exist for other industries. For non-regulated environments reworking or reprocessing is a matter of cost vs. benefit, but in the pharmaceutical environment there are implications that need to be considered as established in 21CFR211.115.

The best description of the FDA expectations regarding Rework and Reprocessing was included in the draft of the "Guidance for Industry Drug Substance Chemistry, Manufacturing, and Controls Information" published by the FDA in January 2004.

COMPLIANCE DETERMINATION TOOL

All the controls previously discussed under each sub-topic were included as a questionnaire in Microsoft Excel to serve as a structured tool to determine the level of compliance of a compression process. This tool will provide a general understanding of the compliance status of an organization that is considering implementing PAT as a competitive advantage or as technology improvement for the tablet compression area.

The tool was designed maintaining independent sheets for main topics (Chemical, Microbiological, Physical, Mathematical and Risk Analysis). Each sheet provides a set of questions to assess the actual level of compliance of each individual topic and a summary screen captures the overall status. A color code was used to help understand the actual status and to help determine areas that need improvements. All questions should be answered following these definitions:

- In Place and In Use: Exist documented evidence that the control referred in the question is implemented and in use (i.e. users understand the nature of the control, exist training evidence and documentation support).
- In Place: Exist the control but it cannot be established assurance of it use (i.e. exist an approved SOP but is not followed).
- Not in Place: The control is not implemented.
- Not Applicable: Do not use unless it can be justified that the control refereed by the question is absolutely unnecessary.

A case study is presented to briefly demonstrate the use of the Compliance Determination Tool. The circumstances described in the following case study were real for a Pharmaceutical Company with operations in Puerto Rico. However the company and drug product names were changed to fictitious names for confidentiality reasons. The tool was applied to demonstrate the use of the questionnaire and the meaning of the results obtained as an example.

CASE STUDY

The U.S. Food and Drug Administration (FDA) announced that ABC, Inc. (Fictitious Company), has signed a consent decree with FDA to correct manufacturing deficiencies at its Puerto Rico facility.

FDA is concerned that ABC's violation of manufacturing standards may have resulted in the production of drug products that could potentially pose risks to consumers.

"The consent decree shows that FDA is serious about enforcing the manufacturing standards essential for safe and effective prescription drugs," said the FDA Associate Commissioner for Regulatory Affairs. "It should also reassure the American people that we are doing everything we can to preserve the integrity of the American drug supply."

FDA's last inspection found “Product A” tablets, approved to treat depression and panic disorder, could split apart. This deficiency could cause patients to receive a portion of the tablets that lacks any active ingredient, or alternatively a portion that contains an active ingredient and does not have the intended controlled-release effect. Additionally, FDA found that some “Product B” tablets, used to treat Type II diabetes, did not have an accurate dose of its ingredient.

Under the terms of this decree the company has agreed to take measures to ensure that its Puerto Rico facility and the two drugs, fully comply with current Good Manufacturing Practice (cGMP) requirements and to ensure that ongoing shipments have the quality attributes they are required to possess.

As a result of the consent decree previously described, company ABC decided to use the Compliance Determination Tool to have an unbiased assessment of its compression process.

Figures 4 to 8 represents some of the results of the compression process assessment made for ABC, Inc.

CHEMICAL	In Place and In Use
MATERIAL VERIFICATION:	
Only Approved Material from previous satge is used?	x
Barcode sanners are used for material verification?	x
A second check of the material identity is conducted?	x
A second check of the material amount is conducted?	x
A second check of containers phisical conditions and quantity (for example 1 of 2 and 2 of 2)?	x
When changing to a different product, processing room is approved for use, before entering the materials?	x
First and Second checks are documented in the Batch Record?	x
Staging Areas are clearly identified?	x
Overall	100%
LUBRICANTS CERTIFICATION:	
Only Approved Food Grade Lubricants are used?	x
Lubricants are stored in secure cabinets?	x
Lubricants are identified with the Stock Number?	x
Overall	100%

Figure 4
Compliance Determination Tool
ABC Chemical Results

Under the chemical section ABC, Inc. maintain controls up to the expected standard as demonstrated by 100% scores for Material Verification and Lubricants Certification. The overall score for the chemical controls is 100% what is highlighted in green representing the desired status for all sections.

MICROBIOLOGICAL	In Place and In Use	In Place
CLEANING VALIDATION:		
Major Cleaning Methods are validated?	x	
Cleaning Validation defines the level of Cleanliness?	x	
Overall	100%	0%
CLEANING PROCEDURES:		
Exist SOPs for the Major Cleaning of compression equipments?	x	
Exist SOPs for the cleaning of compression facilities?	x	
Exist a cleaning certification program for operators performing manual cleaning methods?	x	
Equipment cleaning SOPs defines the cleaning frequency?	x	
Facilities cleaning SOPs defines the sanitation frequency?	x	
Exist an Approved List of Cleaning and Sanitizing Agents?	x	
Exist SOPs prviding dissassembly instructions of the compression equipments?	x	
Exist a schedule for the rotation of sanitizing agents?	x	
Exist SOPs with intructions for the protection and storage of clean equipment?	x	
Equipment is inspected for cleanlinees inmediately before use?	x	
Previous Batch identifications are removed or obliterated before cleaning activities?	x	
Equipment Cleaning process is documented in a cleaning record (ie: Checklist)?	x	
Any associate can detect when equipment, tools, materials or utensiles are located in a wrong place?		x
Overall	75%	25%

Figure 5
Compliance Determination Tool
ABC Microbiological Results

Under the Microbiological section the score obtained was 98%, what is a good score but is highlighted yellow because still areas of improvement with Housekeeping controls.

MATHEMATICAL	In Place and In Use	In Place	Not in Place	Not Applicable
YIELD AND RECONCILIATION LIMITS:				
Compression Yield is calculated at the end of each bacth?	x			
A second verification is documented as part of yield calculation?	x			
Exist reconciliation limits based on the nature of each product?	x			
Reconciliations limits are reviewed based on historical data or trend plots?	x			
Tentative limits are used only during development and validation batches?	x			
Reconciliations out of limits are investigated as a process deviation?	x			
Overall	100%	0%	0%	0%
SAMPLING PLANS:				
Exist approved sampling plans for in-process control?	x			
Exist SOPs describing sample size, sampling location, test method and the acceptace criteria?	x			
Sampling Plans are aligned with the NDA (if Applicable)?				x
Variables and Attributes are clearly defined?	x			
Switching rules are used when current version of ASI/ASQ sampling procedure is used?			x	
Overall	60%	0%	20%	20%
PROCESS ROBUSTNESS:				
Process Capability Assessments are conducted as part of the annual prodict review?	x			
Cpk is known for process variables?	x			
Cpk for process variables is 1.33 or better?	x			
Overall	100%	0%	0%	0%

Figure 6
Compliance Determination Tool
ABC Mathematical Results

Mathematical controls resulted with a overall score of 93% because ABC is Using ANSI standards without monitoring the results to apply switching rules.

PHYSICAL	In Place	Not in Place
FIT FOR USE:		
Exist documented evidence that all compression equipments are qualified?		
All operational parameters are within the qualified range?		
Validation Assessment are conducted to revise the robustness of validation exercises of old equipment?		x
Overall	0%	33%
CHANGEOVER & SETUP:		
Exist SOPs to describe the instructions for machine changeover (Assembly)?		
Exist SOPs to describe the instructions for machine Setup?		
Exist formal training to certify operators and technicians for changeover activities?		
Exist a checklist to document machine changeover?		
A second individual checks the chageover was completed?		
Machine Change over is documented in the Equipment History Logbook?		
Overall	0%	0%
INSTRUMENTS:		
Exist in-process control testing during compression process?		
Instruments used for in-process tests are in the calibration program?		
Compression machine insrumentation is included in the calibration program?		
Calibration verifications are performed and documented for each batch?		
Exist SOPs to describe scales daily verifications?		
Calibration verifications are performed with traceble standards?		
Operator and Instruments variaons are assess using Gage R&R techniques?		x
Exist formal training for the use of instruments?		
Overall	0%	13%

Figure 7
Compliance Determination Tool
ABC Physical Results

Physical controls obtained the lowest score with 85%. In the summary section this area is highlighted in red because needs immediate attention. ABC needs to initiate efforts to raised documented evidence to demonstrate all equipments are fit for use, provide training and fixtures to reduce instrument variability, and training in material handling.

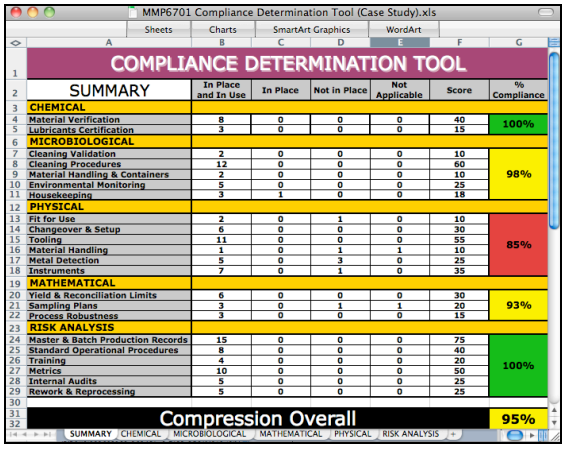

Figure 8
Compliance Determination Tool
ABC Summary Results

Summary sections provide the overall score for all sections with the color code previously described. Chemical and Risk Analysis obtained scores of 100% (green), Microbiological and Mathematical Controls obtained 98% and 93% respectively (Yellow) and Physical Controls obtained 85% (red). Based on these results ABC must initiate remediation efforts of the compression area, emphasizing the plan and interim controls for the deficiencies listed in the Physical Controls section.

METHODOLOGY AND RESULTS

The design of this project was develop using Failure Mode and Effect Analysis (FMEA) procedure to identify the level of controls necessary to improve the compliance status of the compression processing area based on the observations from the FDA and a third party auditors. FMEA is a procedure in product development and operations management for analysis of potential failure modes within a system for classification by the severity and likelihood of the failures. A successful FMEA activity helps a team to identify potential failure modes based on past experience with similar products or processes, enabling the team to design those failures out of the

system with the minimum of effort and resource expenditure, thereby reducing development time and costs.

CONCLUSION

The use of the Compliance Determination Tool provides a structured approach to understand the level of compliance of tablet compression area regulated by the Food and Drug Administration. This tool captures the learning's during the remediation process of a pharmaceutical company in Puerto Rico [7] that successfully improved its GMP compliance status after a seizure and a consent decree raised the United States Department of Justice and the FDA. This project represents a great contribution to the academic population and the pharmaceutical compression process.

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