# How to Reduce the Confirmation Period of Possible Critical Defects Detected During the Quality Assurance Acceptance Sampling Plan for Inspected Drug Product

**Gretchen M. Cruz Guzmán**
**Master in Manufacturing Competitiveness**
**Dr. Rafael Nieves Castro**
**Industrial Engineering Department**
**Polytechnic University of Puerto Rico**

*Abstract - An Acceptance Sampling Plan, or ASP, is a Quality attributes assessment performed during the manual or automated inspection of Drug Products. After inspection, the inspected product then becomes an Inspected Drug Product, or IDP. During the ASP, if any critical defect is identified during inspection, it is segregated for further On the Floor Testing (OFFT) or Process Development (PD) evaluation for additional confirmation. The main focus of this project is how to reduce this confirmation period by implementing portion segregation during the inspection process and sending the defective unit(s) for further evaluation as soon as the portion is completed, instead of waiting for the culmination of the batch inspection process. This implemented modification in current standard operating procedures, reduces the wait period by performing the defect confirmation parallel to the on-line inspection process, thus avoiding delays in the product's final disposition.*

## Introduction

Quality is a set of distinctive, defect-free characteristics that separates a product from the rest [1]. It is an essential part of any product, especially in the Pharmaceutical world. By ensuring the highest quality standards, a company can rise above fellow competitors, and in order to achieve this, a company must provide defect free medicines. Not only will the company gain a patient's trust, but also provide life changing therapeutics.

During the in-process inspection of a DP (Drug Product), certified Manufacturing associates perform a visual inspection for possible defects. All possible defects are discarded by these associates and QA performs a sampling, in order to confirm the units are defect free. Nonetheless, some defective units might still make it to the finished product [2].
This project will be focused on how to better identify and confirm possible critical defects as soon as they are detected during QA sampling, while the batch is still on-line, in order to take action in a timely manner and avoid delays in the product's release to the market.

## Problem

The main objectives are:
- Perform an accurate Acceptance Sampling Plan in order to detect possible critical defects.
- Follow an established procedure when a possible critical defect is identified.
- Reduce the time it takes to perform the corresponding identification by performing on-the-floor testing and timely delivery when on the floor is not available.
- Take action when re-inspection is required due to a critical defect being identified in order to comply with quality standards and patient safety.

This project intends to contribute a process improvement in order to provide defect free medicines that comply with patient needs and safety; provide insight on the most common critical defects observed for an IDP (Inspected Drug Product), and prevent product disposition delays.

## Background

Biotechnology is biology-based technology, especially used in agriculture, pharmacy, food science, the environment, and medicine. It is developed in a multidisciplinary approach that involves various disciplines and sciences such as biology, biochemistry, genetics, virology, agronomy, engineering, physics, chemistry, medicine and veterinary medicine, among others. It has a great impact on pharmacy, medicine, microbiology, food science, mining and agriculture, among other fields [3]. The first to use this term was the Hungarian engineer Károly Ereki, in 1919, who introduced it in his book "Biotechnology in meat and dairy production on a large farm". In the biopharmaceutical industry, monoclonal

antibody derived from genetically engineered mammalian cells can be used to create innovative, life-changing disease curing medicines. These cells are then grown in bioreactors, producing proteins that are isolated and purified using various filtering technologies based on size, molecular weight, and electrical charge.

The purified protein is then transformed into a specific medicine that can be used by patients with life-threatening diseases. This specific result is known as a drug product (DP). In order to comply with FDA regulations, not only must this product produce a therapeutic effect, but it must also comply with drug security, identity, potency, purity and overall quality; thus, producing a defect-free drug product [4]. Drug Products must then go through a manual or semi-automatic visual inspection, performed by operators certified in a manual inspection technique that has been thoroughly validated. These inspected DPs are then known as Inspected Drug Products or IDPs. Throughout this inspection, units that are not considered defect-free are rejected. These defects are most commonly categorized as Critical, Major A, Major B and Minor.

Critical defects are those that are considered threatening to the patient's safety and must be avoided at all costs. Major A defects have the potential to affect the product's quality, Major B defects have the potential to affects the product's functionality, and Minor defects affect cosmetic attributes [1]. The Quality Assurance department performs an Acceptance Sampling Plan or ASP, to units that have been previously accepted by inspection operators. Either a Normal Sampling Plan or a Tightened Sampling Plan is performed, depending on product requisites and whether or not a re-inspection is being executed. Initial inspections are normal, while re-inspections go through a more rigorous inspection, better known as tightened inspections [5]. If the initial ASP fails, the batch must go through a re-inspection process focused on the identified defect. For this specific project, I'll be focusing on the syringe presentation, and what steps should be performed in order to decrease the time period it takes to confirm Critical Defects, while the batch inspection is still on-going, in order to reduce and prevent product delays, authorize re-inspection if necessary, as well as provide defect-free medicines.

**Methodology**

After the Manufacturing operators perform a 100% and 200% inspection to the Drug Product, or units are accepted by the automated visual inspection machine, the Quality personnel performs a Normal or Tightened inspection, depending on the product's requirements. For a normal inspection 315 units will be inspected throughout the batch and for a tightened inspection, 600 units will be inspected throughout [4]. Each shipper will contain 1,700 units. To determine the number of inspections use the formula $\sqrt{N}$ (+1), where N is the total amount of shippers. To obtain the frequency, divide the total number of shippers by the number of inspections. Sort the inspections throughout the Beginning (B), Middle (M) and End (E) portions in order to complete the required quantity.

For a batch of 68,000 units, divide by 1,700 and obtain a total of 40 shippers. Use the formula $\sqrt{N}$ (+1), where N is the total amount of shippers, to obtain the amount of inspections to be made ($\sqrt{40}$ (+1)) = 7.3. If the decimal is value is 5 or higher, round up to the next number. Divide the number of shippers (40) by the number of inspections (7) to obtain the frequency (5.47). Apply the same decimal rule and round up or down. Divide 315 or 600, depending on the type of inspection, by the number of shippers to obtain the amount to be inspected per shipper.

Perform the Acceptance Sampling according to SOP-1234. Categorize any defects found according to SOP-1234. If a critical defect is found, segregate the unit according to SOP-1234. When the portion (B, M or E) the portion is completed, send the defective unit to Process Development or On the floor testing, as applicable, for further study and confirmation. Document results in FORM-1234 or EBR as applicable.

By implementing the Sample Request Form (SRF) in EBR and applying portion segregation, units can be sent for confirmation and aptly identified, instead of waiting for the batch to be completed on-line. Confirmation can be performed in a more efficient way and avoid batch release delays. If a critical defect is identified, generate a Deviation following SOP-1234.

QA Manager authorizes re-inspection focused on the critical defect identified previously identified in the initial inspection. Document ASP results on FORM-1234 or EBR, as applicable and perform the corresponding entries in the systems (EBR/LIMS) according

to SOP-1234 before releasing the batch and granting final disposition to the market.

**Results and Discussion**

In order to discuss results, let's review our project's objectives.

**Perform an Accurate Acceptance Sampling Plan in Order to Detect Possible Critical Defects**

In order to perform an accurate Acceptance Sampling Plan (ASP), SOP-12345 was followed throughout the batch inspection process in order to ensure a validated method was used to detect any possible critical defect(s). The steps were described in the project's Research Methodology section. As previously described, Critical defects are those that are considered threatening to the patient's safety and must be avoided at all costs.

**Follow Established Procedures When a Possible Critical Defect Is Identified**

The flowchart on figure 1 was designed and integrated to the corresponding SOP in order to visually conceptualize the steps that were taken if and when a possible critical defect is identified during the ASP. The unit(s) is segregated in an identified red bin labeled "Rejected ASP units segregated for OFFT inspection" as per the according SOP. When the portion has been inspected (Beginning, Middle, and End) the units are then sent to OFFT/PD for confirmation. If the ASP criteria is not met, for any type of defect (Critical, Major A, Major B and/or minor) a Sample Request Form is generated and all units are sent to PD for confirmation, as per established procedures. PD reaches out via written communication to the Quality unit, so that they can document the results in the electronic batch record.

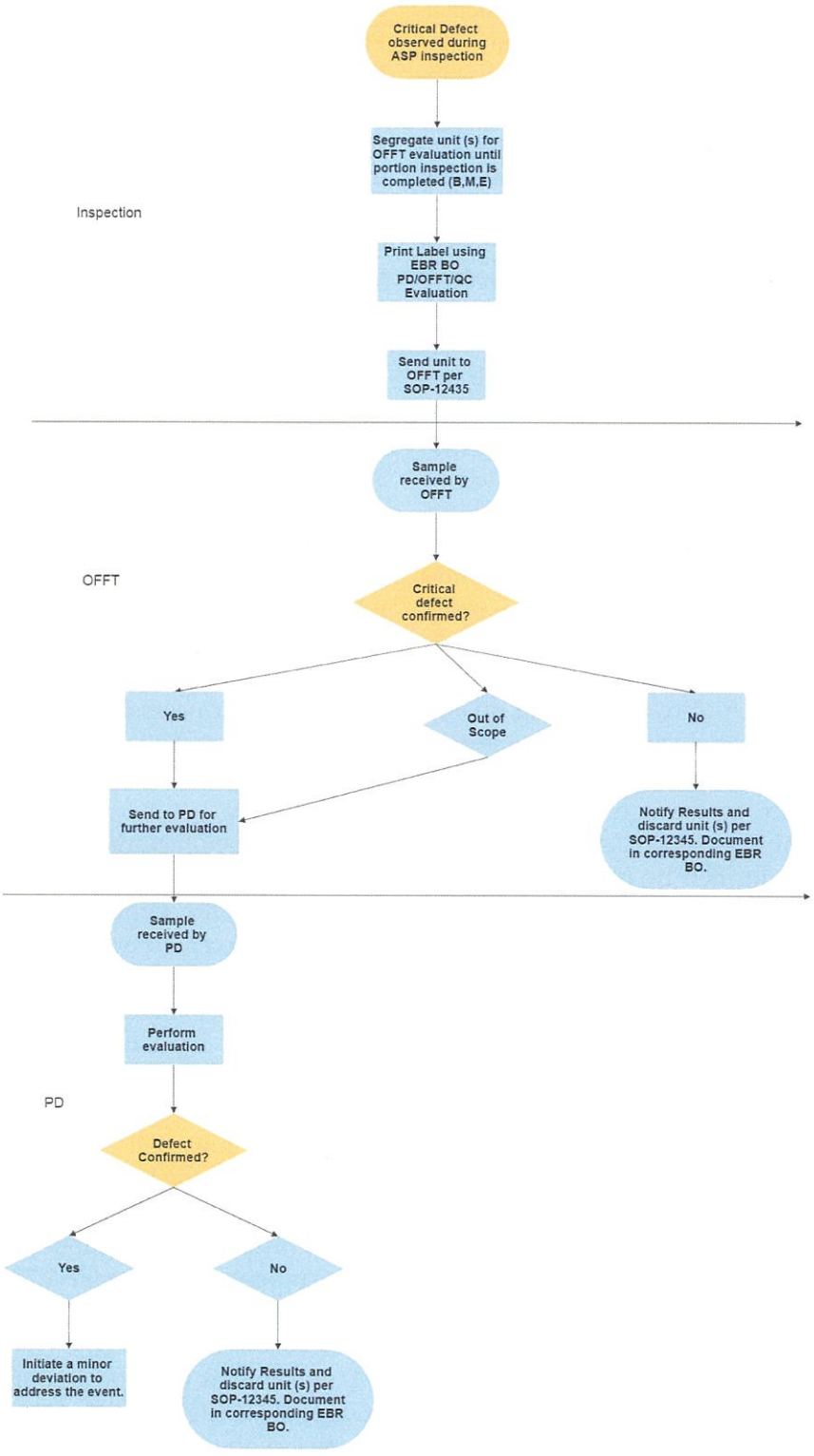


**Figure 1 - Flowchart**

All batches where a Critical defect is detected and identified are re-inspected, as per established procedures, in order to always provide high-quality medicines to patients worldwide that comply with FDA requirements for security, identity, potency, and purity attributes [4].

**Reduce the Time It Takes to Perform the Corresponding Identification by Performing On-The-Floor Testing and Timely Delivery When On-The-Floor Is Not Available**

OFFT, or On-the-Floor Forensic Testing, is a very useful resource that is used to confirm a possible critical defect. If this defect is unknown, as in not yet categorized in the defects library, it is sent for further testing and evaluation to the Process Development area. Product segregation throughout the batch inspection was implemented in order to accelerate the identification of possible critical defects, classifying critical quality attributes, critical process parameters, and identifying sources of variability. Since evaluation is being performed parallel to the batch on-line inspection, instead of waiting for the completion of the inspection process. If the defect is confirmed, a deviation can be promptly generated, addressed, evaluated, and closed, all within a steady timeframe, thus avoiding product disposition delays, as well as unnecessary overtime in order to grant final disposition.

The Gantt chart in figure 2 was generated in order to display the batch inspection time including OFFT/PD evaluation. The approximate number of batch inspection hours is 16.02 (from inspection to QA off-line audit), with 8-hour shifts, it would give PD a 2-day timeframe to report results. Keeping in mind PD testing would be occurring whilst the batch is still being inspected, instead of after the inspection process is completed. An average of 4 hours was assigned for OFFT/PD processing if staff is readily available and assuming they begin testing as soon as the sample is received, reducing confirmation time from 5 days (large batch) to 2-3 days approximately. This not only avoids delays in the product's final disposition, but also allows for additional physical, on-line product segregation if required. The PD time was considered in this Gantt chart as a parallel function, since it takes place in another department.

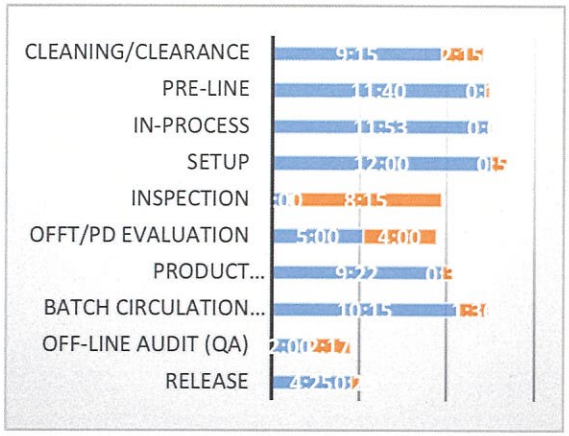


**Figure 2 - Gantt chart**

**Take Action When Re-Inspection Is Required Due to a Critical Defect Being Identified in Order to Comply with Quality Standards and Patient Safety**

In order to adhere to previous implemented CAPAs in accordance with FDA, if a defect deemed high risk to patient security is found during the ASP, re-inspection of the batch is required. If so, a deviation is generated and the batch is re-inspected with a more restricted ASP (Tightened inspection) performed throughout the batch. With the new OFFT/PD design, Supply Chain and Product Disposition can be notified in a timelier manner that the product will be re-inspected, thus avoiding compromising patient safety as well as any penalty fee for late delivery.

**Conclusions**

Through the implementation of the Sample Request Form in EBR and applying product segregation during the inspection process, the time needed in order to confirm any critical defect is reduced, avoiding Overtime and delayed product disposition. It is essential all relevant procedures are revised in order to include the steps necessary in case a critical defect is observed during the ASP inspection. Through the continuous improvement of manufacturing, inspection, product review and final disposition processes, a company can produce consistent quality over time.

**Future Works**

For future investigations, I would suggest the creation of standards containing the most common critical defects observed. This would allow us to "pre-screen" the sample and avoid sending false defects. I would also recommend that Process Development shifts be more similar to our Inspection shifts, since Inspection lines work 24/7, this would help with the timely release of PD results, instead of having to wait till Monday for results submitted for evaluation on Friday night. This would unquestionably help with the product's on time release, especially those pertaining to critical inventory.

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