REDICA Systems

REPORT

5 GMP Case Studies Including FDA Analysis

The GMP inspection case studies Barreto-Pettit provided include an in-depth analysis of the findings, lessons learned, and how companies can avoid similar shortcomings. Areas examined in the case studies are:

- The first countrywide import alert issued by FDA
- Inadequate deviation investigation
- Inadequate product specifications and a product recall
- Process validation
- A different perspective on process validation and the culpability of the quality unit

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PART I: COUNTRYWIDE IMPORT ALERT AMONG RECENT FDA ENFORCEMENT ACTIVITIES

Part I covers Barreto-Pettit's summary and analysis of recent FDA enforcement activities and the case study on a countrywide FDA import alert.

RECENT FDA ENFORCEMENT ACTION STATISTICS

Barreto-Pettit began her summary of recent FDA enforcement activities with a review of the agency's inspection priorities during the last year and the impact of the COVID-19 pandemic on its activities.

Beginning in July 2020, onsite inspection activities resumed in domestic regions with lower COVID-19 risks based on data from the COVID-19 advisory rating system. "We conducted mission critical inspections domestically and in foreign countries throughout the pandemic," Barreto-Pettit emphasized. She noted that "mission critical" inspections are those with the highest priority based on public health benefits or where the risks of not conducting the inspection outweigh the potential for investigators to potentially be exposed to COVID-19.

In reviewing the top FDA 483 observations for FY 2020, the FDA National Drug Expert commented that the same observations recur year after year, sometimes in a slightly different order (for a review of how and why 483 observations perennially repeat, see "Top 10 Pharma Inspection Findings from FDA, MHRA, and the Russian Drug Regulator"). She also reviewed the top ten 211 citations in FDA drug GMP warning letters for FY 2015 to FY 2020, through July 2020 (**FIGURE 1**).

Barreto-Pettit commented, "As you can see, 21 CFR 211.100(a) for process validation was cited the most in warning letters in 2020. It was fourth in the 483s frequency but is the top citation in warning letters. And overall, over the years, inadequate investigations, which is 21 CFR 211.192, and process validation, have been the most common deficiencies that have been cited in warning letters."

FDA FY2020 FDA IMPORT ALERTS

She next addressed import alerts. In addition to issuing warning letters, FDA has the authority to place non-compliant foreign firms under import alert. "This means that their products would not be allowed entry to the US while the import alert is in place. We use this regulatory tool to protect our consumers from potentially unsafe or ineffective products," Barreto-Pettit explained. In 2020, the most common reasons for FDA issuing import alerts were equally distributed among inadequate GMPs, analytical test results, and refusal to inspect.

In 2020, Mexico received about 33.66% of the import alerts due to issues with analytical results for hand sanitizers, which contained methanol or did not meet the label content specifications. Import alerts for Europe were mostly for inadequate GMPs. In China, India, South Korea, and Taiwan, the main reason for import alerts was refusal to allow inspection.

FIGURE 1: Top Ten Part 211 Warning Letter Citations By Fiscal Year FY2015 To FY2020*

				FISCAL YEAR			
CFR CITATION	2015	2016	2017	2018	2019	2020	TOTAL
211.192 - Investigations of discrepancies, failures	6	6	16	21	32	21	109
211.100(a) - Absence of Written Procedures	2	7	13	26	28	33	99
211.84(d)(1)(2) - Reports of Analysis (Components)	0	3	7	28	17	17	72
211.165(a) - Testing and release for distribution	3	8	10	19	12	14	72
211.166(a) - Lack of written stability program	1	6	2	15	22	11	66
211.22(a) - Lack of quality control unit	2	4	6	17	19	5	53
211.194(a) - Complete test data included in records	3	4	6	11	12	5	41
211.160(b) - Scientifically sound laboratory controls	2	5	10	6	7	9	39
211.113(b) - Validation lacking for sterile drug products	2	4	12	3	9	5	35
211.22(a)(d) Procedures not in writing, fully followed	0	0	1	10	11	10	32

*AS OF JULY 31, 2020

If the manufacturer does not let us inspect the facility where they manufacture products that they bring into the United States, we will not allow their products to enter the U.S. market."

CASE STUDY: HAND SANITIZERS WITH DEADLY TOXINS

The first case study the national drug expert discussed is from a warning letter issued to a hand sanitizer manufacturer in Mexico that imported its products into the United States. FDA collected samples and its test results showed that even though the drug product was labeled to contain 70% of the active ingredient as ethanol, it contained an average of 44% ethanol instead of 70% and the remaining was methanol, about 30%.

Therefore, these hand sanitizer drug products were adulterated under the Food, Drug and Cosmetic Act in that the active ingredient of ethanol was substituted in whole or in part with methanol.

FDA has the authority to place non-compliant foreign firms under import alert. This means that their products would not be allowed entry to the US while the import alert is in place.

"You may have seen this in the news," Barreto-Pettit commented. She pointed out that methanol is not an acceptable ingredient for hand sanitizers and should not be used because it is toxic. When methanol is applied to the skin, it can cause dermatitis as well as more serious events facilitated by transdermal absorption resulting in systemic toxicity.

Substantial exposure to topical methanol can result in symptoms such as nausea, vomiting, headache, blurred vision, permanent blindness, seizures, coma, permanent damage to the nervous system or even death. Although all persons using these products on their hands are obviously at risk, young children who accidentally ingest these products and adolescents and adults who drink the product are at a potential life-threatening risk.

After confirming the test results, FDA issued a warning letter to the firm and an import alert to prevent its products from continuing to come into the United States. It also requested a recall of all the affected drug batches already distributed in the United States. The warning letter was issued for an adulterated product, which means a product that was not manufactured under CGMPs or does not meet specifications.

Barreto-Pettit pointed out that the agency had not conducted an inspection of the facility. "We asked for a detailed investigation into how these hand sanitizer drug products manufactured at the facility and labeled as containing ethanol were substituted in part or in whole with methanol. We also requested a list of the raw materials used to manufacture all their hand sanitizer drug products, including the supplier's names, addresses, and contact information."

IMPORT ALERT EXPANDED TO INCLUDE ENTIRE COUNTRY

She explained that the requested information was useful to the agency because the manufacturer receiving the warning letter was not the only one having this kind of problem. FDA found many others that had methanol contaminated hand sanitizers and it needed to investigate whether the root cause of the problem was a supplier providing contaminated ethanol to multiple manufacturers.

FDA also requested a list of all the batches of any hand sanitizer drug products that were shipped to the United States by the firm and a full reconciliation of all the materials they distributed. "And since we had not done an inspection, we wanted to see how it was manufactured," Barreto-Pettit said. "So, we requested copies of the complete batch records for all the batches that were distributed to the US."

In January 2021, FDA issued a MedWatch announcement and placed all alcohol-based hand sanitizers coming from Mexico on import alert to help stop products that are in violation from entering the United States until it could review the products' safety. "And what we at FDA have seen is a significant number of hand sanitizer products from Mexico that were labeled to contain ethanol test positive for methanol or 1-propanol contamination."

A subsequent FDA analysis of alcohol-based hand sanitizers imported from Mexico found that 84% of the samples analyzed by the agency from April to December of 2020 were not in compliance with FDA regulations or their specifications. More than half of the samples were found to contain toxic ingredients including methanol and/or 1-propanol at extremely dangerous levels.

Under this import alert, alcohol-based hand sanitizers from Mexico that are offered for import are subject to heightened FDA scrutiny. FDA import staff may detain the shipment. As part of their entry review, they will consider any specific evidence offered by the importers or the manufacturers that the hand sanitizers were manufactured according to US CGMPs. This is the first time the FDA has issued a country-wide import alert for any category of drug product.

PART II: GMP INSPECTION CASE STUDY FOCUSES ON INADEQUATE DEVIATION INVESTIGATIONS

Part II covers a case study involving failures to adequately investigate root cause.

WHAT HAPPENS WHEN A DEVIATION INVESTIGATION IS INADEQUATE?

Barreto-Pettit presented a case study that involved two related but different scenarios found at a firm that pointed to inadequate investigations under 21 CFR 211.192 involving equipment maintenance issues as the root cause of the problem. However, as the warning letter states, investigations did not sufficiently address the root causes and the company allowed manufacturing risks to persist for extended periods. An overview of the two issues is provided in **FIGURE 2**.

CASE STUDY 1: INADEQUATE DEVIATION INVESTIGATIONS FOR DEPYROGENATION TUNNEL

One investigation reviewed by the agency was related to the depyrogenation tunnel for vials. The firm manufactured a lyophilized sterile injectable drug product in glass vials and various batches of the lyophilized drug product were found to contain black particles over a period of several months.

The company investigation found that the particles were metal shavings that were falling from the upper surfaces of the tunnel into the empty vials that were subsequently filled with the drug product. Various repairs were conducted on the tunnel but the problem continued intermittently.

Rejection of batches of injectable drug product took place due to vials that contained black particles upon visual inspection. The investigation did not extend to other batches manufactured with the same equipment during the same time frame.

"What was concerning about this was that they were rejecting

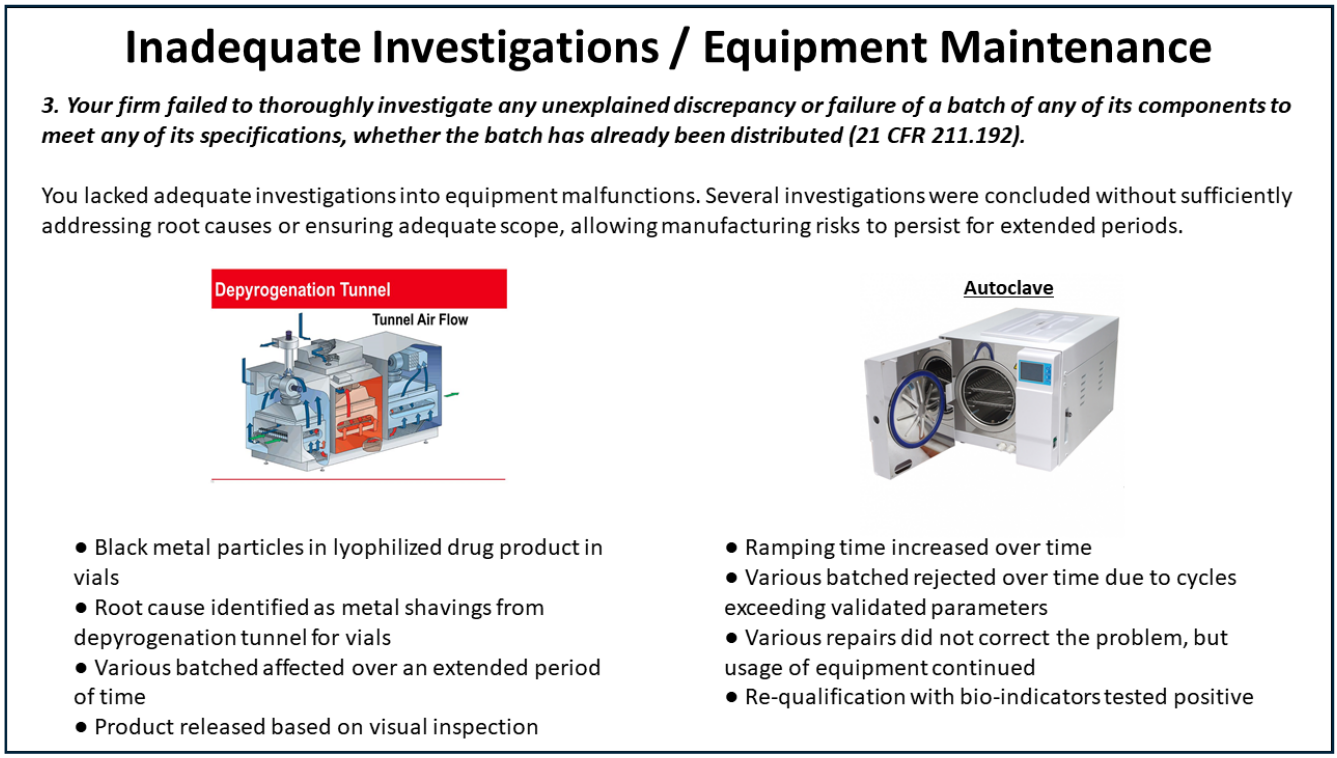

FIGURE 2 | Inadequate Investigations and Equipment Maintenance

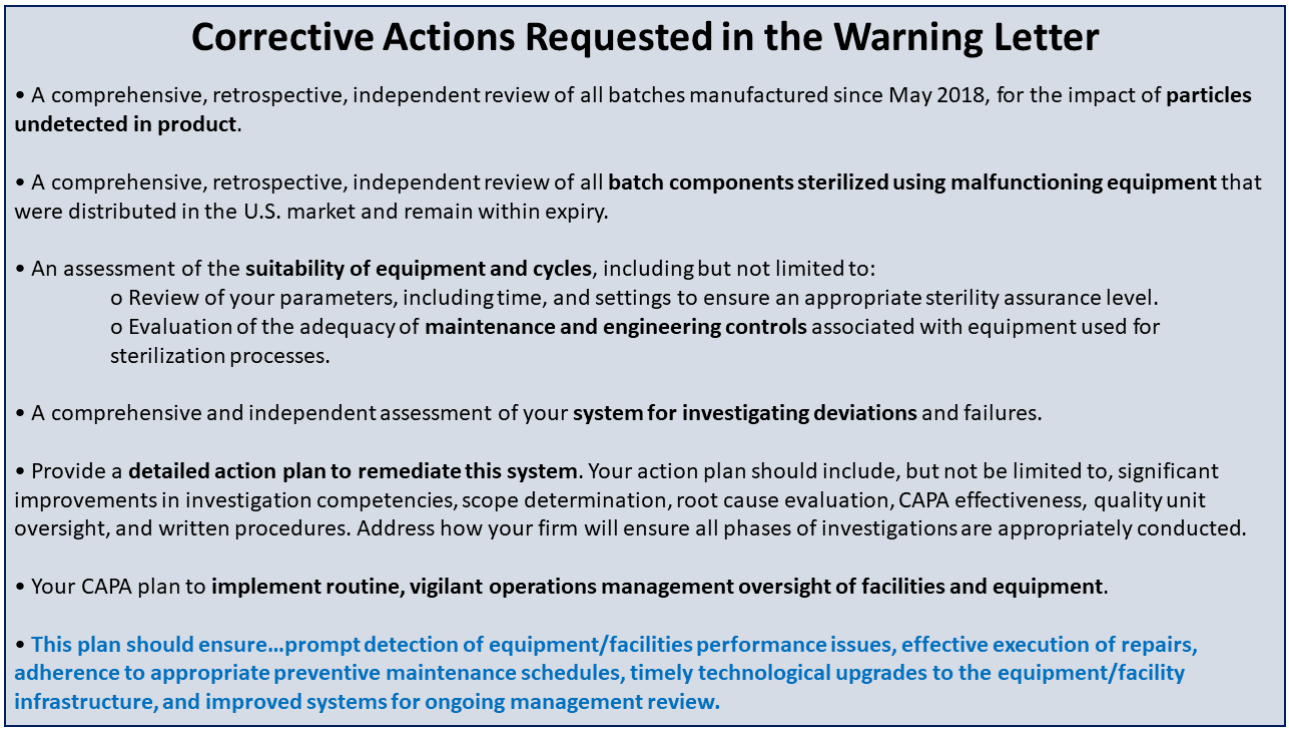

FIGURE 3 I Corrective Actions Requested in the Warning Letter Maintenance

vials that they could see these particles in," Barreto-Pettit stressed. "This is a lyophilized cake. They were only rejecting vials where they could see contamination on the outside of the cake. However, particles embedded within the cake would not be detected upon visual inspection."

CASE STUDY 2: INADEQUATE DEVIATION INVESTIGATIONS FOR MALFUNCTIONING AUTOCLAVE

In the second scenario at the same facility, another injectable drug product was filled in syringes and terminally sterilized in an autoclave. At the time of the inspection, the terminal sterilization cycle for the injectable drug product was exceeding the validated autoclave parameters as the ramping time to achieve the set parameters was increasing. It was taking longer to achieve the set parameters for the autoclave. This resulted in various batches of the product being rejected because the sterilization cycle was taking longer and was not meeting its validated parameters.

Different investigations identified different root causes for the malfunctioning of the equipment. Various repairs were performed but nothing seemed to resolve the issue completely. The investigations did not extend to all batches that may have been potentially impacted that were sterilized using the same equipment.

At the time of the FDA inspection, the requalification of the autoclave had failed in that the bioindicators had shown positive growth. Even after the requalification failure, the equipment was still being used for commercial manufacturing. The firm was certain that the requalification failure was due to using improper bioindicators with the wrong D value and not due to the malfunctioning of the autoclave.

However, this investigation was still open at the time of the inspection, which occurred about a month into the investigation, and the equipment continued to be used. This issue was noted in the FDA 483 and also cited in the warning letter issued to the company.

FDA WARNING LETTER CORRECTIVE ACTIONS

In the warning letter, information was requested from the firm regarding the impact of undetected particles, adequacy of investigations and competencies of those conducting them, and an assessment of the malfunctioning equipment (**FIGURE 3**).

Importantly, the agency targeted what appeared to be issues related to aging equipment (the last bullet point in **FIGURE 3** in blue). "We questioned their equipment as being obviously malfunctioning and possibly aging," Barreto-Pettit pointed out.

"In this warning letter, we specifically requested that the CAPA plan ensure the prompt detection of equipment and facility performance issues, effective execution of repairs, appropriate preventive maintenance schedules, and a timely upgrade of technology for the equipment and the facility infrastructure. We also asked to see how they are going to review their systems—the ongoing management review. We wanted a plan for that."

HOW TO DETECT AND PREVENT EQUIPMENT RISKS

The Drug National Expert Investigator provided the following questions for firms that may have equipment risks like the ones discussed above to explore as a self-evaluation tool:

- "Does your quality unit get involved in identifying poor performing equipment or unreliable equipment based on their review of planned maintenance activities, deviations, the history of the qualification, any findings of calibration, or how the batch performs? Are you getting involved in this or is this a responsibility of other departments such as production, maintenance, engineering, etc.? How does the quality unit make sure that this poorly performing equipment is identified in a timely manner?"

Both the product owner and the contract manufacturer share the responsibilities for adequate specifications.

- "How does the quality unit assess and understand the risks and the potential impact of this poor performing or aged equipment to the manufacturing process capability and the product quality attributes? How are you controlling or mitigating those risks? And are you documenting the review of these risks in your control strategy?"
- "Does your quality unit remove, in a timely manner, equipment that is performing poorly or is obsolete, is unreliable, that cannot adhere to the process parameters, like the autoclave discussed above, or equipment that requires frequent interventions or adjustments by the operators? Or equipment that breaks down frequently or when you do the maintenance and it really does not resolve its performance or improve it? Do you keep using this equipment or do you remove it?"
- "If you keep using equipment that is aged, do you have justification for the continued use that is based on documented risk controls? And are you reviewing these risks periodically to make sure they are not impacting the quality of the drug product?"

PART III: INCORRECT SPECIFICATIONS, PROCESS VALIDATION ISSUES AT CMO LEAD TO ADVERSE EVENTS, RECALL

Part III covers two case studies involving GMP issues at a contract manufacturing organization (CMO).

CASE STUDY 3: INADEQUATE SPECIFICATIONS AND A CONTRACT MANUFACTURER

The third case study Barreto-Pettit presented at the UGA conference involved a scenario that resulted in a mission critical inspection conducted during the COVID-9 pandemic due to adverse events that were reported to the agency after patients took a drug product that was intended for the treatment of thyroid disease.

In this case, the firm, which was both the product owner and the distributor of the product, had established the wrong assay specifications for thyroid tablets in that the upper limit was too high. 21 CFR 211.160(b) requires the establishment of product specifications but the company failed to do so.

The product in this case study is an unapproved prescription drug product for which there is no approved application. Therefore, the manufacturer must follow the USP monograph for the specifications. The product is contract manufactured. "Both the product owner and the contract manufacturer share the responsibilities for adequate specifications," Barreto-Pettit stressed.

The USP specification for assay for this thyroid product is 90.0% to 110.0%. However, the firm erroneously established its specifications with a higher and wider range. "This was probably one of the reasons patients were experiencing adverse events when they were taking this medication," she postulated.

In the Warning Letter, which was issued to the product owner, FDA acknowledged that the product owner changed its specifications to the correct ones and recalled some lots that had exceded the newly established USP specification upon release. However,

since this was a product owner and not the manufacturer, the agency conducted a subsequent inspection of the contract manufacturer and found 13 additional lots manufactured with an API from a previous supplier that also exceeded the USP specifications but were not initially recalled (Author's Note: See the next case study below for more detail).

Agency investigators found upon further review of the validation documents that some of the validation batches also exceeded the correct assay specifications

In addition, FDA investigators collected samples of the product for testing and found several batches that had low out-of-specification results that also had to be recalled. "This was interesting because their specification had a higher upper limit, but when we tested the products, they would come in low. We knew that there was an issue going on with content uniformity," she commented.

CASE STUDY 4: PROCESS VALIDATION ISSUES INVESTIGATED AT CMO

The fourth case study is the follow-up inspection of the contract manufacturer of the thyroid tablets that was the subject of the third case study, where the agency identified an additional 13 lots that exceeded the USP assay specification of 90.0% to 110.0%. Since the agency had seen variable assay values ranging from the upper 80s to values over 110%, investigators reviewed the process validation documents for that product and found other deficiencies.

For example, it found that the firm lacked evidence to demonstrate the homogeneity of the powder blend it was formulating into tablets after it was blended in the V blender. And even though the company collected samples from multiple locations within the blender, personnel combined the samples in the laboratory and tested them as a composite sample, only getting one assay result.

Agency investigators found upon further review of the validation documents that some of the validation batches also exceeded the correct assay specifications of 90.0% to 110.0%. But these were not identified during the company's investigation, which did not extend to the process validation or stability lots or any other batches that were distributed and were still within expiration dating.

FDA found that the most recent validation batches after using a new API supplier were not placed on long-term stability until a year later, which was about a month before the inspection discussed here. Therefore, there was no stability data.

The agency also cited the quality unit under 21 CFR 211.22(b) for not ensuring that the product was manufactured in accordance with CGMPs, that investigations were complete, and that their product met specifications.

WARNING LETTER FOCUSES ON PROCESS VALIDATION, BLEND UNIFORMITY, AND CONTROL STRATEGY

A Warning Letter was issued to the contract manufacturer in January of this year, 2021. The first citation was 21 CFR 211.108, which is inadequate process validation. The Warning Letter states that the company lacked data to show the homogeneity of the powder blend, as the samples that were collected at different locations within the blender were tested as a composite sample and therefore the company only had one result and was not able to detect variability within the blend that could have led to content uniformity issues of the tablets.

During the inspection, FDA collected samples of three different batches, two of which were from the process validation batches. All three samples had results that were low and the samples were subpotent for the active ingredient. One of them also failed content uniformity.

"It is important to understand that blending is a very critical step in the manufacturer of oral solid dosage forms, particularly for narrow therapeutic drug products like these thyroid tablets," Barreto-Pettit pointed out. "And when the blends are not handled adequately, it can promote segregation, increase the moisture levels, cause particles to aggregate, and can lead to inconsistent flow characteristics when they are being compressed."

Additionally, because of the narrow therapeutic range of this product, content uniformity is critical. It is especially important to prevent patients with hypothyroidism from receiving insufficient or excessive doses. As a result of these content uniformity issues, the company had to recall all the lots on the market.

The Warning Letter also stated that the firm's response to the FDA 483 was not adequate in that it did not provide sufficient

data to show where the variability was occurring in its process and what its control strategy was before the company revalidated the process.

CONCURRENT PROCESS VALIDATION NOT THE BEST CHOICE

The firm stated it would perform a concurrent process validation instead of a prospective process validation. In concurrent validation, the firm manufactures validation batches but each batch is evaluated concurrently after meeting specifications but before completing the process validation. "This approach should be rarely used, especially where process knowledge is limited and a control strategy has not been identified fully," the FDA drug expert stressed.

The Warning Letter also cited the firm for not having continued process verification, which is stage three of process validation, to ensure its manufacturing process remains in control and produces a drug product that consistently meets specifications.

The Warning Letter required the contract manufacturer to provide the following:

- A data-driven and scientifically sound analysis identifying all sources of variability, including but not limited to the raw materials and any type of manual steps such as the hand scooping personnel used to transfer the blend to the hopper, etc.
- A determination of the capability of this manufacturing process step and a CAPA to reduce the process variation
- A detailed summary of the validation program to ensure the process remains in control throughout the product life cycle along with any associated procedures
- More specifics about the process performance qualification and how the company is going to monitor both intra- and inter-batch variation to ensure they continue in a state of control

EVALUATING STATE OF CONTROL IN MANUFACTURING

The following is a set of questions Barreto-Pettit prepared for firms to use in evaluating manufacturing practices:

- Do your quality unit and the responsible departments have sufficient knowledge of the manufacturing process and the sources of variability?
- How do you monitor the sources of variability and control them?
- What systems do you have in place? Do you have systems that are adequate as far as procedures to detect a shift in the process and identify new risks?
- And if those risks are identified or shifts are detected, how is that being communicated to the appropriate parties? And how do they correct it? How are they documented and monitored?
- How often do you evaluate your process to determine whether process improvements, new equipment, and/or new technologies are needed? Do you have a system in place in writing for systematically doing this type of evaluation? And how do they correct it? How are they documented and monitored?

PART IV: FLAWED PROCESS VALIDATION, INEFFECTIVE QUALITY UNIT CITED IN WARNING LETTER

Part IV covers a separate case study involving process validation.

CASE STUDY 5: PROCESS VALIDATION, QUALITY UNIT ISSUES FOR DRUG IN SHORTAGE

The fifth and final case study in Barreto-Pettit's presentation was based on the findings from a mission-critical preapproval inspection for an injectable drug product that was in shortage. This was the first commercial drug product for this firm at this location. The product in the application was a sterile liquid drug product filled in large volume parenteral bags that are terminally sterilized.conducted during the COVID-9 pandemic due to adverse events that were reported to the agency after patients took a drug product that was intended for the treatment of thyroid disease.

At the time of the preapproval inspection, process validation had been completed. On inspection, FDA found "a very highly automated and integrated manufacturing and filling process," the national drug expert reported. "And according to the quality unit, the process validation effort had been considered successful. Therefore, we reviewed the process validation documents."

The manufacturing process flow for the product begins with a

compounding step, which in this case is a simple step in which a few ingredients are added to water.That liquid is then pipe transferred into form-fill-seal machines. The bags are formed and printed, filled, and sealed in these machines.

From there, they are sent to a conveyor through an auto tray loading and unloading into the sterilization chambers. Then the bags go through a step to remove the moisture from the outer surface of the bags before going into automated leak detection equipment.

From there, the bags continue on a conveyor belt to a semi-automated bag inspection by visual inspectors.Next, they go automatically to the next station, which is an over-wrap plastic bag that goes over the primary container to protect the outer surfaces and the ports. And then from there to the final secondary packaging and labeling station. In reviewing the completed process validation data, FDA was provided with a table, which contained Process Performance Qualification (PPQ) information."As you can see, the firm manufactured four PPQ batches, one of which required rework due to issues with the over-wrap step crushing the ports of the bags during sealing. When we first got this list, it did not have the last column—the yield column" (**FIGURE 4**).

Information from Process Performance Qualification (PPQ) Batches

PPQ Run	Bag Size	Units Produced	Yield
1	500 mL	26,616	44.82%
2	500 mL	19, 632	--
3	1,000 mL	7,788	27.94%
4	1,000 mL	7,824	32.42%
2 (re-work)	500 mL	18,264	33.74%

$$\text{Percent Yield} = \frac{\text{Actual Yield}}{\text{Theoretical Yield}} \times 100\%$$

FIGURE 4 | PPQ BATCHES

PROBLEMATIC PROCESS YIELD AND RECONCILIATION ISSUES

What FDA investigators found concerning about the table was the number of units produced for batches that had a theoretical size of 30,000 liters. For a yield of 100%, the company should have produced around 30,000 units of the 1,000 ml bag size and around 60,000 units of the 500 ml bags.

The table shows that the number of units produced was well below the expected outcome. Instead of 30,000 units produced, for batch number three, there were only about 8,000 bags. The same with the fourth batch, about 8,000 bags. And for the 500 ml size, there were anywhere between about 20,000 and 26,000 bags as opposed to 60,000 bags.

The investigators asked for the calculated yields and were provided with those figures after they calculated them. And as you can see, the total yield ranged from about 28% to 45%. In addition, the reconciliation yield for each batch was also out of the normal range with values around 69% or so. The company could not account for 30% of the batch.

"To make things even more difficult," Barreto-Pettit commented, "they had not conducted investigations into these low theoretical versus actual yields or into the low reconciliation yields. And the reason they had not conducted these investigations is that they had not set yield parameters in each manufacturing step or a total overall yield."

A primary observation on the FDA 483 had to do with inadequate process validation. The low total batch yields and the lack of documentation for having such high rejection rates indicate that the process is not in control.

In addition, the regulations require that yield parameters be established for each manufacturing stage. The company had not done that for the final or intermediate steps, including the compounding and form, fill and seal, and sterilization steps.

"Each step needs to have specific yield parameters, and if they do not meet those parameters then an investigation needs to be conducted," she pointed out. "They did not do that. They did not have yields even for reconciliation to make sure to account for all the materials used for each batch."

In addition, other information that should be in the batch record, such as extensive stoppages, interventions, or response to critical alarms, was not in the batch records. As a result, it was "very difficult" to determine how well each batch ran in the processing line "because there were not many comments within the batch records."

INADEQUATE AUTOMATED SYSTEMS AND QUALITY UNIT

During the inspection, investigators examined the electronic programming of the form-fill-seal equipment. "We found that it had a lot of settings for critical alarms," Barreto-Pettit commented. "Since this was such an automated system that

required little intervention by the operators, they had set alarms to go off so the operators would take action. What we found was that some of these did not match the established process parameters."

Some of the alarm settings were wider than the process parameters, therefore, they would not go off unless they were far out of range. The company did not have an explanation for the wider settings.

For these and many other reasons in the 483, investigators listed observations for an inadequate quality control unit under 21 CFR 211.22(d). The quality unit approved the flawed process validation, did not conduct investigations, and did not identify the deficiencies that were occurring in the process.

PROCESS VALIDATION EXPECTATIONS

In her presentation, Barreto-Pettit emphasized some of the expectations for stage one process validation, which is also known as process design (**FIGURE 5**).

During this phase, FDA expects the company to build knowledge and understanding of the quality and interaction of raw materials as well as the process and equipment to determine the greatest sources of variation to establish a control strategy. Manufacturers need to understand the functionality and limitations of the manufacturing equipment and how to detect the variation and its degree to implement procedures and strategies to maintain the process under control.

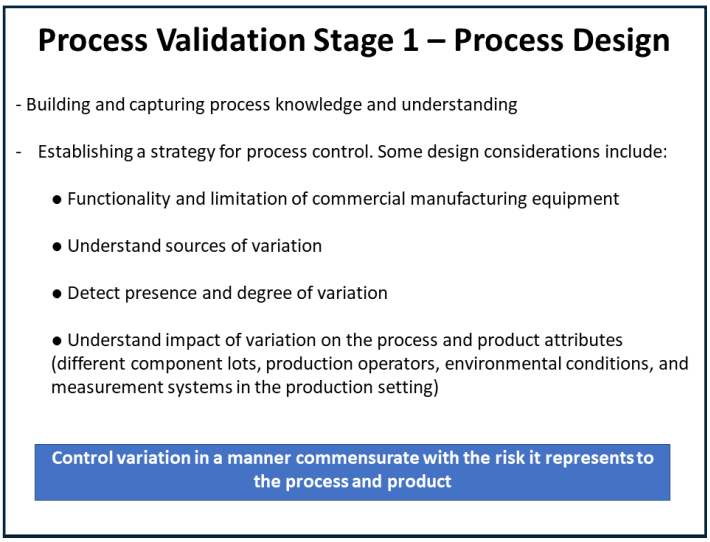

FIGURE 5 | PROCESS VALIDATION STAGE 1

It is expected that the process is challenged. Sometimes design of experiments (DoE) is used with different component lots, different operators, different environmental conditions as applicable, and the measurement systems in the production setting to identify the optimum parameters and conditions for the specific product.

"In this case as evidenced by the low yields and the lack of information in the batch record, the company had a lot of rejected bags that were either filled or unfilled and multiple rejections from form-fill-seal to packaging," she pointed out.

"Telling us that your company is overly conservative and it is rejecting more bags than needed does not mean, at least to me, that you understand the process or have confidence in the equipment measurement systems and the control strategy that you have implemented."

"We did not feel during the inspection that there was sufficient knowledge about this equipment and the rejection rate at each station and the root causes for the rejections. As I said before, there were no investigations as the quality unit did not question the low yields for the validation batches."

QUALITY UNIT RESPONSIBILITIES

In closing, the National Drug Expert emphasized the responsibilities of the quality unit in the pharmaceutical quality system.

"As you know, the quality unit has overall responsibility for the quality and safety of the drug products that you manufacture and distribute to the US market. If we find during inspections that companies are not identifying issues, are not following their responsibilities, or are not implementing systems to ensure that the products are consistently manufactured, those observations will appear in a 483 and could potentially be cited in a warning letter."

"When it comes to contract manufacturers, I often find that the quality units do not have a robust oversight of these types of activities. A company needs to find ways to make sure that whatever product is contract manufactured or tested at a third-party facility is following appropriate procedures and CGMPs and that the product is manufactured in accordance with CGMPs. Make sure that you always have oversight of all operations throughout the life cycle of the product as well as the facilities and equipment."