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GMP Issues With COVID Vaccines and Drugs are Not New Concerns

EXPERT ARTICLE

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Over the past two years, several pharmaceutical firms have received Emergency Use Authorization (EUA) for COVID vaccines and therapeutic products. Although the EUAs can be dry reading with a lot of boilerplate type text, in some instances, these documents and other memoranda provide insight into FDA's ongoing decision-making process balancing the public health needs with the use of drug substances and associated products which may not fully comply with FDA GMP requirements. No easy answers are to be found here, but FDA seems to be making its best attempts at a balance of risk versus benefits.

An interesting takeaway from the inspections described in this article is that the inspections do not identify novel practices and novel interpretations of GMP requirements. FDA simply identifies shortcomings in areas and practices that have long been cited in GMP inspections. Somehow, we in industry just cannot get some of these operations "right." The GAO also recently issued a report that addressed the FDA's limited inspection practices for the three vaccines subject to EUAs in 2021.

The inspections we will address here are those of:

- Emergent BioSolutions in Maryland, who manufactured the vaccine drug substance for both Johnson &Johnson (J&J) and AstraZeneca,
- Eli Lilly facilities in New Jersey and Indianapolis where drug product and drug substance for COVID therapeutic antibody treatments respectively are manufactured, and
- FUJIFILM who manufactures the Novavax vaccine drug substance

EMERGENT BIOSOLUTIONS

Let us start with Emergent BioSolutions. FDA posted two forms 483 from recent inspections of The Emergent Manufacturing Operations in Baltimore, Maryland, one from April 2020 and one from April 2021. It is interesting that in the first form 483, the firm is identified as a contract testing laboratory and yet a year later is identified as a vaccine drug substance manufacture, representing a significant change in ongoing responsibilities. The challenges in the switch to vaccine drug substance manufacture

in this limited time period may explain some of the challenges and failures.

In April 2020, a single FDA investigator conducted a seven-day inspection of the Maryland facility and issued a six-page, five-item form 483. Assuming that FDA form 483s provide observations in their order of importance, Observation 1 questions the firm's data governance and data integrity practices. None of the shortcomings appear unique and are fundamental expectations that we have seen identified in FDA form 483s for at least ten years:

- The firms did not protect electronic data from manipulation or deletion. The Quality unit failed to review audit trails for laboratory systems and thus did not identify and investigate the cause or impact of data deletions.
- Users are able to change system date and time on analytical balances and computers with Windows operating systems.

Observations 2, 3, and 4 from this inspection also identify data integrity deficiencies, including:

- Failure to document data at the time of performance,
- Sample identification that was manually corrected days after the initial entry without explanation, justification, initiation of a deviation, and an investigation to the failures,
- Nine examples were provided of the inability to provide records on the location of laboratory sample storage between the various analyses, and
- The Quality unit fails to provide adequate oversight of these types of events and does not review data in a timely manner.

The final observation addressed the issue of material management that was not adequate to prevent contamination or mix-up. This observation appears in greater detail in the April 2021 inspection and had serious consequences for both the sponsors of the vaccine drug substances made there and for Emergent BioSolutions itself.

In April 2021, three investigators conducted an approximately eight-day inspection of the Maryland site that resulted in a 12-page form 483 with nine multipart observations. The inspection was triggered by an out-of-specification (OOS) finding of cross-contamination in the J&J vaccine drug substance.

- In the first observation, FDA addresses "cross-contamination of client [redacted] viral vaccine drug substance batch…with virus from client [redacted]…." FDA provides an exhaustive, multipart description of procedures and processes that could have led to cross-contamination between the two vaccine drug substances, which were identified by one of the client firms.
- They describe a facility that was not designed and operated effectively including waste flows that could have contributed to cross-contamination, a poorly maintained facility, and a facility that was not of "suitable size, design, and location to facilitate cleaning, maintenance, and proper operation."
- Further, they evaluated security camera footage, badge entry logs, and direct observation of problematic handling of nondisinfected and nondecontaminated waste. They provide eighteen examples.
- Additional security camera footage was used to identify that the personnel were not adequately trained to prevent contamination and cross-contamination.
- They identified a facility that was not of adequate size to effectively perform the processes in a way that would prevent cross-contamination.

After this inspection, many trade publications and news sources publicized these findings. FDA also posted Emergent's April 30, 2021, 52-page response to the form-483. FDA further issued a harshly worded statement to address the public's concerns about the vaccine safety, and instructed J&J to take over the operations of their vaccine drug substance manufacture at Emergent. AstraZeneca moved their manufacture to another location. Manufacturing at the site ceased as J&J and Emergent worked diligently to correct the issues that FDA identified. The story of the AstraZeneca materials made at the facility continues to be the topic of FDA review and comment as AstraZeneca ships product to sites outside the United States. Millions of doses of the J&J vaccine were destroyed because of the cross-contamination.

These events were the subject of several televised congressional hearings. The U.S. Congress subcommittee on the Coronavirus Crisis issued a "Preliminary Findings from the Investigation into Emergent BioSolutions" on May 19, 2021. One of the exhibits in these hearings was the J&J audit report of Emergent BioSolutions

in June of 2020. The report identifies seven observations, two of which were major. No observations were critical in nature. The firm was deemed to be "conditionally qualified" on the basis of this audit.

ELI LILLY AND COMPANY

Eli Lilly and Company received an EUA that was rescinded and then selectively reactivated for monoclonal antibodies as a COVID-19 treatment. The monoclonal antibody drug substance was manufactured at their New Jersey site, one they acquired from ImClone in 2008 with the acquisition of the company. The antibody drugs are aseptically filled at the Lilly site in Indianapolis. We provide the form 483s from two of the sites.

The New Jersey site was inspected by two investigators for ten days in November 2019, resulting in a five-page form 483 that included two heavily redacted observations. The first observation addressed data integrity failures in manufacturing systems. While the observation was heavily redacted, one key sentence remains: "Operators were assigned administrative privileges." We are left to guess at the extensive detail that was redacted from that observation.

The second observation addressed that "…appropriate controls were not exercised over computers or related laboratory systems." So, in these two observations, FDA calls into question the integrity of both manufacturing and laboratory data. This site was also the subject of a whistleblower complaint about reported records that "…had been falsified or destroyed in the wake of manufacturing mistakes".

In what is likely a follow-on inspection to that performed in New Jersey, four FDA investigators issued a 13-page, seven-observation form 483 to Eli Lilly's site in Indianapolis on March 16, 2021. FDA also released Lilly's 95-page response to the form 483. The antibody therapeutics described above and other products, including Glucagon, are aseptically filled at this Indianapolis site. The observations from this inspection ranged from inadequate monitoring of environmental conditions in aseptic filling areas, which covers the first five pages of the form 483 with an exhaustive listing of examples.

Other observations address the failure to have adequate procedures and processes to prevent microbiological contamination, shortcomings in aseptic processing, and a painfully long list of why staff are deemed not adequately trained. The stability program does not use stability-indicating methods even though these methods are used in product release. The sampling size for incoming vial testing is inadequate. The PR&D Development lab that performs release testing for clinical product does not require review of all laboratory data collected but rather relies only on the review of the sequences submitted for review.

The EUA was issued to Lilly on September 16, 2021. In consideration of the serious deficiencies identified by the FDA at the Branchburg N.J. site, Lilly must "…retain an independent third party to conduct a review of the batch records and underlying data and associated discrepancies of the …drug substance at Lilly Branchburg, NJ."

Also, "Lilly will retain an independent third-party (i.e., not affiliated with Lilly) to conduct laboratory release testing of bamlanivimab drug substance manufactured at Lilly, Branchburg (excluding bioburden and endotoxin testing). Any discrepancies found by the independent laboratory must be reported to the Agency in a summary report, submitted every 14 calendar days, and include Lilly's corrective and preventive action plans for each discrepancy."

NOVAVAX

The last of the COVID-19 vaccine drug substance sites we cover is FUJIFILM Diosynth Biotechnologies, Morrisville, N.C. site that manufactures for Novavax. FDA inspected the manufacturing site in Morrisville between April 14, 2021, and April 21, 2021. This COVID vaccine has not yet received Emergency Use Authorization from FDA. The only approval so far for the Novavax vaccine is from Indonesia for a product manufactured by the Serum Institute of India. The team of four investigators issued an eight-page form 483 with ten observations at the close of the inspection of the Morrisville site.

- Again, we begin with the first observation that identifies the lack of "comprehensive risk assessments conducted at this multiproduct facility to justify the containment strategy and controls of manufacturing [redacted] products using microbial and cell culture processes to prevent cross-contamination." This is a similar refrain from observations issued to other firms in this area.
- The manufacturing process is not adequately controlled.
- Four vials of the WCB are not accounted for in the PAS-X

system (I am assuming this is the inventory control system). Further, expired materials were found in the warehouse SAP system. There is no time period for the disposal/destruction of expired materials.

- Cleaning of non-dedicated product contact equipment is not adequate.
- Investigations are not adequate. Environmental monitoring excursions are not investigated for root cause so that CAPAs can be implemented to improve microbial control.
- Controls are not adequate for electronic data acquisition systems to ensure protection from unauthorized manipulation.

CONCLUSION

In conclusion, the observations made at these COVID vaccines and therapeutic product manufacturing sites are consistent with FDA's focus on aseptic processing and microbial controls, controls to minimize and prevent contamination and cross-contamination in multiproduct facilities, and inadequate cleaning of shared multiproduct equipment. These are all topics that FDA cites in many other, non-COVID, inspections.

In addition, the Emergent BioSolutions observations are relevant not only for vaccine manufacturers but also for gene therapy and cell therapy manufacturers based on the cross-contamination of viral plasmids. Cell and gene therapy firms would be wise to evaluate these observations in detail.

The observations, however, do not appear to represent a new interpretation of any regulations, and in particular, the data integrity/data governance observations have been common for the past 15 years. It will be worth following these medical products to see if and when they receive full FDA approval and whether this will require remediation of the observations identified in the forms 483 we provide here prior to approval.

ABOUT THE AUTHOR

Barbara Unger formed Unger Consulting, Inc. to provide GMP auditing and regulatory intelligence services to the pharmaceutical industry. Her auditing experience includes leadership of the Amgen corporate GMP audit group for APIs and quality systems. She also developed, implemented, and maintained the GMP regulatory intelligence program for eight years at Amgen.