"Issues in Drug Quality and Manufacturing: ConOps, Quality Metrics, and Outsourcing" Case Study

- PharmaCo outsources the manufacture of an important sterile injectable product (Product) to a large CMO that manufactures the active pharmaceutical ingredient (API) and the finished product.
- PharmaCo selected CMO in 2014 after conducting significant due diligence of potential manufacturing organizations. PharmaCo ultimately selected CMO for the following reasons:
  - CMO has a good inspection history, with no critical findings in the past 10 years in inspections by FDA, EU, or TGA.
  - CMO manufactures APIs or finished products for a majority of the industry's largest pharmaceutical companies.
  - CMO has the technology, capability and experience to manufacture the Product.
  - CMO has a demonstrated investment in supporting its facilities and equipment.
  - CMO's quality culture is robust with a mindset of "Quality first."
- PharmaCo and CMO entered into a Supply Agreement and Quality Agreement in 2014. The Quality Agreement specifies the roles and responsibilities of each party including quality oversight of investigations, major change controls, regulatory notifications and inspection support. PharmaCo meets with CMO twice a year to review metrics related to on time delivery and recalls. Under the terms of the Quality Agreement, PharmaCo conducts audits of CMO every three years. The last audit, in June 2017, resulted in only one finding, which was rated as minor.
- Last September, PharmaCo noticed an increased number of complaints for black particulate matter in the Product, and has had numerous discussions with CMO regarding these complaints. CMO instituted an additional manual visual inspection step in an attempt to reduce the complaint rate as the investigation into the cause continued. PharmaCo also sent several experts to CMO to work on the investigation. To date, CMO has not identified the root cause of the problem.
- In January, FDA conducted a preapproval inspection (PAI) of CMO for another customer's product, which quickly expanded to a general CGMP inspection. At the conclusion of the inspection, FDA issued a Form FDA-483 with ten (10) observations, with multiple subparts, regarding inadequate investigations, aseptic processing, environmental monitoring, and lack of controls over computerized systems. Because a number of FDA's observations focused on the complaints received for the PharmaCo Product, PharmaCo was heavily involved in reviewing and drafting the Form 483 response.
- Ninety days after the conclusion of the inspection, FDA notified CMO that the January inspection had been classified as Official Action Indicated (OAI). FDA stated further that "this facility may be subject to a CGMP regulatory or enforcement action based on this inspection, and FDA may withhold approval of any pending applications or supplements in which this facility is listed."

Based on the number at the top of this page, you are asked consider this case study from one of the following perspectives: (1) PharmaCo, (2) CMO, or (3) FDA.