During an inspection of your firm we observed:

Observation 1
The accuracy, specificity and reproducibility of test methods have not been established.

Specifically, the specificity studies for the assay test methods (b) (4) “HPLC Analysis for Hydromorphone HCl” and (b) (4) “HPLC Analysis for Fentanyl Citrate or Fentanyl Injection” were inadequate in that the chromatographic separation of impurities and active peaks was not determined. The studies did not include the fortification of known impurities to test samples to optimize the separation of each component observed in the chromatograms. (b) (4) studies were performed according to document: HPLC-SOP-008, “Drug Product Study.” The procedure was deficient in that:

A. (b) (4) concentrations were not specified
B. The exposure times for (b) (4) were not provided.
C. The (b) (4) study did not follow ICH (b) (4) Stability although ICH and USP guidelines were referenced in document no.: (b) (4) “Method Selection, Validation and Verification.”

The test methods were used to assay Hydromorphone HCl and Fentanyl Citrate drug products.

Observation 2
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and written.
Specifically, airflow visualization (smoke) studies, conducted October 24, 2014, are deficient in determining the effect on unidirectional air flow as they do not include considerations for:

A. The presence of maximum sample load and equipment within the ISO 5 classified laminar flow hood.
B. Effect of operators working within the ISO 5 classified laminar flow hood.
C. Maximum number of operators present within the ISO classified areas.

**OBSERVATION 3**
Input to and output from records or data are not checked for accuracy.

Specifically, a Microsoft Excel spreadsheet was used to calculate assay values from reference standard solution concentrations, sample solution concentrations and chromatographic data. The spreadsheet, “HPLC-F006.6 HPLC Sample Prep and Final Data Template,” was also used to evaluate system suitability elements such as injection precision, retention time comparisons and check standard comparison for agreement with acceptance criteria. The document (b)(4) established a procedure by which (b)(4) were defined, administered, controlled and secured. Although the procedure referenced the document (b)(4), “Calculated/Customized Field Validation”, neither the procedure nor the referenced document provided instructions for validating spreadsheets. The procedure did not include instructions to challenge the data inputs into the spreadsheet during verification. Additionally, there was no instruction for periodic assessment of the spreadsheet due to software updates or deterioration of software performance. The Excel spreadsheet was used to calculate test results obtained in the release and stability testing of Hydromorphone HCl.
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<tr>
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<td>Walden H Lee, Chemist/Biologist</td>
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**Inspectional Observations:**

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**Signature:**

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**Employee(s) Signature:**

- Nayan J Patel, Investigator
- Walden H Lee, Chemist/Biologist