

quality control during manufacturing is an issue in FDA-regulated clinical trials on small molecules and biologicals. FDA's Guidance for Industry for manufacturing drugs for use in clinical trials, states that (11):

As indicated in previous sections, **manufacturers should keep complete records** relating to the quality and operation of the manufacturing processes, including but not limited to:

- Equipment maintenance and calibration;
- Manufacturing records and related analytical test records;
- Distribution records QC functions;
- Component records;
- Deviations and investigations;
- Complaints.

Regarding record keeping, FDA's Warning Letter complained that (12):

Your response lacks a comprehensive risk assessment of your failure to follow procedures, your **inadequate documentation** system and your inadequate practices related to microbiological control. Your response failed to evaluate the effect of these violations on product quality, and did not include an assessment as to whether any other batches have been compromised.

[Sponsor's] inability to prevent and detect **poor record keeping** practices raises serious concerns regarding the quality system in place at the time of the inspection. Appropriate controls are essential to assure that the information used for making decisions is trustworthy, accurate, and reliable.

The corrective action requested by FDA's Warning Letter took the following form. The

letter requested an evaluation of inaccuracies in data, and a risk assessment analysis (13):

In response to this letter and including the specific requests noted above, provide the following to the Agency:

- A comprehensive evaluation of the extent of the inaccuracy of recorded and reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices noted above;
- A risk assessment of the potential effect of the observed failures on the quality of drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug product released for distribution; and
- A management strategy for your firm that includes the details of your global corrective action and preventive action plan.

V. FDA'S WARNING LETTER DISTINGUISHED FROM FDA'S FORM 483 NOTICE

Where Warning Letters are issued to a Sponsor conducting a clinical trial, the letters tend to complain about failure to comply with the instructions set forth in the Clinical Study Protocol, failures of an investigator to engage with an Institutional Review Board (IRB), and discrepancies in record-keeping.

FDA's Warning Letters are to be distinguished from another format used by the FDA

¹¹U.S. Department Health and Human Services. Food and Drug Administration. Guidance for industry. CGMP for phase 1 investigational drugs; July 2008 (17 pp.).

¹²Warning Letter No. WL: 320-15-06 (January 13, 2015) from Thomas Cosgrove, JD, Office of Manufacturing Quality, Office of Compliance, CDER, U.S. Food and Drug Administration.

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