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Introduction to Stability in Aseptic Processing Facilities – Part 1

Introduction

NIH Aseptic Processing Facilities (APFs) are cleanrooms which process or support the processing of drugs and/or biologic products in accordance with current good manufacturing practices (cGMP) for human use. These facilities require control of critical environmental parameters, including room differential pressure (dP), temperature (TEMP), relative humidity (RH), and air changes per hour (ACH). They are also designed and operated to limit the spread of particulates to protect the product from contamination, and to promote patient safety by preventing personnel from sweating and shedding both viable and non-viable particles (e.g., mold, spores, fungi, yeast, etc.). Operating a cleanroom facility in a state of control is required by Title 21 Code of Federal Regulations Part 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs, General, Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals. These parameters must remain stable (i.e., exhibit minimal oscillation, noise, and drift) within a specific range during normal operations and recover fully after an upset event (such as failure of a primary air handling unit, exhaust fan, generator testing, or other electrical power disruption, etc.). Room dP is the most critical parameter for assessing the stability of the facility and is the key indicator for ensuring that airflows are maintained as designed.

Importance of Stability with APFs

Environmental monitoring and control systems for APFs utilize high performance and high precision equipment/devices and control methods to maximize the stability of critical environmental parameters (e.g., room dP, TEMP, and RH) and maintain them within specified limits. High performance equipment/devices used in APFs include fast-acting air terminal actuators, which allow for rapid airflow changes to counter any room-side changes. High precision devices used in APFs include sensors with a high degree of accuracy and tight calibration criteria to ensure the data being recorded are reliable and accurate. Airflow tracking and airflow cross limiting are two control methods NIH uses to maintain differential pressures between adjacent spaces. For positive pressure rooms, the exhaust terminals will track the supply terminals. For negative pressure rooms, the reverse will occur. These devices and control methods minimize oscillating conditions (which is the most general stability issue) that can stress processing equipment, cause the overall environmental conditions to become less predictable, and increase recovery time after an upset event. Oscillating conditions can also cause stress to materials of construction and increase worker discomfort, which collectively can adversely impact product quality and patient's safety.

Critical Environmental Parameters Stability Criteria

NIH has established the following acceptance criteria that are evaluated as part of the stability trend review during the commissioning process to assess if the APF is stable for all critical parameters. Typical acceptance criteria for dP stability are established in static (at rest) modes. The following criteria apply to NIH APFs:

- **dP:** The mean average for dP shall be no less than 0.02" w.c. from the alarm limits. If the alarm limits are 0.02" w.c. and 0.1" w.c., the mean average is between 0.04" w.c. and 0.08" w.c. For negative dP rooms, dP values are preceded by the minus sign. The shift in mean dP should not be more than 0.06" w.c. (max-min) in amplitude of oscillation using 1-min trend data. The max-min amplitude should not cross alarm limits; this is referred to as noise. The shift of mean dP over a 24-hour period shall not be more than 0.01" w.c. using 1-min trend data; this is referred to as drift.
- **TEMP:** Shall be within +/- 0.5°F of setpoint and 1°F top to bottom oscillation.
- **RH:** Shall be within 5% of setpoint and no more than 10% top to bottom oscillation.

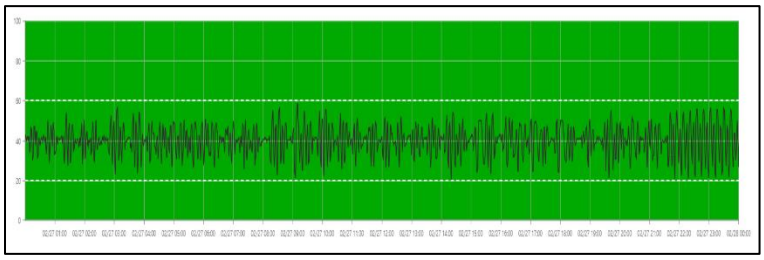

Figure 1: Oscillation (solid black line) of Relative Humidity in an APF illustrating lack of stability.

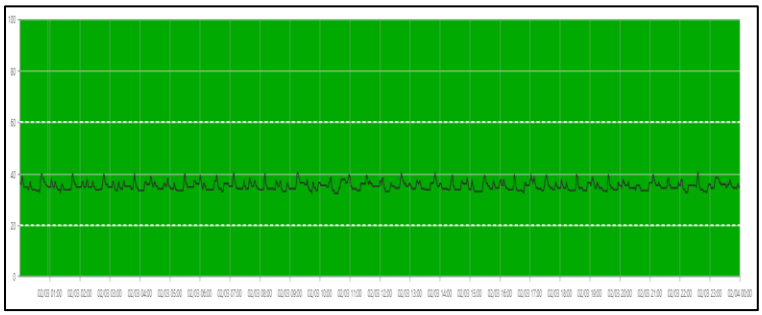

Figure 2: Stable Relative Humidity in an APF

Conclusion

Establishing and maintaining stability for all criterial parameters will ensure all APFs at NIH meet quality and safety standards for all products and processes, as well as provide optimal levels of comfort for workers inside the APFs.

Part 2 of this series will cover the stability trend review process and how it is utilized to ensure that all critical parameters have successfully met the stability acceptance criteria.