Choosing the Proper Equipment for Pharmaceutical Stability Room Humidity and Temperature Mapping

Pharmaceutical and Biotechnology companies are under a great deal of pressure to comply with regulatory requirements from the inception of a product to its final destination. These regulations are in place to ensure safety of the consumer. In the US there are two main agencies responsible for ensuring the safety of pharmaceuticals. The first is the US Food and Drug Administration (FDA) which requires companies to establish and document procedures for every part of the process using best practices to ensure the highest product quality and safety. The second agency is the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use). As the name implies this is an international agency that defines the world standard for stability testing.

One such aspect of the regulatory process is stability testing. Stability testing allows drug manufacturing companies to expose the product to conditions that might occur in the supply chain, as well as provide for stress testing for determination of shelf life. Humidity, temperature, light and other conditions can cause drugs to degrade or lose their efficacy before reaching the consumer. Stability testing is usually performed in some type of environmental chamber which allows for changing conditions of humidity and temperature. These chambers can come in all shapes and sizes from simple bench top units to larger walk in rooms. Depending on the size, shape, loads and air flow within a controlled space, detailed attention must be given to how many sensors are needed and where they are placed.

ICH guidelines suggest that the specified relative humidity be +/- 5%RH of set point and temperature should be within +/-2°C of set point. At first, it may not appear to be difficult to maintain this type of environment, but when you consider the inter-relations between the following three parameters it is a complex environment to create and maintain.

What are these three parameters?

1) **Control Constancy** – The ability of the conditioner and controller to maintain a constant humidity and temperature at the control sensor location.
2) **Uniformity** – Gradients can occur throughout the conditioned space as caused by insufficient air flow, heat or moisture loads within the space, or leakage to or from an adjacent space.
3) **Sensor accuracy** – Calibration is a critical factor of both the temperature and relative humidity measurement devices. Since there are fewer high quality humidity sensors available (compared to temperature) it is important that while mapping you are able to distinguish the difference between uniformity or calibration issues. Since the accuracy of many RH sensors is 1-2% the probes should be placed together at the condition being mapped and the offset of each sensor noted before disbursing them into the chamber.

How do you go about collecting the data to fill out the reports to show the FDA that the tests were done in compliance with the required regulations? When choosing temperature and humidity mapping equipment for validation it is important to consider the following:

1) Chose equipment with a reputation for high accuracy and long term stability that can operate and measure over a wide range of temperatures and humidity. Many relative humidity sensors claim better than 1%RH accuracy but long term stability and non ambient conditions are often overlooked.
2) Select sensors that can be easily checked against a trusted calibration reference and also have the ability to be calibrated or

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adjusted in the field. It is critical to determine the difference between actual uniformity issues in a chamber and calibration accuracy issues.

3) All components of the system should be durable enough to be easily transported around the globe to the next validation location.

Wired Thermal Systems – One poplar method for validation mapping utilizes a wired thermal system with multiple high accuracy temperature inputs for monitoring temperatures throughout the chamber or room. When humidity is also a variable within the controlled environment 2 or 3 humidity sensors are added for reference. This set up infers that dew point across the entire room is constant and any relative humidity variations will be temperature driven. While this can be true there is a false assumption that moisture leakage through a gasketed door, window, or door sweep does not occur. It also assumes no lapses in the water vapor barrier at the walls, ceiling and floor. Finally, it does not account for the ingress of moisture from an evaporator coil or moisture injector.

Wireless Data Loggers – Another popular method for mapping is to use wireless humidity and temperature data loggers. Wireless loggers are easy to program and set up because you are not hindered by wires and cables when placing them in the stability room. The problem with this type of set up is that there is no active "real time" monitoring available. The information is being recorded to the data logger during the stability test. After the test concludes the logger would be connected to a computer for download or access to the recorded data. If a problem occurs with one of the data loggers during a test, it would not be known until after the stability test is complete. If conditions in the chamber are out of tolerance, again this would not be known until after the test is complete. There really is no way to know if a logger is working properly just before or during a mapping. If a problem is discovered after the test period the whole test may need to be repeated. Lastly, if you wish to access the data logger during the testing period, you will likely disrupt the test environment by opening and closing a door for example. This could require quite a bit of time to allow for the chamber to reach set point again before starting the next test especially if your are mapping a very large room or chamber. The graphs below illustrate what happens in a typical mapping set up running at 30°C and 75% relative humidity when the chamber door is briefly opened. From the left graph it can be seen that the temperature in the chamber has still not recovered to 30°C after 90 minutes. The %RH graph on the right demonstrates that after 90 minutes the sensors have not reached the set point of 75%.

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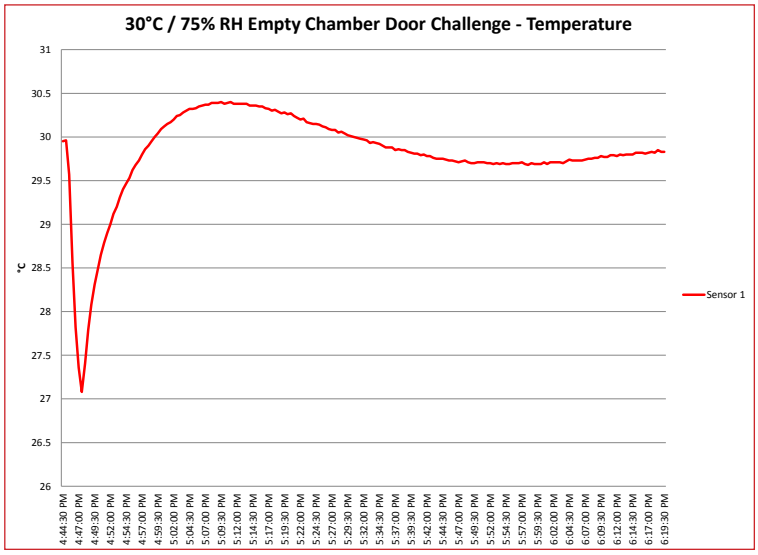

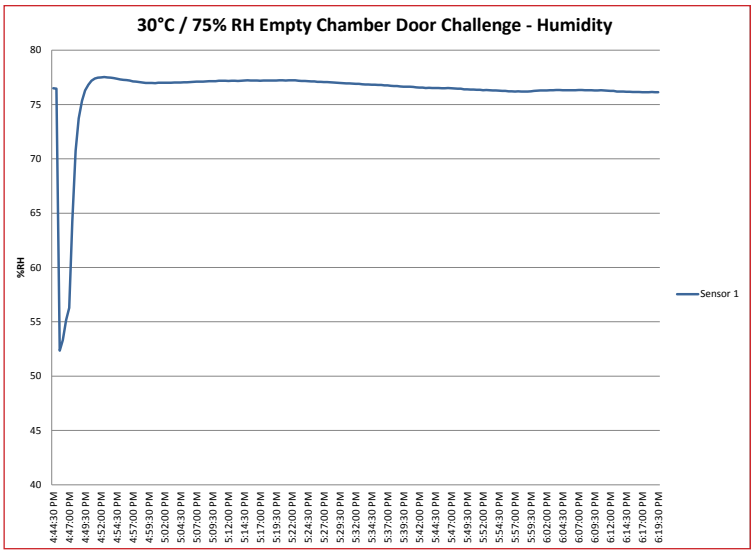

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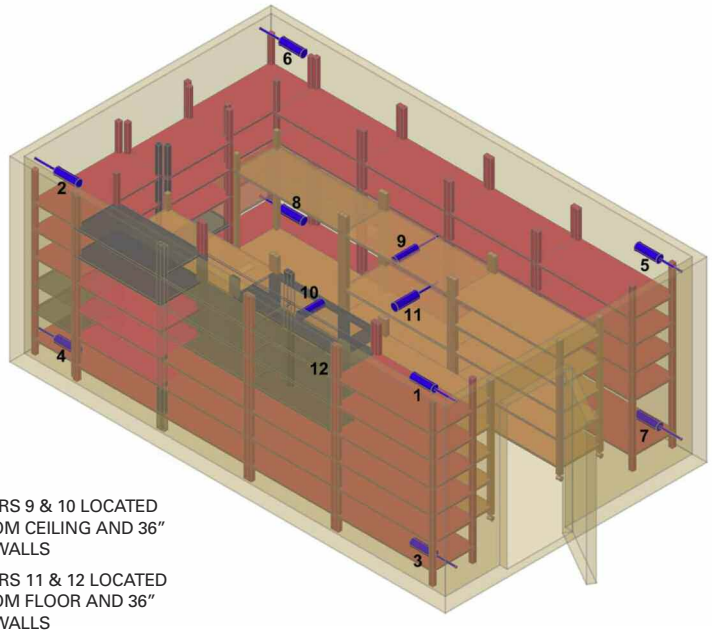
Wired Combination Temperature and %RH sensors – Perhaps the most preferred and complete method of mapping stability rooms is using a high accuracy probe that combines both humidity and temperature sensors wired back to a computer or network. Though this may take a little extra set-up time compared to the wireless data loggers, time will be saved in between and during testing. This set up allows you real time data access to relative humidity and temperature at each mapping point. Computer access to each point confirms whether or not a stability test is ready to commence or not. Once the probes are in place no door openings are required to download data before the next test starts. As mentioned above, the digital humidity probes can be verified against a reference standard and calibrated in the field. They are durable and can be shipped worldwide.

The image below is a typical sensor layout for a stability room:



NOTES:

1. SENSORS 9 & 10 LOCATED 36" FROM CEILING AND 36" FROM WALLS
2. SENSORS 11 & 12 LOCATED 36" FROM FLOOR AND 36" FROM WALLS

Sensors should be placed in typically known reduced air flow locations. This diagram may not be representative of actual chamber shelves, racks, or cages used to store samples. The table below describes actual sensor placement locations.

Sensor Number	Location	Sensor Number	Location
1	Left Top Front	7	Right Bottom Front
2	Left Top Rear	8	Right Bottom Rear
3	Left Bottom Front	9	Center of Room – Right Top
4	Left Bottom Rear	10	Center of Room – Left Top
5	Right Top Front	11	Center of Room – Right Bottom
6	Right Top Rear	12	Center of Room – Left Bottom
		13	Proximity of Control Sensor
Sensors 1-8 will be placed approximately 24 inches (2 Feet) from the interior surface of the chamber.			
Sensors 9-12 will be placed approximately 36 inches (3 Feet) from the interior surface of the chamber.			

Conclusion – At first glance it may seem like a simple task to map out a controlled area. However, actually achieving the desired results as recommended by the ICH is quite involved.

- Attention must be given to identifying stability room load sources, areas of leakage, air flow and control characteristics.
- It is then very important to choose the proper mapping technique and equipment. Carefully select equipment with high accuracy, long term stability, field calibration capability and durability.
- Whatever the method all systems must have the proper software to comply with the FDA's regulations for electronic records and electronic signatures. Paying attention to these critical details can save both time and money in the long run.

References:

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