Lyocycle Optimization – “Hot” and “Cold” Spot Determination (HTC) using TEMPRIS® for Wireless Real-Time Temperature Measurement as Process Analytical Technology (PAT) Tool – Presenting a Production Scale Performance Qualification Case Study

Andrea Weiland[1] and Anton Mangold[2]

[1]Explicat Pharma GmbH, Weidenstr. 22, 85662 Hohenbrunn, Germany; [2]iQ-mobil solutions GmbH, Industriestr. 7, 83607 Holzkirchen, Germany

Introduction

Performance Qualification (PQ) plays an important role in modern approaches towards process validation from as early as lab scale development up to routine manufacture, particularly in aseptic lyophilization technology. PAT tools are crucial in monitoring, optimizing and validating such freeze drying processes, especially if the same tool can be used at all scales.

The present case study showed relevant temperature differences between single vial positions (centre vs. edge) and across different shelves (depending on distance to condenser) – within commercial scale lyophilisation. A standard lyocycle had been instrumented with the novel real-time PAT tool: Wireless **Temp**erature **R**emote **I**nterrogation **S**ystem TEMPRIS®. The definition of hot and cold spots “HCS” [1,2] during Performance Qualification (PQ) employing a “single-vial method” proved to be practical and reliable during routine use, particularly for freezing step optimization and primary drying end-point determination.

Fig. 1 Vial

Fig. 2 IRU-2

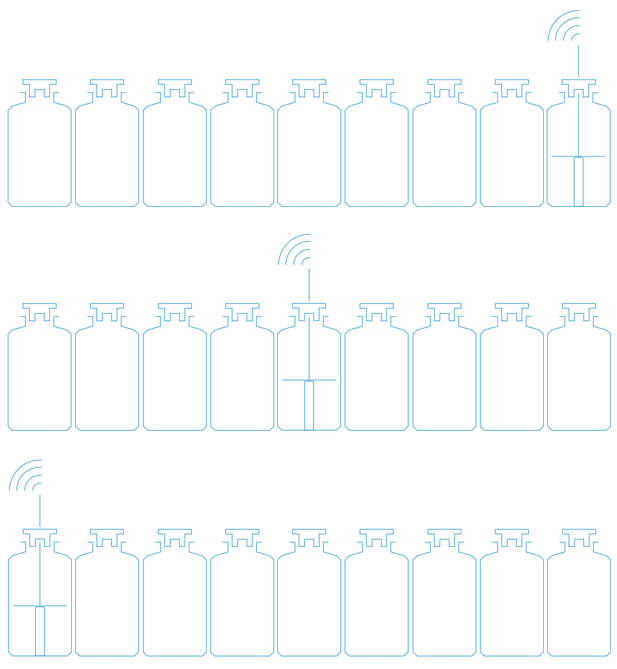

Fig. 3 Sensor positions

Materials & Methods

Experiments were conducted at a pharmaceutical manufacturer’s site on a production scale freeze dryer (HOF, 8.78 m², 9+1 shelves) running a textbook lyocycle, fully loaded with 2R vials, each filled with 1 ml WFI. Analytics were conducted using 16 TEMPRIS® size S sensors (**Fig. 1**), one Interrogation Unit IRU-2 (hardware, **Fig. 2**) and TEMPRIS® Data Server (software). Sensors were placed in the middle of vial and vials at varying center or edge positions on shelves Nos. 2, 4, 5, and 6 top to bottom (**Fig. 3**).

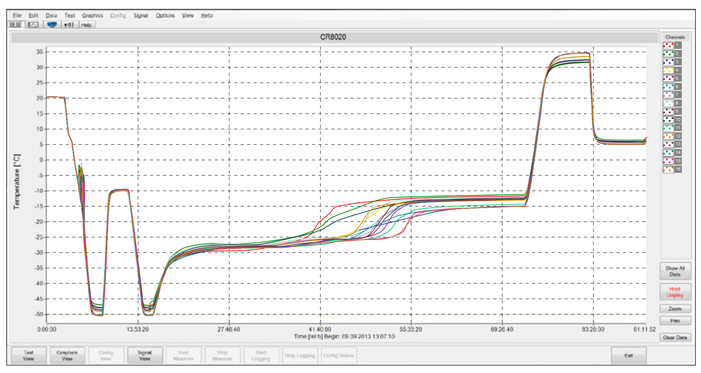

Fig. 4 16 – sensor overlay plot representing temperature measurements from total instrumentation.

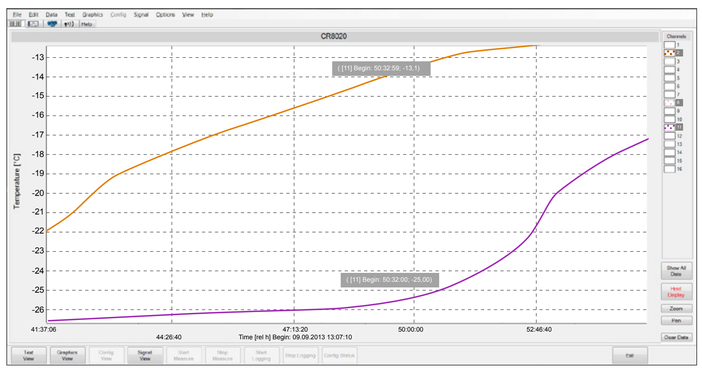

Fig. 6 Overlay of overall hot spot (shelf x, position y) and overall cold spot (shelf z, position z) during drying.

Results & Discussions

Product temperature curves at bottom of vial (T_b) from the 16 sensor positions were plotted and compared (**Fig. 4**). Temperature differences ranged from 3° to 4°C (freezing/annealing, **Fig. 5**) and 3°C to 8°C (primary drying, **Fig. 6**) between overall hot spot at maximum distance to condenser and overall cold spot at minimum distance to condenser (**Fig. 7**), within the studied experimental set-up.

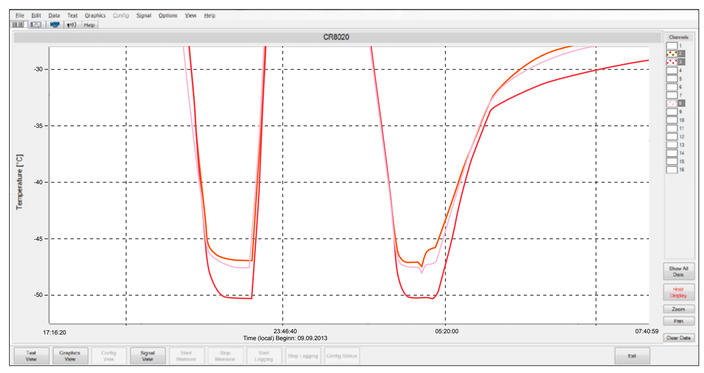

Fig. 5 Overlay of overall hot spot (shelf x, position y) and overall cold spot (shelf z, position z) during freezing/annealing.

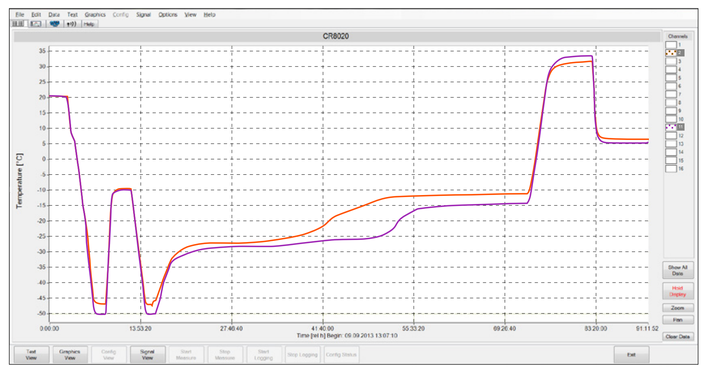

Fig 7 Overlay of overall hot and overall cold spot across entire run.

Conclusion

A lyophilization process should be additionally guided by single-vial measurements at extreme HCS positions, where T_b serves as Critical Process Parameter (CPP) within modern process validation. In spite of being invasive, the high selectivity of TEMPRIS® reveals meaningful PQ data, as opposed to employing standard “batch techniques” only. TEMPRIS® allows placement anywhere on the shelf and across all scales; instrumentation is compatible with automatic loading systems, sensors can be sterilized and handled aseptically.

References

[1] Rambhatla S, Tchessalov S, and Pikal MJ. Heat and mass transfer scale-up issues during freeze-drying, III: Control and characterization of dryer differences via operational qualification tests. *AAPS Pharm Sci Tech. 2006; 7(2): E1-E10.*

[2] Hibler S, Wagner C, and Gieseler H. Vial freeze-drying, Part 1: New insights into heat transfer characteristics of tubing and molded vials. *J Pharm Sci 2011; 101(3): 1189-1201.*