Modern Lyo Cycle Optimization

"Hot" and "Cold" Spot Determination by Wireless Real-Time Temperature Measurement as Process Analytical Technology (PAT) Tool

Dr. Andrea Weiland-Waibel • Explicat Pharma GmbH, Hohenbrunn

Korrespondenz: Dr. Andrea Weiland-Waibel, Explicat Pharma GmbH, Georg-Knorr-Str. 4, 85662 Hohenbrunn;
e-mail: a.weiland@explicat.com

Abstract

Traditional lyo cycle development leads to a predetermined program that usually is subject of process validation. As a consequence this cycle needs to be applied for the fabrication of the product under all circumstances. If for any reasons e.g. only a part of a total batch size can be manufactured, no adaptations are possible, i.e. the shortening of the cycle is not allowed due to regulatory compliance.
This article demonstrates a new conceptual design to the development and modern validation of lyo cycles applying process control by determination of Product Temperature (T_P) in critical positions ("hot" and "cold" spots) which allows for adaptation of the lyo cycle. Furthermore usage of these positions in development scales during scale-up and routine production is shown.

Key Words

- Lyo cycle
- Critical positions
- Process control
- Product temperature
- Critical product parameter

1. Introduction

Modern development following ICH Q8, Q9 and Q10 in the context of freeze drying is based on the objective to design a lyophilization cycle applying a systematic and scientific approach instead of trial and error.

As described by Dr. Henning Gieseler [1] the coupling link between formulation and process is the physicochemical behaviour of the formulation resulting in a maximum allowable Product Temperature T_P during drying.

Product Temperature T_P is of utmost importance in Freeze Drying as

- T_P is a critical product parameter which determines important product quality attributes such as physical appearance, residual moisture, storage stability, reconstitution time, etc.
- T_P cannot be controlled directly, but is influenced by shelf temperature, chamber pressure, product resistance and various other factors such as super cooling, environment, etc.
- T_P must not exceed the critical formulation collapse temperature T_C or eutectic temperature T_E during primary drying to avoid collapse and meltback.

In this article the basis for a new approach to the development of modern lyo cycles is shown. Product Temperature determination by thermocouples and by wireless temperature measurement in the critical positions ("hot" and "cold" spots) of the freeze dryer is applied. T_P as determined by process analytical technology devices may be used as a process control (feedback system) to run the lyo cycle which ultimately allows for flexibility in the adaptation of lyo cycles that are within the regulatory space.

2. Performance Qualification as Basis and First Step in the Design of Modern Lyo Cycles

2.1 Dynamic Performance Qualification (PQ)

Performance Qualification (PQ) plays an important role in modern approaches towards process validation from as early as lab scale devel-

Autor

Dr. Andrea Weiland-Waibel

Dr. Andrea Weiland-Waibel is Managing Director, QP and founder of Explicat® Pharma GmbH and expert in CMC project management. She is a frequent lecturer and holds several patents in pharmaceutical development, GMP-related subjects and lyo formulation and previously was Head of Pharmaceutical Technology at Pfizer.
Explicat Pharma has been assigned several projects in relation to lyo products applying the modern process validation approach, including lyo cycle Robustness Testings.

Fig. 1: Vial with wireless temperature sensor (Source of all figures and tables: iQ-mobil solutions GmbH).

Fig. 2: Interrogation Unit (IRU-2).

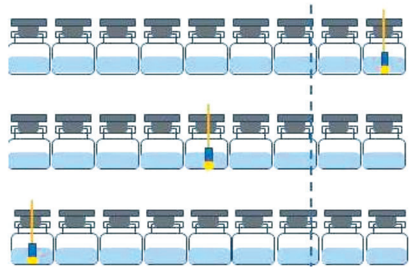

Fig. 3: Sensor positions.

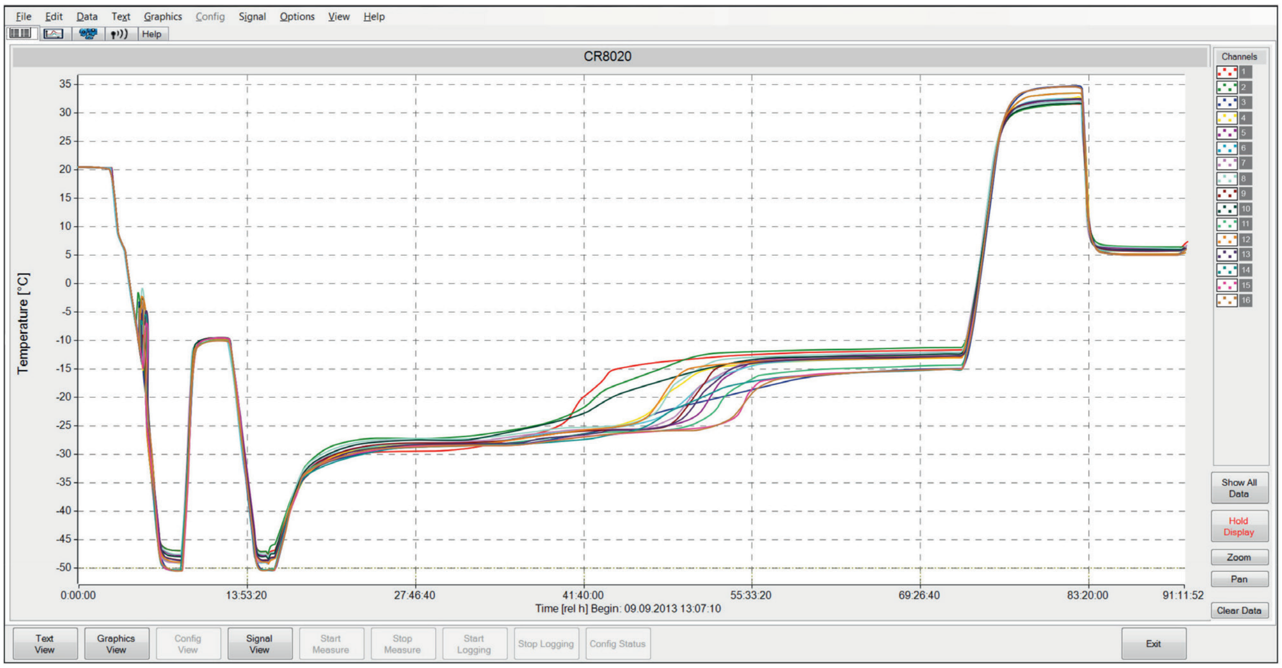

Fig. 4: 16-sensor overlay plot representing temperature measurements from total instrumentation.

opment up to routine manufacture, particularly in aseptic lyophilization technology. PAT (Process Analytical Technology) 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 of a performance qualification shows relevant temperature differences between single lyo vial position (centre vs. edge) and across different shelves (depending on distance to condenser) – within a commercial scale lyophilizer. A standard lyo cycle had been instrumented with a real-time PAT tool: Wireless *Tem*perature *R*emote *I*nterrogation *S*ystem (TEMPRIS®). The definition of "hot" and "cold" spots (HCS) [2,3] during Performance Qualification 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 as demonstrated during scale up and transfer.

2.2 Materials & Methods

Experiments were conducted at a pharmaceutical manufacturer´s site on a production scale freeze dryer (8,78 m^2, 9+1 shelves) running a textbook lyo cycle, fully loaded with 2R vials, each filled with 1 ml WFI (Water For Injection). Analytics were conducted using 16 TEMPRIS size S sensors (Fig. 1), one Interrogation Unit (Fig. 2) and TEMPRIS Data Server (software). Sensors were placed in the middle of vial and vials at varying centre or edge positions on shelves Nos. 2, 4, 5 and 6 top to bottom (Fig. 3).

2.3 Results

Product temperature curves at the bottom of vials (T_{Pb}) from the 16 sensor positions were plotted and compared (Fig. 4). The overall critical "cold" spot is positioned at the bottom of the freeze dryer with a minimum distance to the condenser. The overall critical "hot" spot is located at the edge on the top shelf of the freeze dryer with a maximum distance to the condenser. Temperature differences ranged from 3 °C to 4 °C (freezing/annealing, Fig. 5) and 3 °C to 8 °C

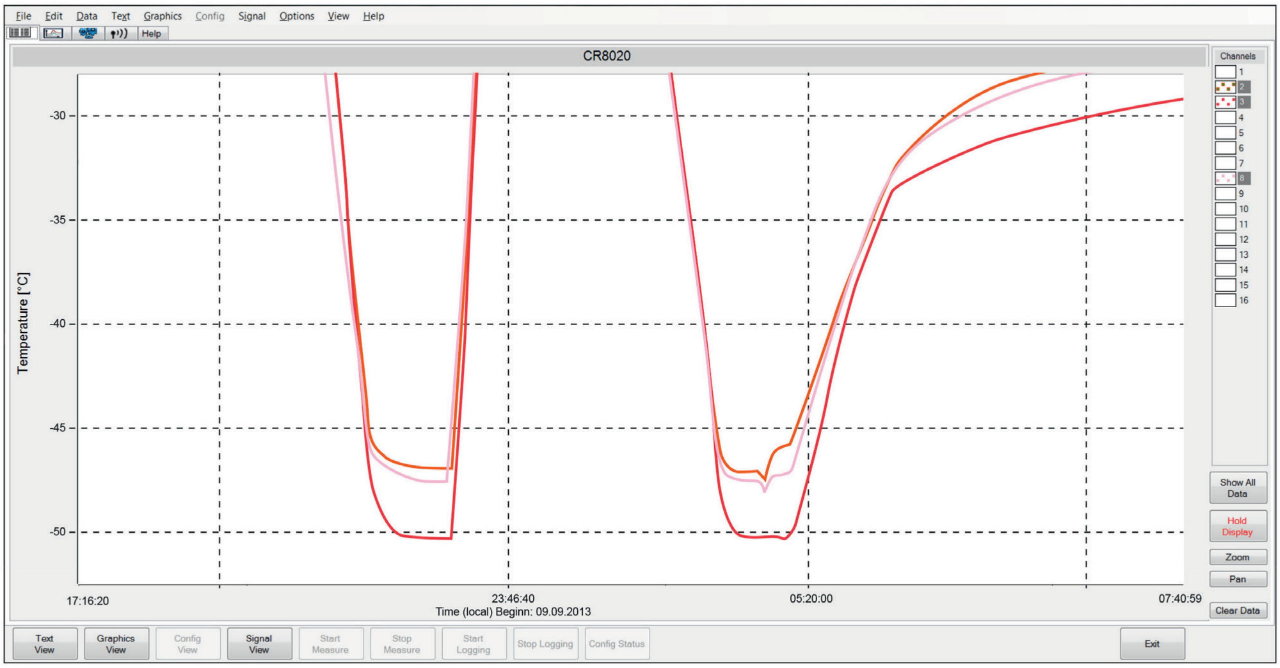

Fig. 5: Overlay of overall "hot" spot (shelf x, position y) and overall "cold" spot (shelf z, position z) during freezing/annealing.

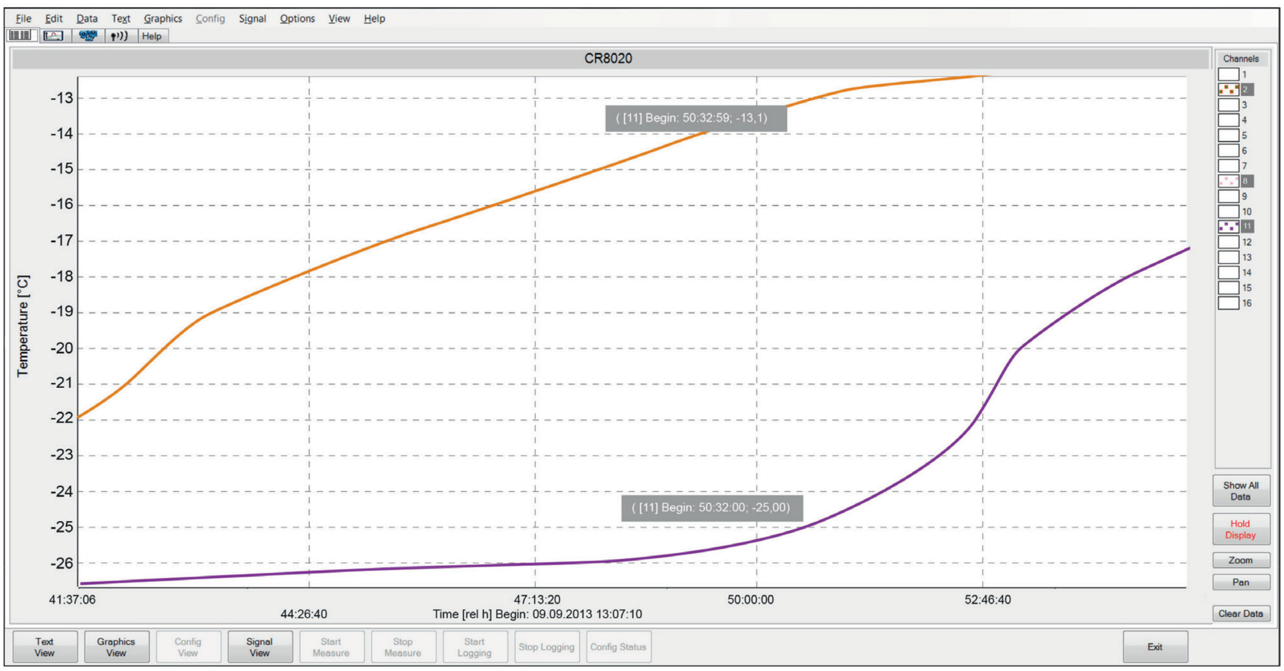

Fig. 6: Overlay of overall "hot" spot (shelf x, position y) and overall "cold" spot (shelf z, position z) during drying.

(primary drying, Fig. 6) between overall "hot" spot at maximum distance to condenser and overall "cold" spot.

2.4 Discussion

As could be shown by the presented data (Fig. 7) of a performance qualification study the differences in heat transfer in edge and central positions are significant as Product Temperature at the bottom T_{Pb} varies significantly between the positions. To locate the extreme positions in a given freeze dryer is the first step to apply the T_P determination in these positions to optimize the lyo cycle and use T_P for scale up and transfer.

3. T_P Determination for Lyo Cycle Development in Lab Scale

3.1 Process Robustness Testing

Based on a formulation developed process robustness was assessed. Process Robustness is defined as "ability of a process to tolerate variability

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

of materials and changes to the process and equipment without negative impact on quality"[1]. The lyo cycle Robustness Testings were performed addressing critical process parameters (CPsP) such as Pressure (P), water vapour concentration (c) and gas flow velocity (u) which yield in critical product parameters (CPtP) such as T_P (Product Temperature), Product Resistance (Rp, area normalized product resistance), Residual Moisture (RM, %). As acceptance criteria for the testings as critical quality attribute (cQA) the physical appearance was applied as assessed by 100 % visual inspection. The lyo product must have correct cake volume and appearance (Fig. 10). Not acceptable cakes are "meltback" (Fig. 8), "collapse" or "shrinkage" (Fig. 9).

Robustness Testings carried out to find out the critical process parameters (CPtP) and relating T_P in the laboratory were done in relation to the following predefined conditions: Vials chosen for commercial scale, need to apply trays for loading and unloading of the production freeze dryer and to allow for an estimated prediction of lyo cycle time (i.e. not more than 70h lyo cycle for commercial viability).

3.2 Materials & Methods of Process Robustness Testings

Lyostar II SP Scientific – 0.43 m^2 shelf area; 3 shelves, condenser temperature (-85 °C); equipped with MTM (Manometric Temperature Measurement) for pressure rise measurements and SMART software;

Thermocouples: calibrated T-Type Copper / Constantan from Omega (Fig. 11);

TEMPRIS wireless temperature system;

Vials: 26.5 mm diameter, clear & amber glass ex Schott, hydrolytic class I;

Stoppers: 20 mm bromobutyl stoppers, igloo.

An optimized cycle based on previous experience during development phase was used as basis for cycle variations. A total of 11 robustness runs (Table 1) were done with different shelf temperatures.

3.3 Results of Lyo Robustness Testings

The crystalline matrix of the formulation (see Fig. 13) allows drying at T_{pb} >Tg' (glass transition – temperature of the maximally freeze-concentrated solute of a glass which still contains a specific fraction of unfrozen water) [1] of the formulation. Within the Robustness Testings the variation of the shelf temperature T_s was tested. The annealing step needs to be sufficiently long to obtain a uniform crystalline matrix. Usage of trays for loading has a significant impact – the annealing time needs to be increased (Fig. 12).

The testings led to a final optimized lyo cycle in the lab as basis for the transfer into production scale and was discussed with the experts of production site.

Fig. 8: Not acceptable meltback cake.

Fig. 9: Collapse/shrinkage cake.

Fig. 10: Acceptable elegant cake.

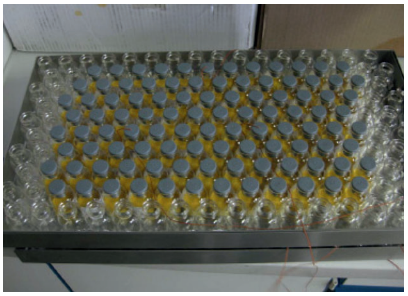

Fig. 11: Typical loading pattern (clear glass vials instrumented with thermocouples).

3.4 Use of TEMPRIS for Scale up/Production

To support the transfer TEMPRIS was applied. In opposition to thermocouples this is a wireless battery free real time temperature measurement system. Its sensors can be sterilized and they can be placed and positioned aseptically within ALUS and Isolators in the critical positions of the freeze dryers.

For the transfer, the final runs of lyo cycle development were performed with this software to allow for a direct comparison of the runs in the lab with the production (Fig. 14).

4. Process Qualification Run in Production Scale

4.1 Scale-up description

A direct upscale from approximately 430 vials (Lyostar II, 3 shelves, see Fig. 14) to approximately 45 000 vials on 18 shelves, 30 m^2 was performed (Fig. 15).

The cycle used in production was agreed mutually with the contract manufacturing organization specialists.

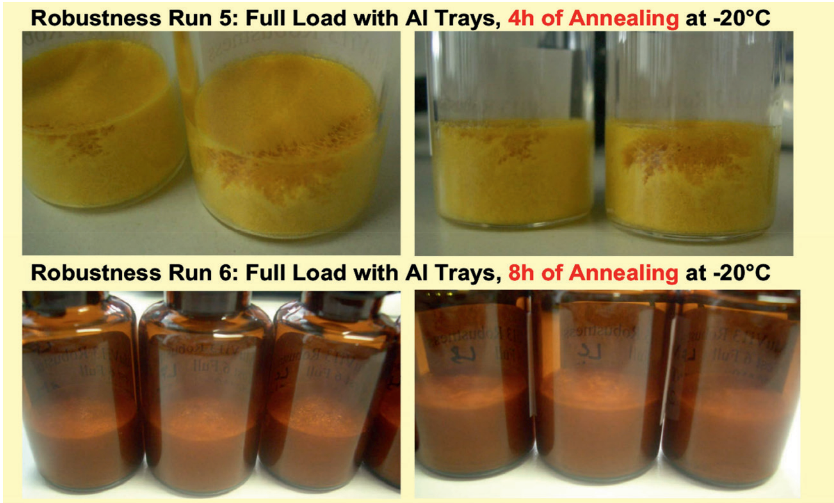

Fig. 12: Consequences of alu tray use in relation to the annealing step.

Table 1

Lyo Cycle Robustness Testing – Example of Cycles

Run Name	$t_{1° \text{ drying}}$ [h] (by Pirani) *(total cycle time)*	T_{shelf} [°C] 1° drying	Pressure [mTorr] CPsP	Ice Thickness [cm]	$T_{p\text{-}bottom}$ CPtP	Cake Appearance CQA
Opt. Run (no tray)*	40 *(total 56)*	-10 (4h anneal)	110	1.32	-26	Acceptable
Opt. Run*	52 *(total 67)*	-10 (4h anneal)	110	1.32	-26	Acceptable
Robustness 5'	34 *(total 70)*	+5 (4h anneal)	110	1.32	-26	Holes at Cake Top
Robustness 6'	41 *(total 70)*	+5 (8h anneal)	110	1.32 Amber vials	-24.5	Acceptable, soft cake
Lyocycle Robustness 11'	33.3 *(total 60)*	+15 (8h anneal)	110	1.32	-26	Acceptable, elegant cake

4.2 Materials & Methods

Commercial manufacturing site 18 shelves freeze dryer with 30 m^2;

TEMPRIS system: equipped with 16 sensors. Installation see Fig. 15 and Fig. 16.

Same formulation and vials as in lyo cycle development.

4.3 Results

16 sensors showing the T_P variability: Sensors were located at different positions ("hot" and "cold" spots – as obtained by previous performance qualification) shelves 1, 3, 5, 6, 9, 12, 15, 18, centre and front door (edge) positions.

As can be seen in figure (Fig. 17) the approximate maximum difference in the freezing step is around 5 °C and in primary drying slightly more than 20 °C.

4.4 Discussion

TEMPRIS feeding back the T_P value of the critical positions into the scada system (supervisory control and data acquisition) controls the process by indicating the end of the respective process step. By this the T_P over time as a critical product parameter in the critical positions is the leading parameter of the cycle.

To fulfil regulatory acceptance the software has to be already applied during the development and process qualification of a lyo cycle. By the lyo cycle robustness studies and process qualification in production scale a process design space can be justified and presented in the relevant regulatory section 3.2.P.3 manufacture (quality section of the common technical document).

On the basis of an accepted process space this process space may be used for adaptations in routine manufacturing, e.g. in case of a partial load to speed up the freeze drying period. As a T_P over time regarding critical temperatures is kept constant the product quality is not affected.

5. Conclusion

The new approach is that the lyo cycle is process controlled by running the lyo cycle through T_P in critical positions. This means the initial freezing step being finished when the vials positioned at the critical "hot" spot positions are reaching the acceptance T_P for the freezing step and the primary drying is at its end by complete sublimation of the ice also of the vials positioned at the critical "cold" spot positions by

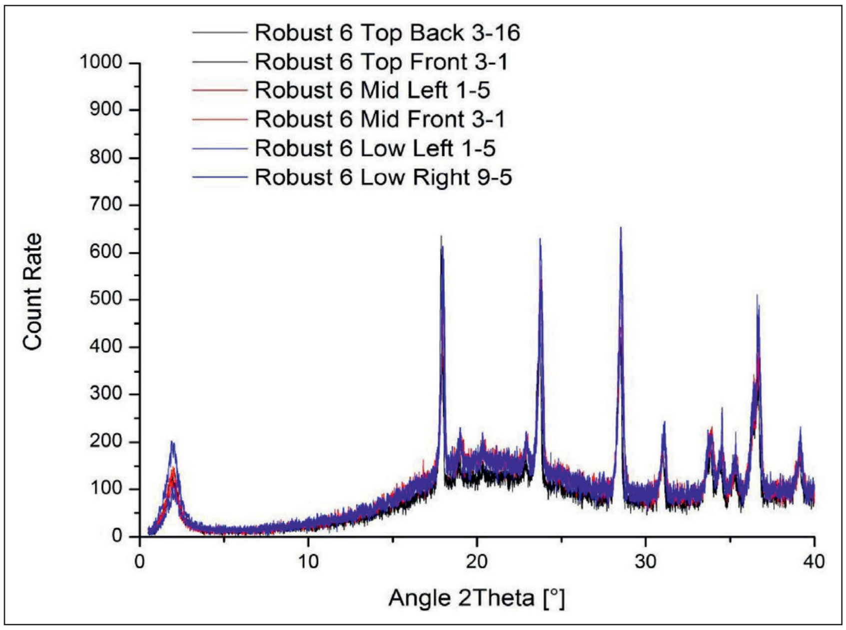

Fig. 13: XRPD (Xray Powder Diffraction) Analysis. The correct crystalline matrix and no significant difference of the positions is seen.

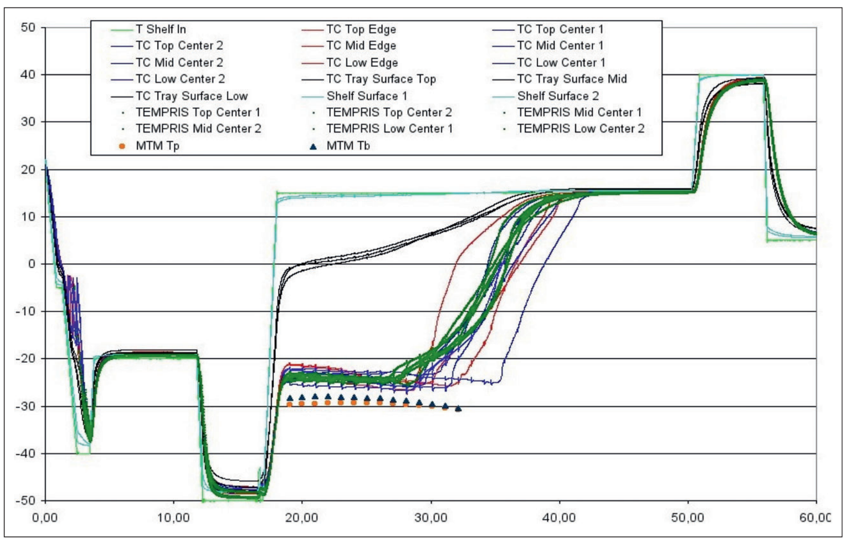

Fig. 14: Final optimized lab cycle run with TEMPRIS – Lyo Cycle Robustness Run # 11.

Fig. 15: TEMPRIS installation from outside through an unused flange.

Fig. 16: TEMPRIS antenna installation in the freeze dryer.

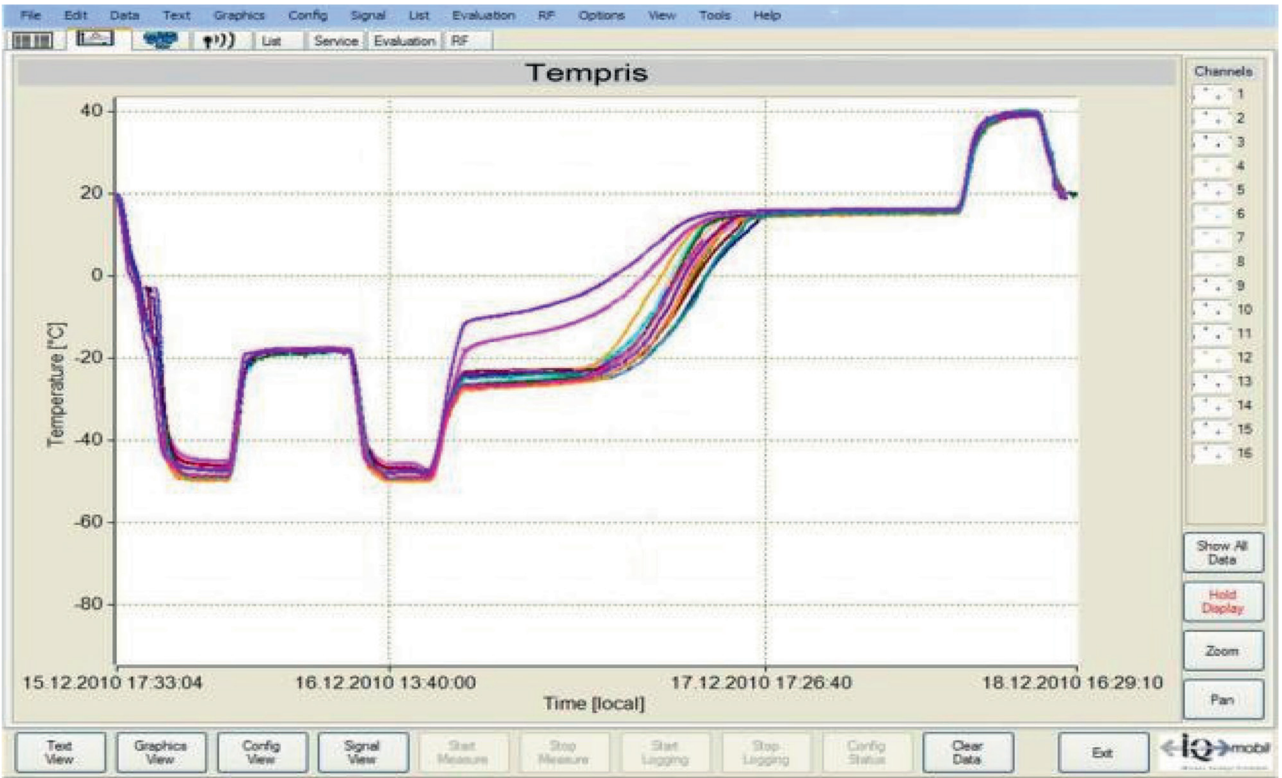

Fig. 17: Cycle from Fig. 14 adapted for production scale (Process Qualification Run).

reaching the acceptance T_P allows for a real time process controlled cycle adaptable among all scales.

T_P as the critical product parameter that is directly linked to product quality attributes should be used over the lyo cycle as an inline feedback process control in modern lyo cycle design. T_P acceptance criteria for the freezing step, primary and secondary drying defined for the extreme positions can be controlled and by this the product quality can be predicted and kept across all scales of lyophilization. This article showed the first step to this context, which is to determine the extreme positions in a given freeze dryer as a dynamic performance qualification study. As a second step the use within scale-up and modern process validation was demonstrated.

References

[1] Gieseler, H. in Encyclopedia of Pharmaceutical Science and Technology, Fourth Edition, Quality by design (QBD) in Freeze Drying (2013)

[2] 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.

[3] 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.

Redaktion: Chefredakteur: Claudius Arndt, Redakteur: Jens Renke. Verlag: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Tel.: +49 (0) 81 91-9 85 78 12, Fax: +49 (0) 81 91-9 85 78 19. e-mail: redaktion-tp@ecv.de. http://www.ecv.de.
Herstellung: Reemers Publishing Services GmbH / Holzmann Druck GmbH & Co. KG. Alle Rechte vorbehalten.