

Table 8 Summary describing various steps of form/fill and inspection along with suitable analytical tools to characterize the product quality

S. No.	Steps	Analytical tools	Characterize
1	Freezing	DSC, FDMS, XrD, optical tomography, etc.	T_g , T_c , nucleation temperature, crystallization, etc.
2	Primary drying	Thermocouple, Pirani gauge, MTM, mass spectrometry, modeling, TDLAS, and other PAT tools, etc.	Sublimation rate, product temperature, cycle time, vapor flow resistance, heat transfer coefficient, etc.
3	Secondary drying	DSC, DVS, TDLAS and other PAT tools, etc	Moisture, product temperature, drying time, etc.
4	Post-drying	Visual inspection, karl fisher, DSC, MicroCT Imaging, XrD, SEM, BET, etc.	Cake appearance, moisture, T_g , reconstitution time, crystallinity, specific surface area, etc.

DSC differential Scanning Calorimetry, *FDMS* freeze-drying microscopy, *XrD* X-ray diffraction, *TDLAS* tunable diode laser absorption microscopy, *DVS* dynamic vapor sorption, *SEM* scanning electron microscopy, *BET* brauner-emmett-teller

Summary

In contrast to other modalities, vaccine drug product development is more challenging and requires a thorough and systematic approach to achieve success. Lyophilization adds to the inherent complexity associated with vaccine development. Additional freeze-drying steps involved in formulation, filling, and inspection of dried products (Table 8) adds additional failure mode in the system. Thus, a GTPP is recommended to be discussed and agreed upon by the team early so that a quality product and efficient processes are established with clean line of sight to commercialization. To ensure the clean line of sight to the commercial process, the early development scientists and the process engineers should be communicating early and often at the respective manufacturing sites to properly align product development. Risk associated (worse case recommended) with scale-up and unit operations known to be critical to the product must be determined on a case-by-case basis and corresponding mitigation strategies should be documented.

Unlike other modalities, in general “the product is the process” for vaccines and minor changes to the process may result in extensive analytical comparability plans to be established, and in certain instances, additional comparability clinical trials to show the changes did not impact product efficacy when analytical comparability cannot be established.

Preformulation, early- and late-stage formulation development and product optimization efforts must all funnel into the desired GTPP, and any technical or strategic failure modes should be identified, documented, and communicated. During this effort, the CPPs must be identified and their impact on CQAs must be documented. Proper documentation and communication between early development scientists and the process engineers will help ensure that a robust manufacturing process has been established (form/fill, inspection, release, and distribution) and the vaccine reaches the targeted population.