temperature determined using LT-FDM. Later sections of this chapter provide additional information on OCT-FDM and its application to lyophilization.

Once the target product temperature has been determined, lyophilization cycle conditions are estimated using fundamentals of heat and mass transfer [13, 14]. Central to the application of heat and mass transfer principles are estimation of K_v (heat transfer coefficient) of the vials, $\hat{R}_p$ (area-normalized mass transfer resistance) of the product and lyophilizer equipment capability to support the mass transfer rate. With the advancements in process analytical technologies (PAT), the task to estimate these parameters has been simplified. PAT tools such as manometric temperature measurement (MTM) and tunable diode laser absorption spectroscopy (TDLAS) have been used and demonstrated to be quite useful in estimation of the parameters critical to development of freeze-drying processes [7, 15–19]. Use of MTM requires the presence of a rapidly closing/opening isolation valve between the chamber and condenser [19]. During primary drying, this valve is closed for a 1-min interval and the pressure rise is recorded as a function of time. The MTM equation is fitted to the pressure rise data to enable the determination of parameters such as product temperature at the sublimation interface (T_p) and $\hat{R}_p$. TDLAS is a noncontact spectroscopic technique which, in conjunction with fluid dynamics modeling of the lyophilizer gas flow in the duct connecting the product chamber and condenser during the lyophilization process, can be used to measure the water vapor concentration and gas flow velocity in the spool connecting the product chamber and condenser. These measurements are combined with knowledge of the spool cross-sectional area to calculate the mass flow rate (g/s) of water vapor exiting the product chamber. The mass flow rate is combined with a heat and mass transfer model of vial freeze-drying to calculate the important freeze-drying parameters, such as K_v, $\hat{R}_p$ and T_p. The advantage of TDLAS over MTM is that it does not require the isolation valve between the chamber and the condenser, provides continuous measurements, does not result in a rise in product temperature associated with interruptions in freeze-drying, and can be used to provide accurate determination of parameters throughout both primary and secondary drying. However, a vapor tube of sufficient dimensions is a prerequisite to apply the TDLAS technique to any lyophilizer. Nevertheless, the TDLAS sensor has been shown to be applicable to estimation of K_v [17], $\hat{R}_p$ [20], product temperature at the vial bottom and sublimation interface [17], residual moisture content [18], and choked flow limits of a lyophilizer [7, 15, 21]. The principle of TDLAS and its application in lyophilization are described later in this chapter.

Other than estimation of choked flow limits (the maximum mass flow of water vapor supported by a vapor tube), equipment capability is also dependent on the condenser design and capacity. Un-optimized condenser design leads to condenser overload and a rise in condenser temperature during primary drying which, if it remains uncontrolled, would cause a loss in pressure control in the chamber. Condenser overload can be caused by loading the lyophilizer with water in excess of the condenser capacity. Other factors to consider when reviewing the condenser design are: vapor tube position inside the condenser, location of vacuum pump outlet, and condenser coil design. These factors affect vapor dynamics and the ice distribution pattern [22]. While the condenser coils surface area may be sufficient to condense