INTRODUCTION
The most important process parameter in freeze-drying is the product temperature at the sublimation interface ($T_p$) which can be controlled indirectly through variation of shelf temperature ($T_s$) and chamber pressure. $T_p$ must be maintained below a predetermined formulation-dependent critical temperature throughout primary drying to avoid damage to the product [1]. Traditional temperature monitoring employs invasive methods like thermocouples and RTDs which are placed in a few selected vials and are not representative for the entire batch. Due to their positioning, they tend to dry at other product temperatures and faster than average vials. In this study, Tunable Diode Laser Absorption Spectroscopy (TDLAS), a novel in-line spectroscopic monitoring technique, was employed to measure the mass flow rate from the product to the condenser. The accuracy of TDLAS mass flow data and its use in the determination of vial heat transfer coefficients ($K_v$) have been shown previously [2, 3]. For this project, mass flow rate measurements in combination with the previously determined $K_v$ values were used to calculate average batch product temperature.

MATERIALS & METHODS

Lab Scale Freeze Dryer and TDLAS Sensor Setup
Experiments were performed on a laboratory freeze dryer, Lyostar II, equipped with Manometric Temperature Measurement (MTM) technology and the SMART cycle optimization algorithm (PTS Systems, NY). A LyoFlux spectroscopic mass flow sensor (Physical Sciences Inc.) was installed in the duct between freeze-dryer chamber and condenser (Fig. 1). The TDLAS sensor optically measured water vapor concentrations and gas flow velocities in the duct, which were used to calculate the mass flow of water vapor exiting the chamber. The sensor then quantified the sublimation rate throughout the run. Instantaneous mass flux measurements were integrated to determine the amount of water removed and the status of the run.

Product Temperature Determination by TDLAS
Product temperature is a balance between heat input from the shelf and heat removal through ice sublimation. During the steady state of primary drying heat transfer is in equilibrium and can be described using equation 1. Since average mass flux is continuously measured by the TDLAS sensor, the batch average product temperature can be calculated using equation 2. While the wall area is constant and shelf temperature is provided from run data provided by the freeze dryer, it is necessary to determine a vial heat transfer coefficient ($K_v$) that is representative for the batch as a whole. $K_v$ values were determined for 20 mL Wheaton vials during sublimation tests at various chamber pressures using equation 3 [4]. Mass flow over time was determined by weighing and calculating mass of loss for each vial. Vial heat transfer coefficients were calculated from gravimetric data for each vial in the array to provide a measure of heterogeneity between edge and center vials and as a reference for TDLAS results. A batch average $K_v$ was calculated from TDLAS data over the entire run to enable comparison to gravimetric results. Additionally, TDLAS data collected at a single point during primary drying was used to obtain more representative heat transfer coefficients during steady state conditions. The $K_v$ results were used to calculate batch average product temperatures during eight different freeze drying runs. The type of vial and their arrangement of the shelf were identical to the sublimation tests. Sucrose, mannitol and glucose were used. Freeze-drying cycles were mostly designed using the Lyostar II SMART mode and include several temperatures changes during primary drying. The calculated temperatures were compared to thermocouple data of edge and center vials.

RESULTS & DISCUSSION
Heat transfer coefficient determination
$K_v$ results were obtained both from gravimetric measurements and from TDLAS data. TDLAS data showed good reproducibility between runs. A representative $K_v$ distribution calculated from gravimetric measurements at 200 mTorr chamber pressure is shown in Fig. 2. Heat transfer coefficients for vials in similar positions on the shelf (i.e. edge or center) were comparable. However, the calculated $K_v$ for edge vials was approximately 20% higher than that of center vials. The results of all sublimation tests between 65 and 500 mTorr were delayed in Fig. 3. $K_v$ from gravimetric measurements were compared with TDLAS data over the entire run were comparable at low and intermediate chamber pressures. Results obtained by one-point measurements are slightly higher due to exclusion of ramping periods and non-steady state conditions. All curves were fitted to a model function [3] to delineate the pressure-dependent and pressure-independent contributions to heat transfer. Employing the fitting equation, it is possible to calculate a heat transfer coefficient for this vial and array type at any chamber pressure between 65 and 500 mTorr. The steady state one point $K_v$ determination using TDLAS was found to be more representative for steady state conditions and the batch average, and was used for temperature calculation.

Heat transfer coefficient determination
Heat transfer coefficients were calculated every minute for all product freeze-drying runs using the average steady-state $K_v$ at the relevant chamber pressure. Shelf temperatures were taken from freeze-dryer data, and mass flux measurements were used as recorded by TDLAS. The temperature profiles of three product runs with 5% sucrose, 7.1% and 7.5% mannitol and 10% (w/w) glycine are shown in Fig. 4-7. Independent of the physical state of the product, i.e. amorphous or crystalline, the steady state heat transfer model appeared to accurately describe the process (TDLAS conditions). Despite the frequent shelf temperature changes introduced by the SMART cycle design, calculated average product temperatures were within 1-2°C of "center vial" steady state thermocouple data after steady state conditions were established. At the start of primary drying and during ramping periods, there are discrepancies in product temperature which is due to non-steady state process conditions. As expected, edge "vial" temperatures were slightly higher than corresponding "center vial" data and also completed primary drying earlier. The calculated product temperature showed little bias towards center or edge vials, the trend was mostly between center and edge vials. During secondary drying, it is not possible to apply the steady state model and product temperature calculations cannot be performed.

REFERENCES