INTRODUCTION
Effective freeze drying process development and control requires knowledge of the vial heat transfer coefficient (Kv). Kv is typically evaluated using pure water sublimation tests at varying product chamber pressures. Kv varies between different types of vials and may even change from the same vial size provided by different suppliers [1]. The degree of heat transfer to the product is influenced by the position of the vials on the shelf. Vials located at the outer edge of the shelf ("edge vials") have been reported to have a different drying behavior compared to vials located in the center of the shelf [2]. Three different mechanisms contribute to the total vial heat transfer coefficient: direct conduction from the shelf to the vial bottom (Kb), radiative heat transfer (Kb), and gas conduction (Kg). While the first two are independent of pressure, Kg increases with chamber pressure. After measuring mass flux and calculating Kv at different pressures, the contributions from Kb, Kg, and Kv can be individually determined [1]. The goal of this study was to measure the vial heat transfer coefficient within a laboratory freeze dryer using two different analytical measurement techniques to evaluate its position dependent. Tunable Diode Laser Absorption Spectroscopy (TDLAS) was used to measure the batch sublimation rate and to provide an average determination of Kv which was compared to gravimetric determinations. TDLAS is a new Process Analytical Technology (PAT) tool that measures the water vapor concentration and gas flow velocity in the duct connecting the dryer product chamber and the condenser.

MATERIALS & METHODS
Laboratory Scale Freeze Dryer and TDLAS Sensor Setup:
A laboratory scale freeze dryer (FTS Lyostar II) was equipped with a LyoFlux™ (Physical Sciences Inc., USA) Tunable Diode Laser Absorption Spectroscopy based mass flow monitor [3]. A fiber optic collimator transmitter and photodiode receiver were mounted to the freeze dryer duct connecting the product chamber and the condenser (Fig 1). The near infrared diode laser beam was launched across the duct at a 45° angle to the dryer with each vial filled with 3 mL of ultrafiltered water. A row of empty “dummy vials” was placed around the water filled vials to shield the product vials from radiative effects. Gravimetric Analysis:

RESULTS & DI SCUSSION
Gravimetric Analysis:

- Kv values calculated using gravimetric results show very good reproducibility.
- As expected, Kv substantially increases with elevated chamber pressure (Kv at 65 mTorr, 3.5 cal/sec/cm² compared to 10 mTorr, 0.36 cal/sec/cm² (Table 1)).
- The increase in Kv is related to an elevated contribution of Kg.
- Calculation of individual contributions (%) show a change in ratio of pressure dependent heat transfer (Kv and Kg) to pressure dependent heat transfer (gas conduction) from 43.7% for 65 mTorr to 15.2% for 500 mTorr (Table 1).
- Drawback of the gravimetric method is that calculations of dm/dt include the initial shelf temperature ramping phase (non-steady state conditions). In addition, temperature differences are averaged over the total drying time which may impact the Kv prediction. Thus, the Kv calculation tends to underpredict the effective heat transfer.

Impact of Vial Position on Calculated Vial Heat Transfer Values:

- Calculation of Kv was performed for each vial by using weighted average temperature differences over the entire run (72 “center” and 40 “edge vials”).
- Kv calculations for “center” vials deviate during a single experiment up to 15% from Kv predictions for “edge vials”. This, in turn, shows that a Kv determined only for a few “center” vials in a batch is not a representative measure for an overall Kv value.
- Designing the use of Alradiative shields for dummy vials, the outermost row of vials is still affected by elevated radiation from the chamber door and/or chamber wall.

TDLAS Mass Flux Calculated Over Entire Run (O.E.R.):

- Calculations were performed using the total primary drying time and weighted averaged temperature differences to ensure direct comparison to gravimetric results.
- Determined K’s are in very good agreement to gravimetric results at lower pressures (65 to 200 mTorr) typically used for product freeze drying.
- At 500 mTorr there is a clear bias between the gravimetric and TDLAS based Kd determinations. This may be due to the low gas flow velocities (< 4 m/s) and the reduced accuracy of the TDLAS dm/dt determinations under these conditions. Future experiments may be performed with a fully loaded freeze dryer to increase the gas flow velocity and compare the TDLAS based measurement to a gravimetric determination.

TDLAS Mass Flux Calculation in Steady State (“One Point Measure”, O.P.M.):

- Kv was calculated at a specific time in the steady state portion during primary drying, i.e. using temperature and TDLAS mass flux measurements for that specific time to evaluate Kv. This procedure results in deviations in steady state conditions due to the ambiguity introduced by ramping periods or averaged temperatures over the entire run.
- Kv values obtained are very similar to results of the other techniques at low and intermediate pressures, with significant difference only at high pressures (Fig. 6).

CONCLUSIONS
- Gravimetric and TDLAS based Kv determinations were in good agreement for chamber pressures between 65 and 500 mTorr, with TDLAS showing an increase in Kv at higher pressures.
- Product temperature and Kv values showed a clear dependence on vial position on a shelf. Edge vials typically ran at higher temperatures resulting in larger Kv values.
- instantaneous and integrated TDLAS based dm/dt determinations resulted in similar Kv determinations. Calculations using the instantaneous mass flow measurements resulted in higher Km values due to the exclusion of the ramping phase.
- The combination of TDLAS based dm/dt measurements, the mass and heat transfer model and careful determinations of Kv may enable continuous, non-intrusive, real-time determinations of product temperature using the TDLAS sensor technology.

REFERENCES