

## **Factors affecting accuracy of carbon monoxide diffusing capacity devices used in clinical trials for inhaled insulin**

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## Abstract

**Introduction:** Measurements of carbon monoxide diffusing capacity ( $DL_{CO}$ ) are a primary safety outcome for MannKind Corporation's clinical trials of inhaled insulin powder (Technosphere® Insulin). Accuracy of  $DL_{CO}$  devices is difficult to assess even with biological controls.

**Methods:** A protocol to control for accuracy of the measurements required use of a simulator for  $DL_{CO}$  (Hans Rudolph, Kansas City, MO) that mimics patient tests and creates exact known  $DL_{CO}$  values. Laboratories measuring  $DL_{CO}$  for clinical studies tested their device every 8 weeks. At each of 3 inspired volumes and 2 simulated gas levels, 4 to 5 sequential simulated  $DL_{CO}$  tests were performed. Data recorded from the  $DL_{CO}$  device were compared to the "target" values generated by the simulator. Devices were considered in control if within  $\pm 10\%$  of target (% Difference). We examined six factors that might have been associated with the degree of error and failing to be within control: 1) Device Type, 2) Inspired Volume (VI), 3) Alveolar Volume (VA), 4) System Dead Space volume, 5) Tracer gas type, and 6) Temperature.

**Results:** 16,369  $DL_{CO}$  simulations were performed. Systems outside of control limits were detected on 948 (5.8%) tests. Significant differences were noted in inter-device average % Difference (% Diff) with ranges from  $-5.0$  to  $+2.1\%$ ,  $P < 0.01$ . Increasing VI and VA were associated with larger  $DL_{CO}$  differences,  $P < 0.01$ . System dead space volume showed no consistent influence on  $DL_{CO}$  differences. Tracer gas type showed a small, but inconsequential difference between gases. Temperature showed a distinctive pattern with larger  $DL_{CO}$  errors for device temperatures less than  $21^\circ\text{C}$  and greater than  $27^\circ\text{C}$ ,  $P < 0.01$ .

**Conclusions:** Testing  $DL_{CO}$  instruments used in clinical trials is necessary to ensure test accuracy due to the many factors that may alter outcomes.

## Methods

Inhaled insulin pulmonary safety is assessed with pulmonary function tests of Forced Vital Capacity (FVC), Forced Expiratory Volume in 1-second ( $FEV_1$ ), Carbon Monoxide Diffusing Capacity ( $DL_{CO}$ ), and Total Lung Capacity (TLC). Global clinical trials are being conducted across multiple PFT laboratories using a wide variety of PFT equipment. Controlling quality for the  $DL_{CO}$  measurements was implemented using a  $DL_{CO}$  simulator (Hans Rudolph, Kansas City, MO) (see Figure 1). Each laboratory was required to first demonstrate that their equipment met the study protocol accuracy requirement which required that  $DL_{CO}$ , VA, and IVC be within 10% of target values. Each PFL completed a minimum of 4 trials at 3L, 4L, and 5L using both a mid- and high-range gas. Subsequent studies were performed at approximately 8-week intervals. Equipment deadspace, filter deadspace, temperature, humidity, barometric pressure, test gas accuracy, sample volumes, washout volumes, actual BHT, calculation method for BHT, calibration, and other QC measures were confirmed and documented to be acceptable prior to testing.



Figure 1:  $DL_{CO}$  simulator.



Figure 2: EasyLab QC™ testing information screen shot.

## Results

16,369  $DL_{CO}$  simulations were performed. Systems outside of control limits were detected on 948 (5.8%) tests and corrective actions taken to bring the systems into control (see Figure 3). Average % Diff ranged from  $-5.0$  to  $+2.1\%$  between devices with different devices being significantly different from one another,  $P < 0.01$  (see Figure 4).

### Quality Control of PF Labs

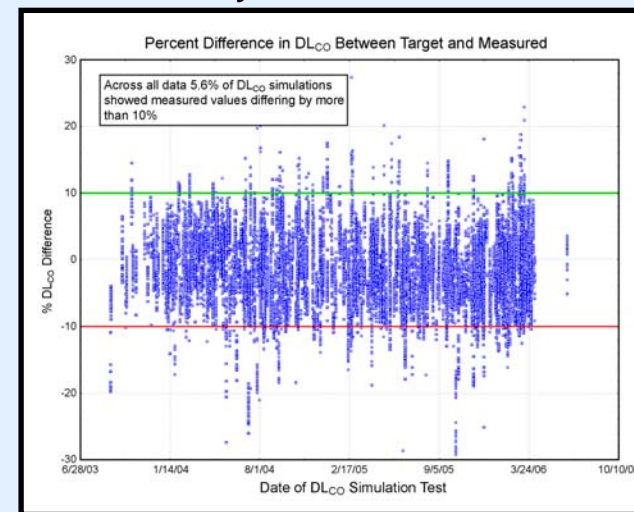


Figure 3: Percent difference in  $DL_{CO}$  between target and measured.

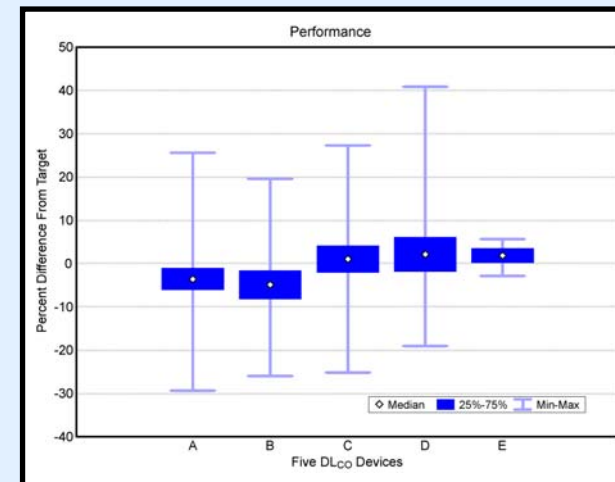


Figure 4: Equipment performance.

### Accuracy Factors

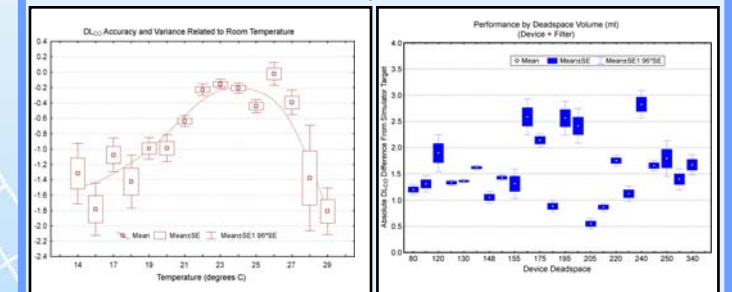


Figure 5:  $DL_{CO}$  accuracy and variance related to room temperature.

Figure 6: Performance by Deadspace Volume (ml).

Temperature showed a distinctive pattern with larger  $DL_{CO}$  errors for device temperatures less than  $21^\circ\text{C}$  and greater than  $27^\circ\text{C}$ ,  $P < 0.01$  (see Figure 5). System deadspace (device + filter) showed no consistent correlation to absolute difference from target  $DL_{CO}$  (see Figure 6).

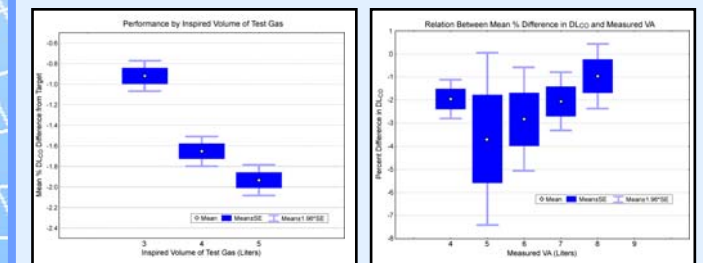


Figure 7: Performance by inspired volume of test gas.

Figure 8: Relation between mean % Difference in  $DL_{CO}$  and measured VA.

Inspired volume of test gas is associated with mean % Diff in  $DL_{CO}$  measurements (see Figure 7). Measured VA has a complex association with mean % Diff in  $DL_{CO}$  (see Figure 8).

## Conclusions

Several factors affect  $DL_{CO}$  instrument performance. Testing  $DL_{CO}$  instruments used in clinical trials is necessary to identify instruments failing accuracy criteria that could affect outcomes.