Measurement of Lactose from Dry Powder Inhalers in Impactors

In vitro testing is a key element in the testing and understanding of dry powder inhalers. The most common excipient used in dry powder inhalers is lactose. Besides the role of lactose as diluent to aid in filling of devices, capsules or blisters, lactose plays an important role during the inhalation event. Here we will discuss two methods to measure the lactose deposited during in vitro testing in the impactor. The first is a wet-chemical method, where lactose is labeled with ammonia in order to allow for colorimetric determination of the content. The second method is based on Raman spectroscopy in order to distinguish between lactose and other ingredients of the formulation.

Materials and methods
Formulations of lactose (Lactohale® (LH) LH100, LH200, and LH300, DFE Pharma, Borculo, the Netherlands) with micronized salbutamol sulphate (Turbula blending) were fired into an MSLI. Formulations of LH200 in combination with LH300 or LH200 with Budesonide as active were fired in an NGI from a Cyclohaler.

Lactose content was tested after reaction with ammonia according to a method described in the pharmacopoeia. The procedure was as follows: lactose was dissolved in water and an equivalent amount of 25% ammonia solution was added. The resulting solution was heated with microwave and an equivalent amount of 25% ammonia at 80°C for 15 minutes. After cooling the UV-VIS absorption spectrum of the solution was recorded. Calibration curves at each absorption maximum were developed (figure 2 for peak at 330-350 nm). A wide range of lactose concentrations can be measured: 0.01-3 mg/mL. Calibration curve UV-VIS absorption at 330-350 nm.

Results and Discussion
The color of lactose solutions that have been treated with ammonia at 80°C is pink to red, dependent on the initial lactose concentration. In the UV spectrum three maxima can be observed at 326, 380, and 511 nm (figure 1).

In figure 3, two examples of in-vitro data were depicted. The composition, lactose versus salbutamol sulphate, was identical for both formulations, only the type of lactose was changed. Morphology C3 inspection of samples fired in an NGI of the material on stage 2, showed single particles and small agglomerates. Raman inspection of these particles and agglomerates revealed three types of material: lactose only particles, budesonide only particles, and agglomerates of lactose and budesonide. By changing the type of lactose, the relative amounts of these three changed as illustrated in figure 4.

Conclusions
With wet chemical and visualization techniques it is relative easy to measure the amount of lactose in impactors. This additional information gave better insight into the role of lactose. Results reported here showed that upon changes in the deposition of the active, there were changes in deposition of lactose and agglomerates as well. The correlation between these is currently under investigation.

References