

# LC-MS-MS Methodologies for the Quantification of Trace Levels of Extractable/Leachable Components in Dry Powdered Inhaled Formulations

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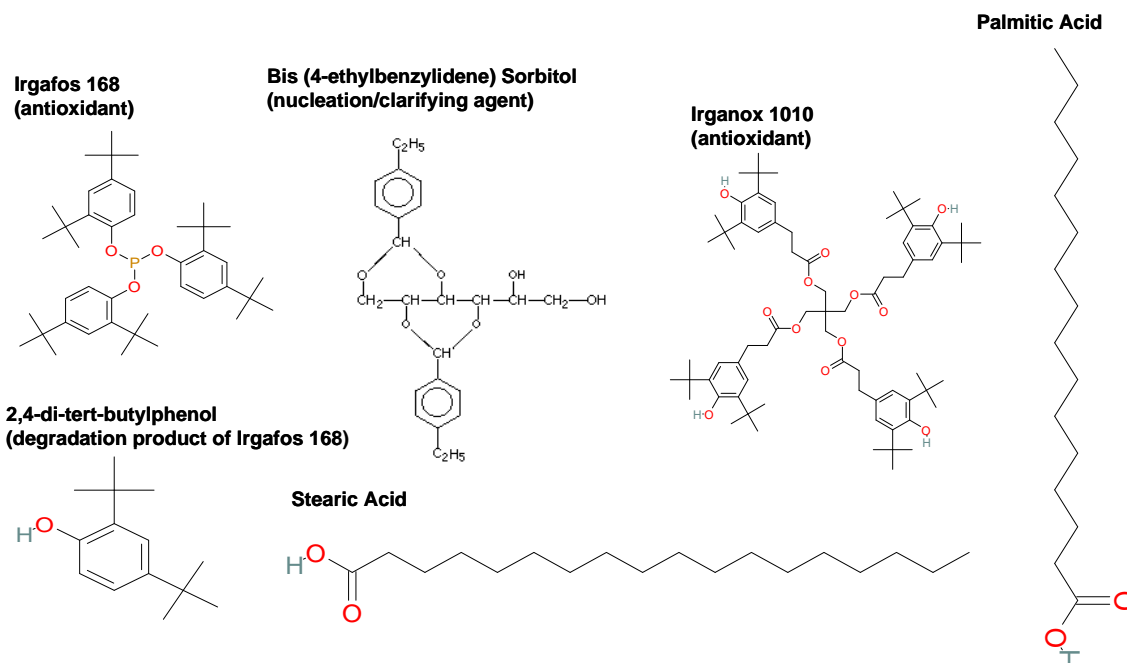
## Summary

Two LC-MS-MS methodologies have been developed to quantify trace levels of additives in the primary container closure materials comprising Pfizer's inhaled drug delivery device. Preliminary validation suggests both methods are fit for purpose demonstrating acceptable precision, accuracy and specificity. The limits of quantification (approx 10-50pg on column) of both methods are in line with the PQRI guidance that states that leachables with a total daily intake of <0.15µg/day would have no carcinogenic or mutagenic toxic effects. Doses, which are representative of what the patient would receive, are actuated into a Dose Unit Sampling Apparatus (DUSA), recovered using the appropriate solvent and analysed. In the case of the fatty acids analysis, an additional derivatisation step is used to increase the sensitivity. Therefore, the patient's dose can be monitored during storage to evaluate if these extractable/leachable compounds migrate from the packaging and into the formulation at a level that may be of toxicological concern to the patient.

## Introduction

In order to understand what additives are present in the device materials and whether or not they would pose a risk to patient health if they leached into the drug formulation, a document detailing the material's composition was obtained from the supplier. To complement this, and to provide a more accurate representation of which compounds are likely to migrate from the device component, a series of controlled extraction studies were carried out in which the component was immersed in a range of solvents at elevated temperatures for a period of time. A toxicological assessment on these extractable materials was performed to ascertain which of these compounds should be targeted in the drug formulation during Phase III or ICH stability.

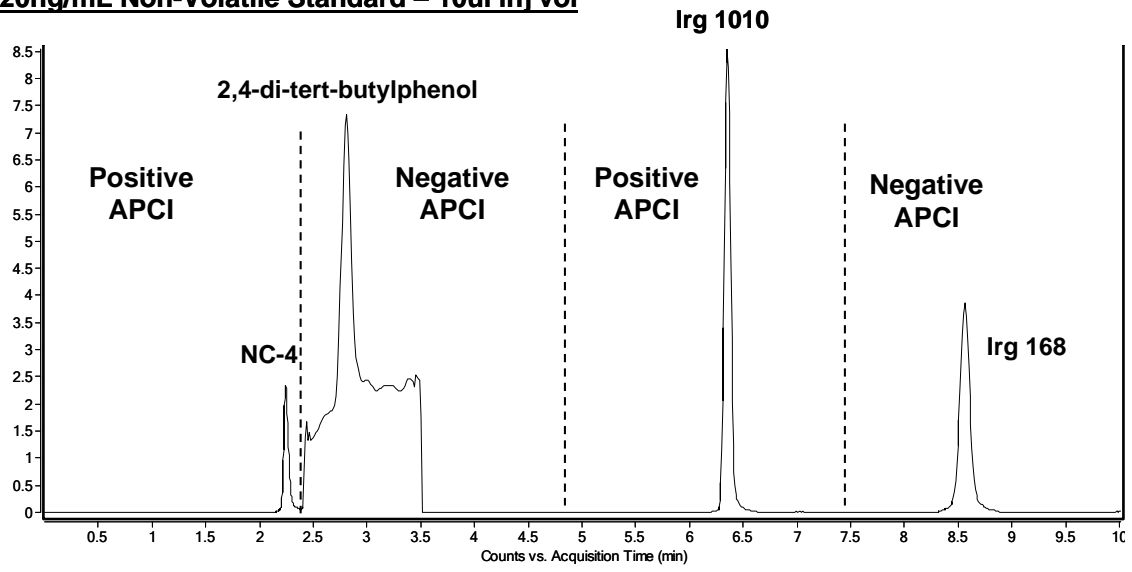
Figure 1 Compounds to Target as Leachables in the Drug Product



## Methodology

Liquid Chromatography – Triple Quadrupole Mass Spectrometry analytical methods were developed to target additives and their degradation products in doses of a Dry Powder Inhaled formulation. The mass spectrometer was operated in MRM mode with the source conditions set to positive ESI for the fatty acid derivatives, and switch between positive and negative APCI for the antioxidants. For the fatty acids and antioxidants methods, Diphenyl and standard C18 HPLC columns were used respectively in conjunction with a Methanol:Water gradient elution profile to resolve the analytes.

**20ng/mL Non-Volatile Standard – 10ul inj vol**



**50ng/mL Fatty Acid Standard – 10ul inj vol**

