Date: January 18, 2018

ATTN: Jan De Backer, M.Sc., Ph.D., M.B.A.
Chief Executive Officer
FLUIDDA, Inc.
228 East 45th Street
9th Floor, Suite 9E
New York, NY 10017

Subject: Biomarker Letter of Support

Dear Dr. De Backer:

We are issuing this Letter of Support to FLUIDDA, Inc. to encourage further study and use of Functional Respiratory Imaging (FRI) measurements of lung and airway structural and functional parameters measured by low-dose high-resolution volumetric computerized tomography scans and quantitative analysis as exploratory pharmacodynamic/ response (PD/R) biomarkers for use in bioequivalence (BE) studies of locally-acting orally-inhaled drug products (LAOIDP) that are indicated for patients with conditions of the lung, including asthma or chronic obstructive pulmonary disease.

Establishing BE of LAOIDP presents a significant challenge due to the lack of established biomarkers characterizing regional physiologic changes in the lungs. Although it is known that lung function testing conveys limited regional information, lung function testing has been used as a measure of overall clinical effect in drug development trials of reference drug LAOIDP and is also recommended in pharmacodynamic studies supporting BE[1]. Measures of lung function testing are inherently variable, and require large studies to demonstrate BE. In addition, it is challenging to measure the amount and location of inhaled drug deposited in the lungs. Biomarkers capable of more directly assessing local drug deposition profiles and measuring *in vivo* regional lung responses (as regional PD) may result in reduced study sizes, and may improve our understanding of regional responses in the lung.

We support the FLUIDDA, Inc., proposed study of FRI parameters as exploratory PD/R airway biomarkers for *in-vivo* studies used in support of BE for LAOIDP. FRI parameters have the potential to measure regional airway responses to LAOIDP. More experience with FRI biomarkers in studies of LAOIDP would be useful to determine their utility in BE determinations for patients with asthma and COPD. There may be limits on the proposed approach, and we ask whether these limits impact the clinical relevance of the FRI parameters compared to the functional parameters, FEV1 and FVC, and how FRI parameters relate to lung

[1] https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

function and/or disease.

No specific imaging technique, methodology or algorithm is endorsed by this Letter of Support. Applying rigorous scientific, laboratory and software development practices for quality control and validation of FRI is imperative. Appropriate reference truth values and anticipated meaningful effect sizes for analytical validation of FRI parameters should be carefully chosen and justified. We recommend the use of standardized imaging acquisition protocols and analysis methods to facilitate analyses across studies and study sites.

We encourage continued exploration of the proposed FRI parameters. We will consider data collection on this biomarker to be exploratory in nature. We believe data sharing and integrating data across trials can foster an accelerated path for assessing FRI use in BE studies. If sponsors intend to include analysis of these biomarkers to support regulatory decision making for a given abbreviated new drug application (ANDA), they should prospectively discuss the approach with the Office of Generic Drugs.

Any groups (e.g. academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Jan De Backer (info@fluidda.com), the FLUIDDA point of contact for this project.

Sincerely,

Christopher Leptak, M.D., Ph.D.
Director, CDER Biomarker Qualification Program
U.S. Food and Drug Administration

Markham Luke, M.D., Ph.D.
Director, Division of Therapeutic Performance
Office of Research and Standards
Office of Generic Drugs, CDER
U.S. Food and Drug Administration