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## Launching the BIOSPIT initiative: Harmonizing sputum outcomes in multicenter trials

Clarke, Graham W.; Diamant, Zuzana; Greenaway, Steven D.; Rainer, Margaret; Allen, Elizabeth; Gispert, Juan

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*Total number of authors:*  
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LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

## Letter to the Editor

### Launching the BIOSPIT Initiative: Harmonizing Sputum Outcomes in Multicenter Trials

Graham Clarke PhD<sup>1,2</sup>, Zuzana Diamant MD PhD<sup>3</sup>, Steven Greenaway MSc<sup>1</sup>, Margaret Rainer<sup>1</sup>, Elizabeth Allen PhD<sup>1</sup>, Juan Gispert MD<sup>4</sup>

<sup>1</sup>Respiratory & Inflammation Early Clinical Development, Quintiles Drug Research Unit, London, UK

<sup>2</sup>National Heart and Lung Institute, Imperial College, Department of Cardiothoracic Pharmacology, London, UK

<sup>3</sup>Skane University, Department of Respiratory Diseases & Allergology, Lund, Sweden.

<sup>4</sup>Quintiles Global Allergy and Respiratory Therapeutic Unit, Madrid, Spain

#### *Corresponding Author:*

Dr Graham Clarke PhD  
Quintiles Drug Research Unit  
Respiratory & Inflammation ECD  
Quintiles Ltd  
6 Newcomen St  
London  
UK  
SE1 1YR  
Email: [Graham.Clarke@quintiles.com](mailto:Graham.Clarke@quintiles.com)

Dear Sir(s),

The incidence of asthma, allergy and COPD is increasing globally. Therefore, asthma represents a major area of R&D interest for several pharmaceutical companies, with presently an estimated 300 compounds in various stages of development, while allergy and COPD pipelines comprise around 140 products.

Both asthma and COPD are highly heterogenic, chronic inflammatory airway diseases. Although inhaled corticosteroids, often combined with long-acting bronchodilators, represent the gold standard pharmacotherapy in milder disease, they are much less effective in severe persistent asthma and in COPD [1]. Thus, as part of (future) customised treatment strategies, phenotyping should help to identify key (inflammatory) components within a disease subset both as targets and for monitoring of existing and innovative therapies.

Sputum analysis already opened perspectives to asthma phenotyping and customized therapy more than 50 years ago, when Dr Harry Morrow Brown from Derby, UK, started to treat symptomatic patients with sputum eosinophilia with corticosteroids [2]. In the 1990s, interest in sputum analysis revived when the late Dr Frederick Hargreave's research group in Hamilton, Ontario, Canada, introduced the technique of sputum induction by inhalation of hypertonic saline [3]. While this protocol required selection of mucous plugs to process samples in parallel, other research groups started exploring processing the entire expectorate [4]. Since then, a large variety of methods and applications have been described for induced sputum.

Today, both the select and the entire sputum processing protocols have been standardized [5] and both allow differentiation between diseased and healthy airways based on inflammatory cell differentials and soluble markers [6,7]. Additionally, several studies have demonstrated responsiveness of these sputum inflammatory markers to both disease exacerbations and effective (targeted) therapies.

Both methods yielded reproducible inflammatory cell differentials of mainly eosinophils and neutrophils and to a lesser extent some of the more robust soluble cytokines and leakage markers in induced sputum from patients with asthma and chronic obstructive pulmonary disease (COPD). On comparison, the split sputum sample method was generally associated with a greater number of viable non-squamous (*i.e.*, inflammatory) cells and higher concentrations of soluble markers [6,7].

Being a reproducible and relatively non-invasive method, sputum analysis has so far been successfully implemented into clinical research, drug development, and even into clinical practice. In the past decade, induced sputum analysis has been particularly useful in defining inflammatory phenotypes within asthma and COPD and, consequently, a valuable tool for identification and monitoring of customized therapy for individual patients. In early clinical drug development, often as part of an exacerbation protocol *e.g.* inhaled allergen or inhaled lipopolysaccharide (LPS), sputum analysis has aided to define a drug's activity in some subsets even in the absence of effect on the more established outcome measures [8,9]. Furthermore, novel and sensitive detection methods of sputum inflammatory cells (such as

mRNA analysis) and soluble markers (such as multiplex, proteomics, and metabolomics) enabled further insight into the disease pathophysiology and targeted therapeutic interventions. Consequently, induced sputum is increasingly being implemented in all development phases of drug development both for phenotyping and as a read-out of drug efficacy. Obviously, involvement of hundreds of patients undergoing sputum induction requires a multicenter collaboration. The selection of collaborating sites for such large studies poses several methodological, technical and logistical challenges. Standardization and harmonization of equipment and methods across participating centers are key elements to reduce variability, while data analysis has to be performed in one certified and experienced laboratory.

The BIOSPIT Initiative has been created with the aim of improving the quality of multi-center respiratory research by harmonizing methodologies and sputum data analysis across collaborating centers. This initiative is the first of its kind to be launched by a contract research organization (CRO). Its main objective being a centralized co-ordination of key partnering sites with adequately trained and qualified staff, standardized laboratory equipment, combined with the capability to recruit respiratory disease populations of all severities. All sites will be trained according to the same standard operating procedures (SOPs) ensuring harmonization of methodologies across centers. In addition, all cellular markers will be analyzed in a certified central laboratory by qualified analysts while soluble markers will also be run centrally ensuring standardized read-outs. Through this initiative, we hope to contribute to more efficiency and an overall better quality in multicenter studies including sputum as an important read out.

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