

New Biomarkers: Why Are They Critical to the Future of COPD Research?

How the COPD Biomarker Qualification Consortium (CBQC) Work Will Deliver Results

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Biomarkers are measures that can be used to capture clinically relevant information. Biomarkers include biochemical, histologic, functional, imaging and patient reported measures. Application of a biomarker to development of new treatments, however, requires that they be accepted by regulatory agencies. The COPD Biomarker Qualification Consortium (CBQC) is a collaborative public-private partnership, aiming to undertake regulatory qualification of emerging biomarkers and clinical assessments to facilitate the development and approval of novel treatments for Chronic Obstructive Pulmonary Disease (COPD). This article summarizes CBQC's origin, goals and progress to date.

Understanding of the pathogenesis and pathophysiology of COPD has advanced considerably during the last thirty years. Unfortunately, these advances have had little impact on availability of new treatments. Only one new class of COPD medication has been introduced during that period.¹ Even worse, the pace of new drug development for COPD is slowing. The development of additional tools for new treatment evaluation has not kept up with knowledge of the disease. In part, this is because qualification of drug development tools requires regulatory review, and no one group has been in a position to undertake the required process of generating sufficient evidence to support regulatory applications. This challenge and the search for ways to address it led to a COPD Foundation-sponsored workshop in January 2010, bringing together representatives from the Food and Drug Administration, the European Medicines Agency, the patient community, the National Heart Lung and Blood Institute and scientists from the pharmaceutical industry and global academic research centers. The group surveyed the available information for potential drug development tools and prioritized those which could reasonably be qualified through a collaborative effort. The COPD Biomarker Qualification Consortium (CBQC) was officially formed in October 2010. Since its formation, CBQC teams have reviewed data from many clinical and observational studies, established an integrated database of data attained in

Industry and Government sponsored studies and initially selected three drug development tools to focus on: a blood biomarker (plasma fibrinogen), an exercise test (6 minute walk), and a health status questionnaire (SGRQ). A second workshop was held in February of 2013 to assess progress and foster dialogue about additional biomarkers of potential interest. The results of this workshop will be detailed in a future publication.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health issue. It is currently the third leading cause of death in the United States, a major cause of morbidity and a key driver of health care costs. Recent advances in understanding the pathogenetic mechanisms that underlie COPD have led to the identification of many new therapeutic targets. This has led to the exploration of a large number of agents as potential treatments, both at the preclinical and clinical levels. The tools used to assess treatments for COPD, however, have been limited and there is currently a need for better ones, as the number of new drugs being approved to treat COPD is declining and attrition rate is high.

The FDA draft guidance for industry² notes that drug development for COPD can be aimed at different aspects of the disease: improving airflow, providing symptom relief, modifying or preventing exacerbations,

altering the disease process, or modifying lung structure or treating extra-pulmonary manifestations. While there has been some success with drug therapies for the first three of these disease aspects, it is in the most crucial areas of COPD treatment (i.e. altering the disease process, or modifying lung structure or treating extra-pulmonary manifestations) that effective therapies are needed.

To date, medications for the treatment of COPD have been FDA-approved primarily on the basis of improvement in lung function, which has generally been measured by the forced expiratory volume in one second (FEV₁). While FEV₁ may be adequate to evaluate treatments aimed at improving the airways obstruction that is associated with COPD, FEV₁ by itself may not be adequate to evaluate the efficacy of novel therapies targeting disease progression, lung structure or extrapulmonary manifestations of the disease. In addition, FEV₁ does not account for all the physiological consequences of airflow limitation. Over the past four years, three US-approved products: Advair™250/50 (fluticasone propionate 250 mcg and salmeterol 50 mcg inhalation powder), Spiriva™ (tiotropium bromide inhalation powder) and Daliresp™ (roflumilast) have obtained a label claim of reduction in COPD exacerbations. However, the initially approved indication for two of these three products (improvement in lung function for Advair, and maintenance treatment of bronchospasm for Spiriva) was based on FEV₁.

COPD's natural history is one of progressive deterioration of lung function and functional status, worsening quality of life, and, in many cases, demise. However, this progression is slow, occurring over years or decades, complicating interventional studies using these endpoints. In addition, COPD is an very heterogeneous disease, and while a number of attempts have been made to define subsets of COPD patients, efficient strategies to develop treatments targeting specific groups of COPD patients have yet to surface. The extrapulmonary manifestations of COPD are becoming increasingly recognized as substantial causes of morbidity and mortality that need timely characterization and treatment. Biomarkers can potentially reflect disease

process and activity, and provide a better understanding of the COPD subtypes, especially the systemic or non-pulmonary manifestations. Thus biomarkers may allow for the development of therapies aimed at treating COPD using endpoints other than FEV₁. A large number of biomarkers have been explored in this context, however, the application of biomarkers in drug development requires rigorous evaluation of their usefulness.

Biomarker Qualification

Recognizing the importance of biomarkers to advance the development of new treatments, the United States Food and Drug Administration (FDA) initiated a Biomarker Qualification Process, which is part of the Drug Development Tools (DDT) Qualification program. The process was implemented to support FDA's work with external scientists and clinicians in developing biomarkers to serve as tools in clinical trials. The importance of this effort is evidenced by the FDA Critical Path initiative, which identifies Biomarker qualification as one of the Critical Path Opportunities³. Furthermore, the importance of the Drug development Tools qualification programs (including biomarker qualification) is highlighted by the 2010 publication of the draft guidance for industry on the Qualification Process for Drug development Tools², and by the identification of "Advancing Regulatory Science and Innovation" as one of the five cross-cutting areas to serve as FDA strategic priorities over the five-year period 2011-2015.⁴ The goal of the biomarker qualification process is to qualify biomarkers for specific "contexts of use," which could impact drug development and may shorten the time necessary to develop a successful new drug application. A context of use specifies how a qualified biomarker will be used in clinical or nonclinical decision-making. Some specific examples of contexts of use include: stratification of patient populations, use in dose ranging and use as outcome (efficacy or safety) measures.

For details on the biomarker qualification submission process, the reader is directed to the DDT guidance at the Agency's website of biomarker qualification:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm>

2010 COPD Biomarker Workshop

A pathway for qualification of biomarkers as novel tools to aid drug development, therefore, has been defined. The process requires a substantial data set to be compiled and then supported by a rigorous analysis. As such, it is expensive and time-consuming and the resources required are likely to exceed those that could be justified for any single pharmaceutical company or that would be likely to merit high priority in competitive publically funded research. However, a rich body of information about biomarkers is already available as a result of industry and government-funded research. Whether sufficient information might be available to support qualification of selected biomarkers for drug development in COPD, if data from various sources could be shared, was a major motivator unaddressed question.

For this reason, the “COPD Biomarkers Qualification Workshop” was organized in Bethesda, MD under the auspices of the COPD Foundation on January 10th, 2010. The Foundation was able to provide a neutral ground for representatives of the FDA, European Medicines Agency (EMA), Industry, Academia and the NIH to meet and discuss available data in an open forum. The format for the workshop consisted of a series of sessions in which various biomarkers and classes of biomarkers were openly discussed with regard to several specific questions:

Questions Asked to Evaluate Potential Biomarkers of Interest

1. Why was the biomarker selected for study?
2. Why is the biomarker relevant?
3. What is the biomarker’s clinical relevance?
4. Is the biomarker responsive to intervention over the short and/or long term?
5. What was the population or subtype or segment for which the biomarker is relevant?

6. Is the biomarker currently qualified?
7. Are the results obtained with the biomarker reproducible and appropriately sensitive?

Participants from government, academia and industry presented and led discussions relevant to individual biomarkers from unpublished data sets. This was followed by voting on whether the various biomarkers were of interest and had sufficient data to merit consideration for qualification. A complete evaluation of the biomarkers discussed can be found in the recently published article in the *Journal of Chronic Obstructive Pulmonary Disease*.⁵ There was considerable enthusiasm for the prioritized biomarkers, which led to the formation of the CBQC under the auspices of the COPD Foundation.

Formation of the COPD Biomarker Qualification Consortium.

The 2010 Workshop delivered several important assessments:

- For several biomarkers sufficient data may exist in the form of completed studies to support a dossier for qualification.
- There was willingness of many parties, including pharmaceutical companies, to collaborate in an effort to prepare dossiers for qualification of biomarkers, including sharing unpublished proprietary data.
- The COPD Foundation seemed an ideal organization to provide a “neutral” platform that could facilitate a collaborative effort based on pooled existing data.

With this background, the COPD Foundation embarked on the creation of the COPD Biomarkers Qualification Consortium (CBQC). The purpose of the CBQC would be to qualify biomarkers that could practically advance development of new treatments for COPD. Importantly, this would be accomplished entirely with existing data. Identification of biomarkers for which gaps in data existed would be made available as it could drive research agendas, but generation of new data is outside the scope of the CBQC.

An organizational structure was created and arrangements made (Figure 1), and the CBQC

was officially launched on October 4th, 2010. Founding members included GlaxoSmithKline, Boehringer-Ingelheim, AstraZeneca and Pfizer. Novartis joined in October, 2011. The consortium is supported by restricted funds contributed by participating pharmaceutical companies. All intellectual property resulting from the CBQC efforts will be owned by the COPD Foundation and will be made freely available to all, thus facilitating the development of new treatments. The consortium is governed by a Steering committee with elected representatives for each partner as well as specific working groups.

The Consortium is supported by member pharmaceutical companies, each of which contributes financial support, data and expertise. The consortium also includes experts from academia with the FDA, EMA and NHLBI in an advisory role.

The CBQC organized several working groups that evaluated the prioritized biomarkers in some detail. Several were felt to merit consideration for qualification. Because a parallel effort for qualification of CT Scanning was currently in progress through the Society of Thoracic Radiology, action on this biomarker was deferred.

The three biomarkers that were selected for candidates for qualification are discussed below.

Biomarkers Selected for Potential Qualification

Blood biomarkers (Plasma Fibrinogen selected). Blood biomarkers have attracted considerable interest and were discussed in detail. The systemic component of COPD may be reflected by raised mean values of blood fibrinogen, C-reactive protein (CRP) and IL-6. CRP and fibrinogen are associated with GOLD stage of disease and are elevated during COPD exacerbations of COPD. Elevated levels of CRP and fibrinogen have also been associated with increased risk for exacerbation^{6,7}, hospitalization and death^{8,9} from this disease. CRP shows significant variability in COPD while fibrinogen is much more stable. Moreover blood fibrinogen is sensitive to intervention with inhibitors of p38

MAP kinase (diltapimod¹⁰ and losamapimod¹¹) in COPD. Because of its stability, association with COPD-related outcomes (exacerbation, hospitalization and death) and sensitivity to intervention, fibrinogen was felt to be a very promising biomarker

Health status (St. George's Respiratory Questionnaire selected). Health status/health-related quality of life measures are designed to provide a summative measure of the overall impact of COPD on health, regardless of phenotype. They are also designed to measure the overall benefit of treatment regardless of mechanism or site of action. While there are other health status measures that have been developed for COPD, by far, the most widely used is the 50-item St. George's Respiratory Questionnaire (SGRQ). It has proven discriminative and evaluative properties and predictive validity. Much experience has been gained from its use in clinical trials including many pivotal trials in COPD over the last decade. It uses empirical patient-derived weights to provide a valid overall measure of health impairment. The very rich data set available with the SGRQ combined with the many analyses performed using this tool, led to a strong consensus that the SGRQ would be an excellent candidate biomarker for qualification.

Exercise/Performance (Six Minute Walk Test selected). Several measures of exercise dependent performance were considered. Peak oxygen uptake is a predictor of survival^{12,13} and constant or incremental work rate cardiopulmonary exercise testing provides rigorous assessment of performance and oxygen uptake, but both tests require specialized equipment and methods, making studies in large groups of subjects problematic. The 6-minute walk test (6MWT) measures performance, although exercise capacity is only one determinant of the 6-minute walking distance. The 6MWT, however, is attractive because it has been performed in large cohorts and is predictive of long-term outcomes on its own^{12,14} or as part of the widely used BODE index¹⁵. There is great experience in the use of 6MWT, particularly in North America, and it is accepted for labeling claims in other conditions (e.g. pulmonary hypertension) by the FDA. The incremental

shuttle walk test (ISWT), more popular in Europe, has the advantage of being externally paced. It is reproducible and captures improvements conferred by treatments of known efficacy such as pulmonary rehabilitation. Areas of concern for both tests include a ceiling effect so that they are less responsive in individuals with mild exercise intolerance. A practice walk increases precision and can reduce sample size. For the 6MWT, new analyses suggest the minimal clinically important difference (MCID) may be close to 25m for a variety of disorders¹⁶⁻¹⁸ and the available data permit establishment of a well-validated MCID in COPD.

Because of the wealth of experience available, its current use by the FDA and acceptance in the clinical community, the 6MWT was felt to be the performance measure with the best available data set for qualification. Other measures including physical activity, quadriceps strength and exercise performance were considered of interest for further research. The first two of these are currently being evaluated by a UK government-funded consortium, COPD MAP.

Progress Towards Qualification

Having identified candidate biomarkers, the first step toward qualification was to organize available data that could be used for qualification. The working groups then conducted a series of assessments confirming the viability of these biomarkers and collected a set of data from specific studies that could support a dossier or other analyses (Figure 2). Based on these reviews, letters of intent to submit a dossier for qualification of each these biomarkers were submitted to the FDA, which led to a meeting with the FDA to discuss the overall process. The FDA expressed enthusiasm for the development of biomarkers to aid as tools in drug development. Specific comments were also made regarding the three letters of intent. Based on the discussion, CBQC developed the following plan:

- **Plasma Fibrinogen** - The letter of intent for fibrinogen was accepted, and a full Qualification Package would be developed and submitted to the FDA for review.

- **St. George's Respiratory Questionnaire** - Since the SGRQ was already used in clinical trials for COPD, it did not need to go through the full qualification process, however rigorous analysis of the compiled larger dataset could provide clear delineation of the cut-points used for stratification and evidence based estimates of sample size needed for clinical trials. Results of the analyses would be prepared as a White Paper.

- **6-Minute Walk Test** - The 6MWT could be used in clinical trials for stratification via direct interaction with the review Division without going through a full qualification. However, the Consortium was encouraged to consider the 6-Minute Walk Test as an outcome for which the Agency would be willing to engage in the process of qualification. Although FDA will accept the 6-Minute Walk as a stratification tool for patient enrollment, careful review is still necessary for rigorous study design. Results of the integrated dataset analyses would be prepared as a White Paper.

A data analysis structure was created for the integrated dataset, and, a contract was awarded to INC Research who assembled a database by pooling data provided by collaborators from industry, government and academic sources. This structure allowed sharing of anonymized clinical trials data in a pre-competitive setting, a key component for Public-Private-Partner-ships.

Expected Output

A key part of the FDA review process is publication of the data submitted in the dossier. In this context, "publication" means make public. This is essential both for there to be public review and comment and for the data and analyses to be widely usable. The CBQC Working Groups intend to publish the analyses and summaries of the combined data sets as White Papers. At present, three such publications are expected, one each for fibrinogen, SGRQ and 6-Minute Walk Test. We expect that these will be online publications that will be freely available. It is also anticipated that, as these data and analyses are completed, they will contribute to

future Guidances prepared by the FDA relating to drug development in COPD. Of the three biomarkers that are being reviewed, it is currently anticipated that a formal regulatory application for fibrinogen, supporting a subject stratification context of use, will be submitted in 2013. SGRQ and 6-Minute Walk Test, which have already been used in applications approved by the FDA, will be supported by White Papers that will define their measurement characteristics, as well as their use in clinical trials as stratification tools. Whether the 6MWT will be submitted for qualification as an outcome measure is pending ongoing analysis and discussion with the FDA.

Going forward, CBQC's hope is that the process pioneered by these efforts will represent a paradigm for the development of

additional biomarkers that can serve as tools to facilitate the development of new treatments for COPD. To that end, a second workshop was held in February, 2013, to review progress to date and three additional biomarkers are now the subject of initial review by working groups: constant work rate exercise testing, assessment of lung volume and, in collaboration with the Quantitative Imaging Biomarker Alliance, lung density.


Biomarkers hold great promise to facilitate the evaluation of patients with COPD. Advances in our understanding of the biology of COPD hold great promise for new and better therapies. Establishing the use of novel tools to facilitate development of these new therapies will be an important step in improving the care of COPD patients. The CBQC will help deliver on these promises. 

Figure Legends

Figure 1. Structure of the COPD Biomarkers Qualification Consortium

Figure 2. Number of studies and subjects that will be included in the analysis of the initial biomarker targets by the Consortium.

Figure 1

COPD Biomarkers Qualification Consortium (CBQC) Collaborators

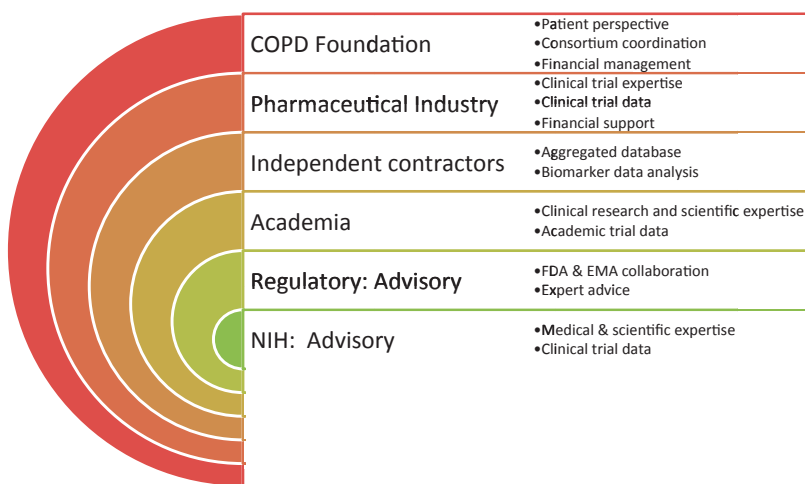


Figure 2

Studies and Subjects to Be Included in CBQC Biomarker Analyses

Biomarker	# Studies	# Subjects
Plasma Fibrinogen	5	6,376
St. George's Respiratory Questionnaire	21	35,571
6 Minute Walk Test	11	14,589

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CBQC Steering Committee: Compton, Christopher, Novartis; Disse, Furtwaengler, Armin, Boehringer-Ingelheim; Goldmann, Mitchell, AstraZeneca; Lomas, David, Cambridge University; Martin, Ubaldo, AstraZeneca; Martin, Thomas, Novartis; Merrill, Debora, COPD Foundation; Tal-Singer, Ruth, GlaxoSmithKline (co-chair); Rennard, Stephen, University of Nebraska, (co-chair); Tetzlaff, Kay, Boehringer-Ingelheim; Thomashaw, Byron, Columbia University; Walsh, John, Alpha-1 Foundation and COPD Foundation; Liaison - NHLBI

CBQC Working groups: Fibrinogen: Barr, Graham, Columbia University; Compton, Christopher, Novartis; Goldmann, Mitchell, AstraZeneca; Lomas, David, Cambridge University; Lowings, Michael, GlaxoSmithKline; Mannino, David, University of Kentucky (co-chair); Miller, Bruce, GlaxoSmithKline (co-chair); Merrill, Debora, COPD Foundation; Rennard, Stephen, University of Nebraska; Snyder, Jeffrey, Boehringer-Ingelheim; Tal-Singer, Ruth, GlaxoSmithKline; Tetzlaff, Kay, Boehringer-Ingelheim; Vestbo, Jorgen, University of Manchester; SGRQ: Glendenning, Alastair, Novartis; Goldmann, Mitchell, AstraZeneca; Jones, Paul, University of London (co-chair); Karlsson, Niklas, AstraZeneca; Menjoge, Shailendra, Boehringer-Ingelheim; Merrill, Debora, COPD Foundation; Muellerova, Hana, GlaxoSmithKline; Rudell, Katja, Pfizer; Rennard, Stephen, University of Nebraska; Tabberer, Margaret, GlaxoSmithKline (co-chair); 6-minute Walk: Celli, Bartolome, Harvard University (co-chair); Casaburi, Richard, LA BioMed; Cerasoli, Franklin Jr, Pfizer; Compton, Christopher, Novartis; Criner, Gerard, Temple University; Croxton, Thomas, NHLBI; Goldmann, Mitchell, AstraZeneca; Locantore, Nicholas, GlaxoSmithKline; McLoughlin, Katrina, GlaxoSmithKline; Merrill, Debora, COPD Foundation; Polkey, Michael, Royal Brompton; Rennard, Stephen, University of Nebraska; Sciruba, Frank, University of Pittsburgh; Tal-Singer, Ruth, GlaxoSmithKline; Tetzlaff, Kay, Boehringer-Ingelheim (co-chair); Weisman, Idelle, Novartis; Lung Volumes: Casaburi, Richard (Co-Chair), LA BioMed; Cerasoli, Franklin Jr. (Co-Chair) Pfizer; Goldman, Mitchell, AstraZeneca; Lazaar, Aili, GlaxoSmithKline; Kesten, Steven, Boehringer-Ingelheim; Tetzlaff, Kay, Boehringer-Ingelheim, Rennard, Stephen, University of Nebraska; Gomes, Joe, Roche; Mattes, William, COPD Foundation; Walsh, John, Alpha-1 Foundation and COPD Foundation; CBQC Data committee: Locantore, Nicholas, GlaxoSmithKline; Menjoge, Shailendra, Boehringer-Ingelheim; Peppe, Dennis, Boehringer-Ingelheim; Sutradhar, Santosh, Pfizer; Walsh, Simon, Novartis; CBQC Regulatory Committee: Aprile, Peter, Pfizer; Lowings, Michael, GlaxoSmithKline; McLoughlin, Katrina, GlaxoSmithKline; Snyder, Jeff, Boehringer-Ingelheim

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