

# CHPA Acute Cough Symposium

*This two-day symposium organized by the Consumer Healthcare Products Association (CHPA) was held in Washington, DC, on March 1 – 2, 2007*

## **SUMMARY REPORT**

*March 28, 2007*

### **Expert Panel:**

Brendan J. Canning, PhD, Associate Professor of Medicine, Johns Hopkins Asthma and Allergy Center; Baltimore, MD (**Panel Chair**)

Surinder S. Birring, MD, MRCP, Consultant Respiratory Physician, Department of Respiratory Medicine, King's College Hospital; London, United Kingdom

Peter Dicipinigaitis, MD, FCCP, Professor of Clinical Medicine, Albert Einstein College of Medicine; Director, ICU, Weiler Division, Montefiore Medical Center; Director, Montefiore Cough Center; Bronx, NY

Lorcan McGarvey, MD, MRCP, Consultant Physician, Senior Lecturer in Respiratory Medicine, Department of Medicine, The Queen's University of Belfast, Belfast, Northern Ireland

Alyn H. Morice, MD, FRCP, Professor of Respiratory Medicine, University of Hull; Head of Division of Cardiovascular and Respiratory Studies, Castle Hill Hospital, Cottingham; East Yorkshire, United Kingdom

Ronald B. Turner, MD, Professor of Pediatrics, Associate Dean for Clinical Research, University of Virginia School of Medicine; Charlottesville, VA

### **Observer Panel:**

Paul Desjardins, DMD, PhD, Senior Vice President, Global Clinical and Medical Affairs, Wyeth Consumer Healthcare; Madison, NJ

David Hull, PhD, Principal Scientist, The Procter & Gamble Company; Egham, United Kingdom

Luis Salmun, MD, Senior Director, Medical and Scientific Affairs, Schering-Plough HealthCare Products; Summit, NJ

Gail Solomon, Director, Clinical Development, Adams Respiratory Therapeutics; Chester, NJ

Alberto Paredes-Diaz, MD, Head of Global Medical Affairs, Novartis Consumer Health; Parsippany, NJ

Linda Suydam, DPA, President, CHPA; Washington, DC

Heinz Schneider, Dr. med., Vice President, Regulatory & Scientific Affairs, CHPA; Washington, DC

Marcia Howard, PhD, Associate Director, Scientific Affairs, CHPA; Washington, DC

## Introduction

Cough is one of the most commonly reported symptoms in patients seeking medical advice and accounts for billions of dollars in expenditures on over-the-counter (OTC) remedies, physician office visits, lost time at work and costs associated with impaired quality of life. Acute cough is almost always self-limiting and due to respiratory tract infections (Irwin et al., 2006; Morice et al., 2004).

The primary users of OTC cough medicine are individuals seeking relief from an acute onset of (likely virally induced) cough. Over-the-counter remedies for acute cough contain a variety of active ingredients with some evidence for their ability to inhibit cough either in animals or in human subjects. The active ingredients in OTC cough remedies include (but are not limited to) dextromethorphan, menthol, antihistamines, phenol and guaifenesin. Most of these medicines have known pharmacological properties that are consistent with their ability to inhibit coughing (e.g., opiates) or have been shown to reduce the triggers of acute cough (e.g., mucus hypersecretion). Dextromethorphan is the primary active ingredient in most OTC cough remedies.

Recent analyses have called into question the efficacy of OTC cough medicines in acute cough (Irwin et al., 2006; Schroeder and Fahey et al., 2004). Concerns raised include questions about adequate dosing of the active ingredients, poor experimental design in many of the studies that have been published and numerous reports of limited benefits of OTC cough remedies over placebos in acute cough.

The Consumer Healthcare Products Association (CHPA) assembled a panel of experts on the causes, diagnosis and treatment of upper respiratory tract infections and cough to discuss the issues related to OTC cough remedies described above. The two-day meeting included a review of current knowledge and approaches to studying cough and its causes, and a session in which five key questions posed by CHPA members were addressed by the panel. A summary of the discussion of these five questions is presented below. This information should be considered recommendations based on best available scientific evidence and not rigid guidelines for subsequent clinical studies.

### 1) What is the relationship of experimentally induced cough to natural cough?

There are two approaches to studying cough in human subjects: Cough can be studied when manifest naturally in patients having either an acute onset of cough (typically associated with a respiratory tract infection) or a chronic cough due to some underlying disease (e.g., asthma, gastroesophageal reflux disease [GERD], chronic obstructive pulmonary disease [COPD], upper airways diseases). For the purposes of this summary statement, we will refer to this cough as natural cough. Secondly, cough can be evoked experimentally in a laboratory with challenges to tussive agents such as capsaicin or citric acid. This approach will be called experimentally induced cough. Studying both naturally occurring cough and experimentally induced cough is and will remain essential in ongoing research into the causes and triggers of cough and for studies of the efficacy of putative antitussive agents.

The panel strongly emphasized that efficacy of a putative antitussive in experimentally induced cough is not necessarily predictive of efficacy in natural cough. Moreover, the panel agreed that a lack of efficacy in experimentally induced cough does not necessarily predict a lack of efficacy in natural cough. Efficacy in either setting will depend upon the cause of the cough in naturally occurring cough and the specific pharmacology of the putative antitussive agents evaluated. Examples illustrating these points were discussed in detail by the panel and have been described in several publications. Guaifenesin, for example, has been reported to

have some efficacy in naturally occurring cough but provided no benefit in experimentally induced cough in healthy volunteers. Guaifenesin provided a modest but significant benefit, however, in preventing experimentally induced cough in patients with an active upper respiratory tract infection (Dicpinigaitis and Gayle, 2003). In contrast to the clinical experience with guaifenesin, codeine has been shown to be somewhat effective in inhibiting experimentally induced cough but ineffective in multiple clinical studies against cough associated with an acute upper respiratory tract infection (Irwin et al., 2006; Morice et al., 2004). These examples along with several others described by the panel encourage caution when interpreting data about the efficacy of putative antitussive agents when evaluated in a limited setting.

## 2) What is the induced cough model of choice for testing an antitussive drug?

The panel agreed that the induced cough model of choice for evaluating the efficacy of antitussive agents is the method described in detail by Dicpinigaitis (2003). The European Respiratory Society also recently approved these methods. In brief, tussive agents are delivered in single breaths using a nebulizer/dosimeter. Currently, upwards of ten laboratories at institutions worldwide are using the Koko Digidoser with an inspiratory flow resistor valve. Tussive agents are delivered in incremental, doubling concentrations with random saline breaths delivered as vehicle control (and to ensure subject blindness to challenge). The concentration (C) of tussive agent producing two (C2) and five (C5) coughs is determined and analyzed statistically after log transformation ( $-\log C_2$  and  $-\log C_5$ ). The panel agreed that standardized methods and equipment for evoking and monitoring experimentally induced cough should be adopted worldwide.

Many stimuli have been used in clinical studies to evoke cough, including capsaicin, citric acid, tartaric acid, bradykinin, fog, resiniferatoxin, ammonia, prostanoids, hypertonic saline and even mechanical stimuli delivered transcutaneously. With few exceptions, however, information about safety, reproducibility, and methodology for cough evoked by these methods is limited. Two exceptions to this generalization are capsaicin and citric acid. The panel agreed that for both of these tussive stimuli safety and efficacy data are sufficient and methods are established for use in experimentally induced cough. Dicpinigaitis and colleagues have described in detail the reproducibility, methods and safety data for capsaicin challenge (Dicpinigaitis, 2003; Dicpinigaitis and Alva, 2005). At present, in the United States, a Food and Drug Administration Investigational New Drug Application (FDA IND) is required for clinical use of capsaicin in cough challenge models. The required source of capsaicin is the Formosa Labs (Taiwan). There are currently no similar regulatory issues in Europe, where Sigma chemical grade capsaicin is deemed acceptable. Similar data on the safety, methodology and reproducibility of citric acid challenges are in preparation for publication (A. Morice, personal communication). The panel agreed that cough evoked experimentally by either capsaicin or citric acid can be used to evaluate the efficacy of putative antitussive agents. In some instances it may not be readily apparent which tussive stimulus is preferable, but it was also generally agreed among panel members that the specific pharmacologic properties of the putative antitussive agent may favor study in either the capsaicin or the citric acid challenge models. An example of a putative antitussive agent best evaluated in a study of capsaicin-evoked cough would be an antagonist of the capsaicin receptor TRPV1. By contrast, an example of a putative antitussive agent that may be best evaluated in a study of citric-acid-evoked cough would be a blocker of Acid Sensing Ion Channels (ASICs). With regard to active ingredients in currently available OTC cough remedies, the citric acid and capsaicin challenge models have no apparent advantage over one another, provided the established methods as described above are employed.

### 3) What are the recommended characteristics of an efficacy trial with an antitussive drug in natural, acute cough?

The panel agreed that four key elements should be considered when designing an ideal or at least optimized clinical trial to evaluate a putative antitussive agent in naturally occurring, acute cough. These elements are as follows:

a) Preferred characteristics of subjects. The appropriate study population for any given clinical trial will be determined in large part by the objectives of the study. Early proof-of-concept or efficacy trials will generally benefit from designs that minimize variability and maximize the sensitivity for detection of the therapeutic signal. Later-phase studies may sacrifice sensitivity in the interest of demonstrating efficacy in a more broadly representative study population.

Variables that might be expected to impact the evaluation of an antitussive agent in naturally occurring acute cough are: (1) the pathogen responsible for the illness, (2) the timing of treatment in relation to the onset of illness, (3) severity of cough at initiation of treatment, (4) gender, (5) age, (6) smoking status, and (7) underlying disease. In a study of naturally occurring colds, the study population can be enriched for a single pathogen by conducting the study during the epidemic period for a single virus and defining the eligibility criteria in a way that optimizes selection of the epidemic pathogen. For example, when subjects with fever or myalgia are excluded from the study population, 65-80% of common cold illnesses that occur in the fall of the year will be caused by rhinovirus infections (Arruda et al., 1997; Hayden et al., 2003). The duration of illness prior to the therapeutic intervention and severity of cough may also be important variables in a study of cough. Recruiting patients with a similar duration of illness and cough severity (as assessed by visual analog scale [VAS] or some other accepted symptom assessment tool) is in recognition of the observation that acute cough associated with upper respiratory tract infection is a "moving target", often preceded by other symptoms (e.g., sneezing) but often persisting for weeks thereafter, with tapering severity and changing patterns of associated symptoms (e.g., productive vs. nonproductive cough, runny and/or itchy nose). It seems logical (although unproven) that cough of differing severity and at different stages of an acute illness may be differentially responsive to intervention. It is also possible (but again unproven) that a clinical trial to study cough associated with acute upper respiratory tract infection can be tailored to the specific pharmacologic properties of the medicine under study.

One potential option for enhancing the homogeneity of the study population is the use of experimentally induced colds (Gwaltney et al., 1996). This model has the advantages of including subjects infected with a single viral pathogen and a precise definition of onset of illness. The model can be run at any time of the year without regard to season and provides a predictable infection and illness rate and symptom profile in the study population. These advantages must be balanced against the disadvantages of the model. These disadvantages include questions about the generalizability of results against a single virus or virus serotype to the broader universe of common cold symptoms and the logistical difficulties of enrolling and challenging a sufficient number of subjects to provide an adequate sample size of subjects with cough. Previous data suggest that only 20-40% of rhinovirus-infected volunteers in the induced cold model will have any cough and a much smaller percentage will report moderate or severe cough (Rao et al., 1995; Tyrell et al., 1993).

The other potential variables in a study of naturally occurring induced cough may be addressed either by the use of restrictive enrollment criteria or by stratification of patients or the analysis for these parameters. There are well-established differences in cough severity and sensitivity between men and women and changes in sensitivity and severity of cough with age

(Chang and Widdicombe, 2006; Dicipinigitis and Rauf, 1998; Irwin et al., 2006; Kastelik et al., 2002; Morice et al., 2004; Newnham and Hamilton, 1997). Control of these variables would be expected to increase the sensitivity of an efficacy study of cough. Other measures to promote subject homogeneity would be exclusion of smokers and subjects with pre-existing pulmonary disorders. Patients reporting chronic cough or a recent upper respiratory tract infection should also be excluded from a study of acute cough. The rationale for excluding asthmatics and smokers and any patients reporting a pre-existing condition associated with chronic cough is that the underlying illness producing their chronic cough may persist even with effective treatment of their acute presentation of cough associated with an upper respiratory tract infection. This would limit the ability of an otherwise well designed study to detect the beneficial effects of a treatment targeting acute cough.

b) Preferred characteristics of patient outcomes/ assessments. For nearly half a century the primary outcome in OTC cough remedy efficacy trials has been the patient diary. Although the panel discussed at length emerging tools for assessing cough in patients and the limitations and shortcomings of patient diaries, it was generally agreed that clearly defined, well established outcome measures that assess whether or not treated patients *feel better* should be employed, including patient diaries, quality of life assessments (e.g., LCQ, CQLQ; see below), cough frequency measures, VAS or categorical severity scores and patient assessment of intervention efficacy.

It seems likely that future clinical studies of antitussive efficacy will require objective measures of cough (Raj and Birring, 2006). In only a very limited number of institutions worldwide that have validated cough counting methods are such objective measures now feasible and routinely combined with other measures, including cough questionnaires and VAS assessments of cough severity and even such subjective measures as diaries (Matos et al., 2006; Raj and Birring, 2006). The panel agreed that it might be premature to recommend including objective measures of cough, given the limited availability of validated equipment. The panel did however recommend that including objective measures of cough be a goal for the industry in their ongoing efforts to evaluate antitussive efficacy.

c) Preferred characteristics of the study. The panel agreed that randomized, multiple dose, double blind, placebo controlled, parallel group trials were desired for ideally evaluating the efficacy of a putative antitussive agent in natural acute cough.

Another important consideration in designing an efficacy trial for existing OTC cough remedies is a careful consideration of the number of participants that need to be recruited. The panel recognizes that the number of study subjects that need to be recruited will depend on a number of factors such as the outcome variable deployed. The panel suggests that clinical trials are appropriately powered using the best and most up-to-date data available. An example of a successful trial may help illustrate the point. In a series of randomized controlled trials of single dose dextromethorphan, Pavesi et al. (2001) reported a modest 12% reduction in objectively recorded cough frequency that was highly statistically significant in 356 patients with acute cough. The panel agreed that in order to obtain adequately powered clinical trials of antitussive drugs it is likely that large numbers of subjects need to be studied. Investigators should continually review emerging data to determine accurate group size needed for a given outcome parameter.

d) Preferred characteristics of the analysis. No criteria for stratifying patients based on cough severity in acute cough are currently established or accepted. Statistical analyses should be tailored to the specific outcome measures used in the trial.

The panel raised a few additional points to consider about the recommended characteristics of an efficacy trial for antitussive agents in natural acute cough. Specifically, in addition to evaluating the severity of cough at any given timepoint, it may be equally important to evaluate the rate of recovery (or return to normal values) of cough responsiveness/frequency/intensity. Secondly, given the profound influence of placebo in studies of cough in some systems, it was asked whether a vehicle effect should be evaluated in parallel with drug effect studies. The panel did not answer these questions in consensus and presents them here in the form of points to consider to be addressed later.

#### **4) What is the best QOL tool for a trial with an antitussive in acute cough?**

There are three quality of life (QOL) tools specific for cough. The Leicester Cough Questionnaire (LCQ) and the Cough-specific Quality of Life Questionnaire (CQLQ) have been validated and used in several publications, including in patients with acute cough (Birring et al., 2003; French et al., 2002). A third cough-specific QOL tool, the Chronic Cough Impact Questionnaire (CCIQ), shares features with both the LCQ and the CQLQ, but repeatability and responsiveness data from its use are awaited (Baiardini et al., 2005). These three QOL tools have in common assessments of the physical, social and psychological impact of cough on quality of life. The panel noted that no currently available QOL tool was designed specifically for acute cough. The CQLQ in particular includes elements (e.g., questions relating to fear of severe illness [AIDS, cancer, TB]) that are likely to be irrelevant to acute cough. Nevertheless, both the LCQ and CQLQ have been used effectively in small studies of acute cough.

The panel noted that QOL tools have been used most effectively when combined with some additional measure of cough severity, either cough frequency or a VAS assessment of cough severity. Hence, always combining QOL assessments with a VAS assessment of cough was encouraged whether or not cough frequency was going to be measured. Also, as mentioned above, the panel agreed that diaries are still an important method of evaluating efficacy of putative antitussive agents in acute cough and may be useful when paired with QOL measures. The panel also agreed, however, that cough researchers should work to develop a standard on the content and collection methods used in keeping patient diaries, and that diary data acquisition should be interactive and easily validated (e.g., time of data entry, proof of symptom assessment measurement).

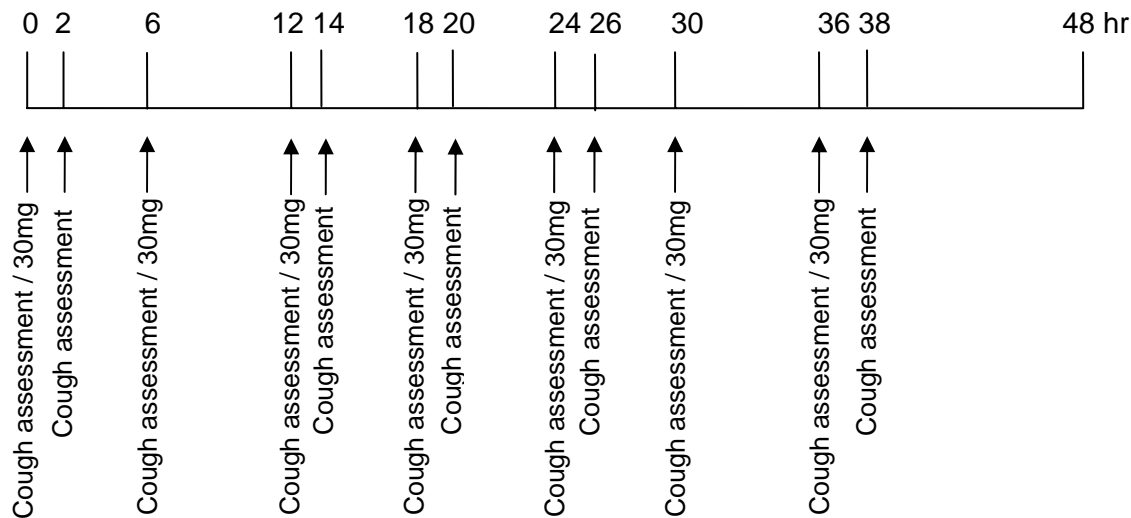
The existing QOL tools have the potential to be useful in studies of acute cough. The panel left open the question of whether or not a QOL tool specific for acute cough should be developed and validated.

#### **5. What methodology would provide the maximum sensitivity for a trial with dextromethorphan at current OTC doses (up to 120 mg/day)?**

The panel agreed that many of the same recommendations made in addressing Question 3 about characteristics of an efficacy trial also apply to addressing this question related specifically to dextromethorphan administered at current OTC doses and evaluated in the setting of natural acute cough. These recommendations include selecting patients with the most severe cough symptoms associated with their infection, selecting patients with less than a 7-day duration of illness, using a randomization process that produces treatment groups matched for age, gender and disease severity, and excluding patients that smoke, have pre-existing pulmonary disease, GERD-associated cough, chronic cough or recent upper respiratory tract infection. In addition, however, in emphasizing the objective of evaluating or

demonstrating efficacy of a specific agent, the panel agreed that the ideal study design would have a multiple dosing strategy at the upper limit of dose permitted based on current OTC guidelines, administered at appropriate intervals over a 36- to 48-hour period and not to exceed 120 mg/day.

Assessments and dosing could be carried out using the following scheme:



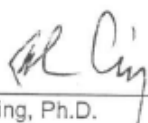
The methods for assessing cough should be identified in advance and should include those measures summarized above under Question 3, including VAS (or other accepted symptom scoring method), diaries, cough frequency and QOL. At a minimum, all patients should provide a subjective assessment of their cough at the timepoints indicated. This may best be obtained by interview. A subjective measure of cough using a diary would also be an important element of the study design. Secondary measures would include QOL assessments. Based on historical precedence, however, the data gathered from the VAS and patient diaries and symptom assessments may be the most valuable data in a study designed to evaluate or demonstrate efficacy of dextromethorphan when administered at OTC doses. As discussed above in answering Question 3 the panel agreed that the industry should aspire to including objective measures of efficacy in their studies of putative antitussive agents.

An alternative approach to evaluating or demonstrating efficacy of dextromethorphan would be to conduct a study using a modification of the protocol described by Abdul-Manap and colleagues (Abdul-Manap et al., 1999). In a randomized, double blind placebo controlled crossover design, these investigators showed that a single loading dose of 60 mg dextromethorphan inhibited citric-acid-induced cough in healthy volunteers (monitored over the 12 hours after initial dosing). Potential modifications to a subsequent study might include recruiting patients with acute cough and using a dosing regimen of 30mg every 6 hours (to comply with current OTC guidelines for immediate-release dextromethorphan). Given the imperfect predictive value of results obtained in experimental cough studies for efficacy in natural acute cough, however, it was argued that an experimental cough challenge would be less desirable than an efficacy study in natural acute cough.

## Conclusions

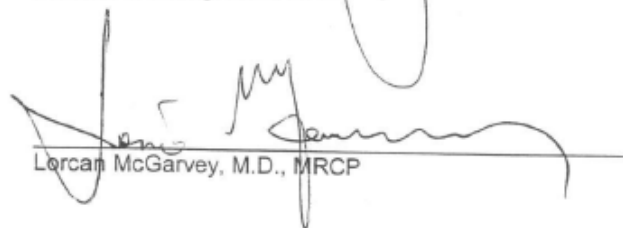
The panel agreed that the discussions summarized above did not produce controversial conclusions or recommendations that are unrealistic for the makers of OTC cough remedies, overly problematic for those inclined to reevaluate the efficacy of existing medicines, or discouraging to those inclined to assess the efficacy of novel cough therapies. Although the panel agrees that there is an unmet need for better, more effective and selective antitussive agents for treating both acute and chronic cough, the panel also agreed that existing therapeutic approaches are based on rational and scientifically validated concepts. Moreover, although the approaches used to evaluate antitussive efficacy in human subjects have varied considerably over the years, ample evidence from published randomized controlled trials demonstrates efficacy of the active ingredients in OTC cough remedies (Curley et al., 1988; Parvez et al., 1996; Pavesi et al., 2001). These observations support the conclusion that a well designed clinical trial evaluating the antitussive effects of existing OTC cough remedies could potentially demonstrate efficacy in the treatment of naturally occurring cough. The desired attributes of such trials are discussed in detail above. The panel cautions, however, that showing efficacy against acute cough with any treatment has proven difficult regardless of the pharmacological properties of the medicine studied. A number of factors contribute to these shortcomings in studies of cough, including medicines that have limited efficacy or were administered at minimally effective doses, the lack of a "gold standard" antitussive for comparison with test agents, the potentially profound placebo effects often seen in well designed clinical studies of cough, and a continued reliance on subjective outcome measures and/ or poorly validated measures of cough severity and frequency. Ultimately, objective measures of cough severity may be key to future studies of antitussive therapy. Such measures are currently used in a limited number of institutions but are likely to be used worldwide in the near future. More problematic is the utter lack of positive ("gold standards") or negative (placebo) control studies that are feasible, appropriate and necessary for evaluating antitussive efficacy. Utilizing the design of the idealized clinical trials summarized above may limit the influence of placebo effects and permit demonstration of the beneficial effects of the active ingredients used routinely in the treatment of acute cough.

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Brendan J. Canning, Ph.D.

  
Surinder S. Biring, M.D., MRCP

  
Peter Dicipinigaitis, M.D.

  
Lorcan McGarvey, M.D., MRCP

  
Alyn H. Morice, M.D.

  
Ronald B. Turner, M.D.  
University Principle Contact

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