Sirs:

To:
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Guidance for Industry
Sinusitis: Designing Clinical Development Programs of Nonantimicrobial Drugs for Treatment
[Docket No. 2006D–0463]

I am a fellow of the American Academy of Otolaryngology-Head and Neck Surgery. I am the immediate past chairman of the academy's Rhinology and Sinus committee and have authored/co-authored a number of publications/textbooks on this subject. The FDA's guidance document for Sinusitis: non- antibiotic treatment appears to be based upon limited resources and biased input by members of your committee. I am not interested in injecting politics into this topic. I do believe that terminology and discussion should be based upon expert consensus and science (when possible!).

Comment 1:

In 1997 I chaired our academies Task Force on Rhinosinusitis. The purpose of this Task Force was to standardize terminology for researcher's and clinicians. Much of this information was consensus based as we acknowledged in our document, but as this disease has been in the hands of our speciality for over 100 years, we believed this was a reasonable undertaking. The FDA's manuscript on Sinusitis: Non- antibiotic Treatment appears to be biased with limited references and ignores the current standards of terminology/concepts utilized by our field. This document in its current form, will confuse the issue, rather than improve the situation.

A patient with acute disease with facial pressure, nasal drainage and congestion for example, has a *rhinosinusitis*. Sinusitis alone may occur. The patient may have no nasal complaints, but symptoms may be referable to the region of the sinuses and a CAT scan for example may demonstrate isolated sinus pathology. While not as common, this is a *sinusitis*. The term *rhinitis* is applied to disease confined to the nose. This is actually not as common as one may believe. Gwaltney et al (Computed tomographic study of the common cold. Gwaltney JM Jr, Phillips CD, Miller RD, Riker DK. NEJM Vol 330 1994) showed almost 90% of patients with a viral URTI have abnormal CT scans of the sinuses. Schwartz et al confirmed this finding in the pediatric population. (Computed tomography imaging of the maxillary and ethmoid sinuses in children with short-duration purulent rhinorrhea OTOLHNS 2001). The nose and sinuses have an anatomic and physiologic relationship which should not be ignored.

The terminology associated with length of the disease process was based upon accepted terminology for otitis media. The ears and sinuses have many similarities (enough so that it sometimes jokingly said the ears are simply misplaced sinuses) which led to our commonality of terms. The FDA document recommends the following:

"The general consensus for the classification of sinusitis is as follows:

- Acute — when the duration is less than 4 weeks
- Subacute — when the duration is 4 to 8 weeks
- Chronic — when the duration is longer than 8 weeks
- Recurrent — when three or more episodes of acute sinusitis occur in a year "

Our Task force 10 years ago (historical precedence) used the following terms:

Table 1. Clinical categories of rhinosinusitis (1997 Task Force)

	Duration	Strong history	Include in differential	Special notes
Acute (ABRS)	Up to 4 wks	≥ 2 major factors, 1 major factor + 2 minor factors, or nasal purulence on exam	1 major factor, ≥ 2 minor factors	Fever or facial pain does not constitute suggestive history in absence of other nasal symptoms or signs.
Subacute	4–12 wks	Same as chronic	Same as chronic	Complete resolution after effective medical therapy
Chronic (CRS)	≥ 12 wks	≥ 2 major factor, 1 major factor + 2 minor symptoms, or nasal purulence on exam	1 major factor, ≥ 2 minor factors	Facial pain does not constitute suggestive history in absence of other nasal symptoms or signs
Recurrent, acute	≥ 4 episodes/year + each episode last ≥ 7–10 days. Absence of intervening signs of chronic rhinosinusitis	Same as acute rhinosinusitis		
Acute exacerbations of chronic	Sudden worsening of chronic rhinosinusitis, return to baseline after treatment			

The Sinus and Allergy Health Partnership (SAHP consisting of the 3 major national otolaryngology societies) published Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology (OTOLHNS 2003) and further clarified sinusitis definitions as "*Rhinosinusitis* is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses. *Chronic rhinosinusitis* is rhinosinusitis of at least 12 consecutive weeks' duration. Therefore, *chronic rhinosinusitis* is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration."

Page 2 Line 66 "Chronic sinusitis is not usually caused by bacterial infection. " This is inaccurate. CRS is the end result of various underlying pathologies. Depending upon which researchers are polled, the answers to this question vary. The role of bacteria in this process is under investigation. New theories on biofilm and exotoxin/superantigens clearly implicate bacteria as the prime substrate for an inflammatory response.

Page 2 Line 74 "Subacute sinusitis and recurrent sinusitis have an intermediate pathophysiology. Some cases resemble acute sinusitis with a preponderance of bacterial infection and some resemble chronic sinusitis where bacterial infection often is not present." Subacute sinusitis is a disease purely based on an arbitrary time scale. The pathophysiology of sinusitis has not been elucidated to the point whereby this phase of the illness can be determined by scientific means. Further, recurrent sinusitis is a "man-made" term. Most of these are probably allergy or another inflammatory process. Recurrent acute bacterial sinusitis also remains poorly studied.

Page 3 Line 84 "FDA considers rhinitis and sinusitis as distinct disease entities." Once again, this is an arbitrary use of terminology which goes against current thinking. The FDA does not have a mandate to develop new terminology. Acute rhinosinusitis can be viral or bacterial. Rhinitis rarely occurs without sinusitis. Sinusitis alone can occur but rarely without nasal symptoms. The terms most appropriate would be: Rhinitis, rhinosinusitis and sinusitis depending upon physical findings, patient symptoms and maybe a CT scan.

Page 3 Line 90 "recent U.S. literature has adopted the term sinusitis over rhinosinusitis (Slavin and Spector et al. 2005)"- while bright individuals, the general allergist does not set the standard for terminology in this field. As mentioned previously, the FDA demonstrates political bias in this regard.

Page 3 Line 100 "There is interest within the pharmaceutical industry in the development of new drugs, including drugs other than antibiotics, for the treatment of sinusitis." What does this mean? Is industry seeking to have an indication for ALLERGIC etiology of sinusitis for antihistamines or nasal steroids? Is this VIRAL sinusitis? Very broad use of language is not appropriate. The FDA needs to have a panel to set guidelines for terminology!

Page 5 Line 205 "Since it is known that sinusitis patients have accompanying rhinitis, the clinical program should convincingly demonstrate that the efficacy is from improvement of sinusitis and not solely from improvement of rhinitis. " It appears the FDA is giving a circuitous argument—sinusitis has rhinitis—this is why "rhinosinusitis" was coined !

Page 5 Line 211 "Objective assessments of sinusitis include imaging techniques such as a computerized tomography (CT) scan or a magnetic resonance imaging (MRI) scan, ultrasonography, microbiological assessment of sinus aspirate, and direct visual examination of the sinus cavity by endoscopic examination when an antral window has been created surgically. However, if a drug will be delivered systemically and is not expected to reach the nasal cavity or is known not to be effective in rhinitis, objective evidence may not be necessary." These diagnostic tests cut a long swath through the range of tests without regard to sensitivity and specificity. MRI plays almost no role in evaluating patients for sinusitis. A plain film X-ray is a reasonable low cost test. (Antimicrobial treatment guidelines for acute bacterial rhinosinusitis - Otolaryngology–Head and Neck Surgery Volume 130 Number 1). Also, I see no role for NOT using objective evidence when determining superiority of a treatment-even if it does NOT reach the nasal cavity.

Page 5 Line 219 "For entry into clinical studies for acute, subacute, or chronic sinusitis, symptoms should be continuously present for at least 10 days" This does not make sense.

Page 5 Line 221 "For entry into recurrent sinusitis studies, an effort should be made to obtain objective evidence from previous sinusitis episodes to ensure that patients with reliable diagnosis of recurrent sinusitis are enrolled in the study. However, because of the historical nature of the diagnostic criteria, we acknowledge that objective assessment may not be reliably available for all patients and for all previous episodes." Relying on history from a patient or a primary care physician is fraught with problems. Objective information is a requirement for proper diagnosis and subsequently appropriate treatment.

Page Line 275- Has the FDA validated this symptom scoring method?

Page 9 Line 357 "The narrow opening of the sinuses into the nasal cavity and the ciliary action that is directed away from sinuses toward the nasal cavity can prevent the drug from reaching these spaces. " Pharmaceuticals are prevented from entering the middle meatus (and thus the frontals, maxillary and anterior ethmoids) by the protective role of the uncinate process (*"Anatomy of the Paranasal Sinuses" by JB Anon, M Rontal and SJ Zinreich, Thieme, New York, 1996.)*

Page 9 Line 359 "The FDA believes that to be clinically effective the drug should reach the sinus cavity or the ostiomeatal complex area to open up the sinus drainage." Sinus disease is a pan-mucosal phenomenon with up-regulation of inflammatory mediators. It is naïve to believe that "opening the sinuses" will improve or prevent disease. Post-operative maxillary sinuses with LARGE openings can be filled with purulence. The thought that obstruction is key minimizes the importance of the global nasal/sinus aspect of the disease.

CONCLUSION:

The FDA has produced a document riddled with scientific inaccuracies. The lack of a logical approach to this disease state will only further confuse industry and researchers. This muddies the waters even further and provides little to this illness.

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