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Sent via email: CommissionerFDA@fda.hhs.gov and Janet.Woodcock@fda.hhs.gov

Dear Dr. Sharpless and Dr. Woodcock:

There is a significant health care concern that affects 10% of the U.S. population: unverified penicillin allergy. Carrying a label of penicillin allergy has been shown to be associated with a clinically and statistically significant increase in morbidity for patients, and even an increased risk for mortality. Ironically, the vast majority of patients who undergo penicillin skin testing are found not to be allergic to penicillin. **We are writing you to emphasize that penicillin skin testing is essential for eliminating the increased morbidity and costs associated with a false label of penicillin allergy.**

A hindrance to penicillin testing is the lack of a commercial product containing the necessary reagents. A newly developed product containing all of the essential reagents for skin testing is currently seeking FDA approval. **We strongly urge the FDA to expedite this review process.** As you know, penicillin is the most common drug allergy; 11-12% of patients have a label of penicillin allergy in their health record.^(1, 2) Recently, several studies have demonstrated that having a label of penicillin allergy is associated with increased morbidity. Large case control studies both in the U.S. and United Kingdom involving more than 50,000 patients labeled as penicillin allergic reported higher rates of infections with MSSA, VRE, and C. difficile.^(1, 3) In addition, prolonged hospitalizations, higher readmissions, and higher surgical site infections have been found in patients labeled penicillin allergic.⁽⁴⁾ Patients with a label of penicillin allergy also have higher costs of care. A study published this year demonstrated that a label of penicillin allergy is also associated with higher risk of all-cause mortality.⁽⁵⁾

While penicillin allergy is the most commonly listed drug allergy in the medical record, the rate of confirmed penicillin allergy is much lower and appears to have declined over time. Studies from the early 1970's reported that more than 60% of patients with histories of penicillin allergy were positive on penicillin skin testing.⁽⁶⁾ Longitudinal studies from Kaiser Permanente in Southern California found the rate of positive penicillin skin tests linked to a label of penicillin allergy to have decreased from 15% in 1995, to 3% in 2007,⁽⁷⁾ and <1% in 2013.⁽⁸⁾ The largest data on penicillin skin testing comes from the Mayo Clinic, based on evaluating a total of 30,883 patients

with histories of penicillin allergy who underwent penicillin skin testing; only 1% were found to be skin test positive (personal communication from Miguel Park, MD).

Approximately 10% of the U.S. population, (~30 million patients) are labeled as being allergic to penicillin. Given the increased morbidity and mortality associated with a label of penicillin allergy, removing the label of penicillin allergy (i.e., “de-labeling”) is critical to ensure this population does not experience untoward health care outcomes. A number of national organizations have recommended this, including the Infectious Diseases Society of America (IDSA), and the Society for Healthcare Epidemiology of America (SHEA).⁽⁴⁾ Recently, at the Presidential Advisory Committee on Combating Antibiotic-Resistant Bacteria (PACCARB) meeting, Chairman Blaser specifically mentioned the importance of further study of appropriate identification and verification of patients with penicillin allergy. Thus, a penicillin de-labeling strategy is integral to antimicrobial stewardship efforts.

Penicillin allergy de-labeling can be accomplished in several ways. The method that has been utilized for the longest period of time is penicillin skin testing. While it is known that penicillin is metabolized to antigenic minor determinants, these minor determinants have never been available commercially in the United States for skin testing. Positive reactions to minor determinants have long been associated with risk for anaphylaxis to penicillin.⁽⁹⁾ Early large studies of penicillin skin testing using the major determinant and a minor determinant mixture evaluated patients with histories of penicillin allergy, including many patients with anaphylaxis, and found the negative predictive value to be 98%.^(10, 11) In these studies 10-16% of patients were positive only to the minor determinant mixture. Recently, a multicenter U.S. study of a penicillin skin test kit containing both major and minor determinants as well as amoxicillin evaluated 455 patients with “convincing” histories of penicillin allergy.⁽¹²⁾ A higher rate of positive skin tests was seen in this group (13.8%), which is not unexpected given this was a high risk population. The negative predictive value was 97.9%, similar to previous studies.

Commercially available penicillin skin test reagents containing minor determinants are available in many countries throughout the developed world, but not in the U.S. The lack of complete testing reagents has served to generate uncertainty for many allergists in the U.S. who do not perform penicillin testing due to fear of false negative results. Having a diagnostic test with a high negative predictive value is critical for de-labeling higher risk patients. Given the scope of false penicillin allergy labels and its associated morbidity/mortality in the U.S., we cannot afford to continue without the capability of optimal penicillin skin testing due to the lack of a commercial product with a high degree of precision that enables safely de-labeling patients.

On behalf of our members and the patients served, we strongly urge the FDA to rapidly move forward with the review and potential approval process of a commercial product containing the essential penicillin antigens. This will enable the safest and most accurate identification of patients with true penicillin allergy.

Sincerely,

American Academy of Allergy, Asthma & Immunology
Allergy and Asthma Network
American Partnership for Eosinophilic Disorders
Asthma and Allergy Foundation of America

Association for Professionals in Infection Control and Epidemiology
Campaign Urging Research in Eosinophilic Disorders
Emory Antibiotic Resistance Center
FARE: Food Allergy Research & Education
Food Allergy & Anaphylaxis Connection Team
The International FPIES Association
National Association of Pediatric Nurse Practitioners
Pediatric Infectious Diseases Society
Society of Critical Care Medicine
Society of Infectious Diseases Pharmacists
The Mastocytosis Society, Inc.
Tufts Center for Integrated Management of Antimicrobial Resistance (CIMAR)

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