AMERICAN COLLEGE RHEUMATOLOGY
POSITION STATEMENT

SUBJECT: Use of FDA Labeling

PRESENTED BY: Committee on Rheumatologic Care

FOR DISTRIBUTION TO: Members of the American College of Rheumatology
Medical Societies
Members of Congress
Health Care Organizations/Third Party Carriers
Insurance Companies and Commissioners
Pharmacy Benefit Managers
Managed Care Entities

Positions:

1. Official Food and Drug Administration (FDA) drug labels establish parameters governing the advertising and promotion of drugs; they do not address every acceptable use of every drug and should not be regarded as the sole authority determining the standard of acceptable or accepted medical practice.
2. The guidelines in official FDA drug labels are not a substitute for sound clinical judgment and should not limit the use of therapeutics in medical practice. Rather, information in FDA labels must be interpreted by clinicians in the context of an individual patient's condition as well as established and emerging data that are often not contained in labels.
3. Providers should and may lawfully recommend and prescribe FDA-labeled products for off-label indications when their use is based upon sound clinical judgement and the patient's best interests.
4. When the use of FDA-labeled products is medically necessary, based on sound clinical judgment and the patient's best interests, and/or when FDA-approved alternatives are lacking, and/or when FDA-approved drugs have failed due to intolerance or lack of efficacy, insurance plans, including Medicare, should be required to fulfill their obligation to their beneficiaries by covering such therapy.

Background:

Prescribing information contained in FDA labels is submitted by manufacturers with new drug applications and provides official descriptions of drugs including but not limited to indications, doses, adverse drug reactions, recommendations for use in pregnancy and safety information for patients. This information is meant to inform prescribers and patients about the safe and effective use of therapeutic agents. FDA labels are written so as to be devoid of explicit or implied claims of efficacy or suggestions for use in circumstances where safety or efficacy data are not robust or have not been reviewed by the FDA.

FDA regulations governing the content and format of prescription drug labeling were updated in January 2006 (Code of Federal Regulations Title 21). These rules do not limit the use of labeled products to indications described in the label. Indeed, current FDA guidance explicitly directs providers to use "legally available drugs, biologics and devices according to their best knowledge and judgment." The FDA recognizes off-label use of products as appropriate and elaborates by clarifying that "If physicians use a product for an indication not in the approved labelling, they have the responsibility to be well-informed about the product, to base its use on firm scientific rationale and on sound medical evidence,

and to maintain records of the product's use and affects."
(http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm [Last accessed: May 9, 2019])

Without off-label use of prescription products, the therapeutic options for many common rheumatologic conditions are vanishingly few. Indeed, the standard of care for many patients with rheumatologic diseases *requires* the off-label use of prescription products. Some examples below illustrate this point.

- Systemic sclerosis affects approximately 75,000 to 100,000 people in the U.S. and has the single highest mortality rate of any autoimmune rheumatic disease (1,2). Despite the grave threat posed by this diagnosis, there is no FDA-approved therapy for systemic sclerosis. Thus, rheumatology providers and other providers routinely and appropriately recommend the off-label use of a range of therapies including cyclophosphamide, mycophenolate mofetil, and methotrexate.

- Methotrexate is a first-line agent and the standard of care for a large number of rheumatologic conditions but is only FDA approved for three (rheumatoid arthritis, psoriasis and polyarticular juvenile idiopathic arthritis).

- Sarcoidosis, a multi-organ system disease that commonly threatens vital organ functions, is appropriately treated with a number of drugs including hydroxychloroquine, methotrexate, azathioprine and tumor necrosis factor inhibitors (TNFi), none of which has FDA approval for this indication.

- Colchicine has been used in the US as effective therapy for gout for over a century, but gained FDA approval only in 2009.

Despite the evidence and broad clinical experience supporting the use of these and other agents, and despite a lack of alternatives, insurance coverage for the use of such drugs is often denied on the basis that they are not approved by the FDA.

FDA labels are further limited by the fact that the information and advice they contain is not updated as quickly as advances in accepted medical practice. By design, post-marketing surveillance and widespread, real-world experience with new drugs do not begin until the FDA labels are approved. Unfortunately, new information is often slow to be incorporated. For example, dose acceleration of TNFi's is widely accepted as medically necessary and effective for a subset of patients with psoriatic arthritis and inflammatory bowel disease-associated arthritis, but the use of higher doses is not addressed in the FDA labels for all of these agents. Thus, insurance coverage for the higher doses is frequently denied. Another example: TNFi's are emerging as one of the safest alternatives for patients with rheumatoid arthritis during pregnancy, but this nuance of care is not reflected in FDA labels. In these and similar circumstances, denial of coverage based on FDA labels stands in stark opposition to FDA guidance that providers base the use of legally available drugs "according to their best knowledge and judgement".

Even government payers deny and delay coverage for drugs explicitly on the grounds that the drugs are not FDA approved. Medicare Part D, for example, requires beneficiaries to seek the support of the prescribing provider, traverse layers of review, and submit proof in support of the use of off-label drugs from one of three officially recognized drug compendia. Access to these compendia is limited and costly and their navigation is beyond most laypeople (having been written for medical practitioners and in highly technical language.) (42 U.S.C. §1395w-102(e)(4)(B)). These practices delay and limit access to appropriate therapy and thereby harm patients.

In summary, the ACR agrees with the FDA and supports and recommends the use off-label therapies when medically necessary and appropriate. The ACR recognizes that patients who rely on off-label therapies for rheumatologic conditions, including many diseases for which no FDA-approved therapies are available, face tremendous hurdles and delays in gaining access to treatments due to the inappropriate use of restrictions in coverage based on FDA labeling. The ACR recommends such practices be abandoned and supports consistent policies that allow fair access to medically appropriate drugs both on- and off-label.

References:

1 The American College of Rheumatology. Scleroderma (also known as systemic sclerosis). Available at: https://www.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Scleroderma_(also_known_as_systemic_sclerosis). [Last accessed: May 9, 2019]

2 Khanna D, Denton CP. Evidence-based management of rapidly progressing systemic sclerosis. Best Pract Res Clin Rheumatol 2010; 24: 387–400.