AMERICAN COLLEGE OF 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 Food and Drug Administration

POSITIONS:

1. Food and Drug Administration (FDA) drug labels should not be regarded as the sole authority determining the standard of acceptable medical practice.

2. Information on 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. FDA labeling should not preclude "off-label" use of medications. Many rheumatologic conditions are rare, and large-scale studies may not be available to fulfill FDA requirements.

4. The ACR opposes prior authorization denials based solely on the lack of FDA labeling. Payers must fulfill their obligation to their beneficiaries.

5. The process by which to appeal for coverage of off-label treatments with both commercial and government payers must be transparent and streamlined to ensure timely access to prescribed treatment.

6. Correspondence to patients from insurance companies denying off-label drug coverage should not describe the use as 'investigational' when the drug is prescribed as part of routine medical practice since such language is misleading and may threaten the provider-patient relationship.

BACKGROUND:

Prescribing information contained in FDA labels is submitted by manufacturers with new drug applications and provides official descriptions of drugs including indications for use, dosing information, 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. “Safe” in this context means the FDA has determined the benefits of using the drug for a particular condition outweigh its potential risks (1). FDA labels are intentionally silent regarding the use of a drug in circumstances where safety or efficacy data have not been reviewed by the FDA.

FDA regulations do not limit the use of labeled products to indications described on the label. Indeed, FDA guidance explicitly directs providers to use “legally available drugs, biologics and devices according to their best knowledge and judgment” (2). The FDA recognizes off-label use of products as appropriate and elaborates by clarifying that when prescribers “use a product for an indication, not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and sound medical evidence” (2).

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

- There is a paucity of FDA-approved therapies for most systemic autoimmune diseases. For example, systemic sclerosis (SScl) affects approximately 100,000 people in the U.S. and has the highest mortality rate of any autoimmune rheumatic disease (3,4). Sjögren's disease (SjD) is another systemic autoimmune disease commonly treated by rheumatologists and may cause major organ disease in up to 50% of patients (5). Despite the substantial number of Americans affected and the grave threat associated with these diagnoses, there are few FDA-approved therapies for them. Furthermore, some of the FDA-approved medications are labeled by the FDA for treatment of only a few disease manifestations, despite the fact that these are multi-system diseases that commonly involve multiple organs. Thus, rheumatology providers have routinely and appropriately recommended the off-label use of a range of therapies including rituximab, mycophenolate mofetil, hydroxychloroquine, 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 rheumatic indications (rheumatoid arthritis, psoriasis, and polyarticular juvenile idiopathic arthritis).
- Canakinumab is an effective treatment for pediatric patients with periodic fever syndrome and systemic juvenile idiopathic arthritis and is used to treat children under 2 years old despite FDA labeling that recommends age cutoffs of 4 years and 2 years, respectively (6).
- 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 United States as an effective therapy for gout for over a century but only gained FDA approval in 2009 and remains widely used off-label for a number of indications such as calcium pyrophosphate deposition disease (CPPD).

Despite published peer-reviewed evidence and broad clinical experience supporting the use of these and other agents, and despite a lack of suitable alternatives in many instances, insurance coverage is often denied on the basis that they are not FDA-approved.

FDA labels are further limited by the fact that the information they contain is not updated as quickly as advances in accepted medical practice. By default, post-marketing surveillance of new drugs does not begin until the FDA labels are approved. Unfortunately, new information is slow to be incorporated into labels even after that information influences routine practice. 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. 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 these data are 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 judgment."

Government payers also deny and delay coverage for drugs explicitly on the grounds that the drugs are not FDA-approved. Medicare Part D, for example, will only pay for drugs whose off-label use has been listed in one of three officially recognized drug compendia, typically after provider groups go through a burdensome process of submitting supporting literature to the compendium. Access to these compendia is limited and costly and their navigation is beyond most laypeople and providers. These practices delay and limit access to appropriate therapy and thereby harm patients. At a minimum, the process to submit off-label treatment to the compendia must be transparent and streamlined. The sources of information that are used to justify coverage should be expanded to include medications in treatment guidelines from accredited specialty organizations, or treatments recommended in high-quality peer-reviewed publications.

Payers often use misleading or confusing language when trying to justify denials of coverage. Calling off-label use of medication 'investigational' is incorrect, given that FDA guidance defines this as "use of an approved product in the context of a clinical study protocol" (2). Such misuse of the term 'investigational' has the risk of patients questioning whether they might be subject to experimentation, adding to medical mistrust that threatens to erode the provider-patient relationship (7).

In summary, the ACR agrees with the FDA and supports the use of 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.

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