



**2021 FDA-Arthritis Foundation Osteoarthritis  
Drug Development Workshop:**  
Regulatory Considerations on Biomarkers and  
Assessment of Long-term Benefit in OA

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# Outline

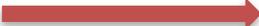
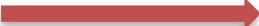
- Benefit-risk Framework
- Biomarkers in OA: Challenges and Opportunities from FDA Perspective
- Summary

# Background

- Significant public health issue, affecting over 30 million people in the US<sup>1</sup>
- Causes significant pain and disability
- Can be a serious disease<sup>2</sup>
- Current treatment options limited to symptomatic therapies and have toxicities
- Unmet need for therapies that would impact the natural history of OA

<sup>1</sup> Castaneda MG, et al., Arthritis Care and Res (Hoboken), 2016 May; 68(5):574-80

# Benefit-Risk Assessment

- Basis for FDA’s regulatory decision-making
- Benefit = Clinical Benefit = an improvement in how a patient
  - Feels  Feel
  - Functions  Function
  - Survives  Survival (Joint survival)
- Endpoints in trials of OA treatments need to demonstrate the clinical benefit directly or at least be interpretable with respect to the clinical benefit to be expected

# Outcome Measures

- Efficacy assessment
  - Clinical endpoint
    - Measures how a patient feels, functions, or survives
  - Surrogate endpoint
    - A measure expected to predict clinical benefit or harm
  - Biomarker
    - Objective measure of normal biologic process, pathogenic process, or pharmacologic response to an intervention
- Safety assessment
  - Descriptive and empiric
  - Guided by drug class, prior experience, events of interest, etc.

# Current Approach of Drug Development for OA

- Drugs approved for OA to date have been approved based on patient-reported outcomes (PROs) assessing two key OA domains
  - Pain  Feel
  - Function  Function

## Structural Outcomes in OA: Challenges

- Clinical benefits related to inhibition of structural damage remain elusive to capture in OA and represent an unmet need
  - Structural Outcomes  Biomarker, ? Surrogate
- Treatment affects one of multiple pathways
  - What magnitude, duration of effect on structural outcome is required?<sup>1</sup>
  - Do on-target effects outweigh off-target effects?

Complex Relationships:  
*Disease – BM – Clin Outcome*

- **Correlation between a biomarker and a clinical endpoint is not sufficient** to demonstrate that an effect on the proposed surrogate endpoint will reliably predict an effect on the clinical outcomes of interest
- **Ideally**, this demonstration would be based on empirical evidence from randomized, controlled comparisons from clinical trials and/or on a comprehensive understanding of the disease process and drug mechanism of action



## Biomarkers in OA: Challenges

- Endpoints are needed to reliably assess the ability of a product to alter OA disease progression
- Knowledge gaps in the relationship between the structural/pathophysiological elements of OA and the clinical outcomes of OA apply to imaging and other biomarkers
- To use structural outcomes in the benefit-risk assessment, we need to be able to describe the clinical benefit expected from the structural change
- Structural outcomes could be used in addition to clinical outcomes in OA trials

## Biomarkers in OA: Challenges

- Approaches to use of structural or other biomarkers in OA trials will depend on level of information available to characterize clinical benefit
  - With less information, structural outcomes may still be useful as adjunct or secondary endpoints
  - To be used as the primary endpoint to support approval, a high level of characterization would be needed about the relationship of the endpoint to the anticipated defined clinical benefit

## Biomarkers in OA: Opportunities

- Study designs to assess direct clinical benefit of therapies that inhibit structural damage or target the underlying pathophysiology associated with OA
  - Composite endpoints that capture joint replacement, and “end-stage” joint disease, i.e. the severe, irreversible, intolerable pain or functional impairment
  - Enrichment strategies
    - Models of accelerated OA
    - Trials in subjects prior to knee replacement
  - Innovative clinical trials, i.e. platform, pragmatic trials

# Summary

- Complex relationship between pathophysiology, structural damage, and clinical outcomes in OA
- Ultimately, the goal of OA treatments is to provide **clinical benefit to the patient**
  - Goal of clinical trials is to demonstrate this benefit
- FDA recognizes the important public health need in OA and wants to collaborate with sponsors and other stakeholders to bring safe and effective treatments for OA to market

# Key References

- OA Guidance
  - <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071577.pdf>
  
- OA Patient-Focused Drug Development (PFDD)
  - <https://www.arthritis.org/Documents/Sections/Science/OA-Voice-of-the-Patient-Report.pdf>



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