Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment

Guidance for Industry

DRAFT GUIDANCE

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION AND BACKGROUND

The purpose of his guidance is to assist sponsors who are developing drugs, devices, or biological products (medical products) to treat the underlying pathophysiology and structural progression of osteoarthritis (OA).[2]

Approvals for OA to date have been based on patient-reported outcome measures that assess pain and function. However, treatments that inhibit structural damage or target the underlying pathophysiology associated with OA remain elusive and represent an unmet medical need. This draft guidance is intended to serve as a focus for continued discussions among FDA, sponsors of medical products, the academic community, and the public regarding the assessment of structural endpoints. This guidance does not address improvement of symptoms of OA, such as pain or functional impairment. FDA recognizes the importance of these outcomes, which will be addressed in future guidance.[3]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. For drugs and biological products, those topics are addressed in the ICH guidances

[1] This guidance has been prepared by the Division of Pulmonary, Allergy, and Rheumatology in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] The previous draft guidance for industry *Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA)*, published July 15, 1999, has been withdrawn.

for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. CONSIDERATIONS FOR DEVELOPMENT

Sponsors should consider the following regarding structural endpoints for developing medical products for the treatment of OA:

- FDA recognizes that OA can be a serious disease with an unmet medical need for therapies that modify the underlying pathophysiology of the disease and potentially change its natural course to prevent long-term disability. However, there are several ongoing issues with developing such products, including the multifactorial and complex etiopathogenesis of the disease, the well-recognized discordance between structural changes and signs/symptoms/function, the lack of standard definitions of disease progression, and, correspondingly, the absence of endpoints to reliably assess the ability of a product to alter OA disease progression.

- Because of the complex and variable pathologic changes through which OA impairs function and leads to long-term disability and/or joint replacement, at this time it is unclear what magnitude of change in structural endpoints would translate to a clinically meaningful benefit to patients (i.e., reliably predict both reduced pain and increased function or prolonged time to end-stage disease). Thus, no structural endpoints have been used for traditional or accelerated approval in OA to date.

- To accept structural endpoints as valid outcome measures for accelerated approval, there should be substantial confidence, either based on empirical evidence from randomized, controlled comparisons from clinical trials and/or based on a comprehensive understanding of the disease process and product mechanism of action, that an effect on the candidate structural endpoint will reliably predict an effect on the clinical outcomes of interest.[5] The ultimate goal of treatments related to inhibition of structural damage or targeting the underlying pathophysiology associated with OA is to avoid or significantly delay the complications of joint failure and the need for joint replacement, and also to reduce the deterioration of function and worsening of pain.

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[5] Fleming TR and Powers JH, 2012, Biomarkers and Surrogate Endpoints in Clinical Trials, Statistics in Medicine, 31.25: 2973–2984.

At this time, the ability of treatment effects on common measures of structural progression to reliably predict treatment effects on direct measures of how patients function and feel, has not been established. Therefore, FDA welcomes efforts to address the above considerations and is open to work with all stakeholders on such programs.