Federal Register Notice: Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment; Draft Guidance for Industry

August 23, 2018

Docket No. FDA-2018-D-2896

EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) has recently published a Federal Register notice requesting comments on a new draft guidance for industry entitled *Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment.* The purpose of the draft guidance is to assist sponsors who are developing drugs, devices, or biological products to treat the underlying pathophysiology and structural progression of osteoarthritis (OA). The draft guidance does not address improvement of the signs and symptoms of OA, such as pain or functional impairment, which will be addressed in future guidances.

In 2011, the Osteoarthritis Research Society International (OARSI) responded to a Federal Register Notice published in August of 2007, seeking a critical appraisal on a number of questions that would help to inform the updating of the 1999 guidance for *Clinical Development Programs for Human Drugs, Biological Products, and Medical Devices for the Treatment and Prevention of Osteoarthritis,* [Docket No. 1998D-0077 (formerly 98D-0077)]. Dr. Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research, responded that the OARSI response highlighted vital issues that could benefit from further research such as approaches for clinical trial design and analysis, endpoints and progression of disease.

Subsequently, in response to the *FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* published in 2014, OARSI submitted a White Paper to the FDA in December of 2016 providing a comprehensive review of OA as a potentially serious disease. The goal of this White Paper was to demonstrate that evidence from numerous data analyses provided justification for the consideration of allowing the use of surrogate markers in studies of some patients with OA for the early approval of structure modifying drugs per subpart H and E of the Food and Drug Cosmetic Act. The White Paper was distributed internally at the FDA and subsequently OARSI received feedback that the FDA would be interested in receiving a description of scenarios for post-approval studies, if a drug were to be provisionally approved on the basis of a surrogate, to demonstrate the clinical relevance of the surrogate measure.

As a result, an OARSI committee was established to consider potential post-approval study design scenarios that could be applied to applications for new therapies which might impact structural progression. These study design scenarios are discussed below. Additionally, we are also providing the aforementioned previously submitted documents, specifically the critical appraisal submitted in 2011 as well as the White Paper submitted in 2016. As there have been some advances since the critical appraisal was submitted, an addendum was created to provide important updates on the understanding of OA, especially the areas of imaging and clinical endpoints.

OARSI has also completed an in-depth appraisal of core and ancillary trial outcomes for structural as well as functional and symptomatic endpoints. This appraisal was published in 2015 as a full issue of Osteoarthritis & Cartilage (Volume 23). Lastly, OARSI continues to participate in the FNIH qualification of biochemical and imaging biomarkers for prediction of OA progression and the results may influence potential new guidance documents.

In the August 2018 draft guidance, *Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment; Draft Guidance for Industry*, the FDA acknowledged that OA can be a serious disease in some patients 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 or overall mortality, thus allowing a pathway for use of surrogate markers as evidence for accelerated approval of treatments for OA with subsequent post approval requirements to demonstrate clinical relevance of the outcome thresholds used for drug approvals.

With the totality of the work undertaken by OARSI, a public meeting is being planned by OARSI during the first quarter of 2019 to allow for an open dialog on the issues surrounding the development of therapies that treat structural progression of OA and the continued unmet medical need for new therapies being available to patients diagnosed with OA. OARSI appreciates this unprecedented opportunity to advance treatments for this prevalent, serious and disabling condition.

OARSI RESPONSE TO:

- **FEDERAL REGISTER NOTICE**
- **REQUEST FOR POTENTIAL POST APPROVAL STUDY DESIGNS FOR DRUGS APPROVED ON THE BASIS OF A SURROGATE ENDPOINT**

The current understanding is that drugs are approved in the United States based upon evidence from adequate and well-controlled trials demonstrating the clinical benefit of how a patient feels, functions or survives along with identifying potential harms of the therapy. In 1992, the FDA instituted the accelerated approval regulations, allowing for drugs being developed for serious conditions and fulfilling an unmet medical need, to utilize the pathway for approval on the basis of a surrogate endpoint which might be a biomarker, either soluble or imaging, which would be reasonably likely to predict a clinical outcome.[1] In 2014, the FDA published a *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*. In response, OARSI submitted a White Paper to the FDA demonstrating that OA was a serious disease. Subsequently, OARSI received a request from the FDA to provide clinical trial scenarios that would allow such an approach to be applied to applications for new therapies which might impact structural progression. It was suggested that standard measured benefits such as signs and symptoms might not be achieved concomitantly with improvements in structural characteristics due to problems with the timing of these measurements, as well as powering of trials for various complex outcomes.

The use of imaging and/or biochemical markers during disease modifying OA drug (DMOAD) trials could potentially provide early indications of a potential treatment's effect on structure. Initial approval on the basis of a surrogate could allow for marketing of a product and the acquisition of revenue to facilitate the funding of the required post-marketing confirmation trials with patient report outcome (PRO) endpoints and/or joint survival assessments to verify and describe its clinical benefit, as required under the FDA's accelerated approval regulations (21 CFR 314.510) when there is uncertainty as to the relationship of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.510)

PROPOSED POST MARKETING STUDY DESIGNS FOR DRUGS APPROVED UNDER SUBPART E OR H: ONE SIZE DOES NOT FIT ALL

For the purposes of DMOAD claims, OARSI proposes two major study design scenarios (**Figures 1 and 2**) and describes variations on these designs as well as the drug profile categories (**Table 1**) to which they might apply. These trials involve an initial Phase 3 trial period of up to 2 years with collection of surrogate and patient-reported outcomes (PRO) with initial approval based on the surrogate. In one case, the subsequent phase of the trial follows the same patients over an additional period of time (to be determined based on the anticipated time to an effect of treatment on a clinical endpoint) with collection of PROs and/or some measure of joint survival.

For both scenarios, it is important to note that the consideration to pursue either one of these strategies could be predicated upon the failure, or likelihood of failure to attain a treatment effect on a clinically relevant outcome within a time frame that is reasonable within a standard drug development program. When the PRO is not achievable in the short-term, an accelerated (conditional) approval might be sought on the basis of a surrogate endpoint likely to predict clinical benefit in a longer study.

Table 1. OA general drug profile categories.

Drug Profile	Description of Profile	Expectations	Type of Approval	Challenge to the sponsors
Pain-lowering-anticatabolic-profile	• Candidate which demonstrates durable symptomatic and/or functional benefit in a Phase 3 trial,	• The structural EP might have failed because of a short trial duration (one or two years only); the profile is similar to a	• Traditional approval for a signs/symptoms claim • Post-marketing study to determine DMOAD effect	• Cost of drug based on signs/symptom benefit • Difficulty later changing cost to get return on additional investment

	but does not achieve statistical difference or the MCID on a radiographic structural endpoint	NSAID after Phase 3	• Concurrent accelerated or subsequent traditional approval of a DMOAD claim on the basis of an MRI surrogate?	required to show DMOAD effect • Difficulty in powering a trial for both signs and symptoms and DMOAD effect within a time frame which can reflect change in both
Pure-anticatabolic-profile	• A drug candidate which demonstrates statistical difference on structure (less worsening compared to placebo) but failed to demonstrate symptomatic and/or functional benefit in a Phase 3 trial	• It might be expected that the structural difference to placebo will result in clinical benefit in longer trials (e.g., by less worsening on symptoms and/or function or by delaying joint replacements); the profile is similar to a protease blocker without immediate direct effects on symptoms and/or function	• Accelerated approval on the basis of an OA progression surrogate EP • Post-marketing trial to confirm benefit on signs/symptoms	• Risk of post-marketing withdrawal of regulatory approval for drug if it fails to show benefit for signs/symptoms
Pure-anabolic-profile	• Candidate which demonstrates statistical difference on	• It might be expected that the structural difference to placebo will	• Based on draft 1999 FDA guidance (withdrawn in August 2018),	• Need to show, for instance by specialized imaging, that growth of

	structure by increasing cartilage or some other change demonstrating no worsening such as less change in shape of the joint but failing to demonstrate symptomatic and/or functional benefit in a Phase 3 trial	result in clinical benefit in longer trials (e.g., by less worsening on symptoms and/or function or by delaying joint replacements; the profile is similar to a growth factor without direct effects on symptoms and/or function	demonstration of new or regrowth of cartilage or other change would be convincing and require no formal parallel concomitant evidence of improvement in clinical outcomes • Alternatively, could pursue accelerated approval on the basis of a surrogate EP • Post-marketing trial to confirm benefit on signs/symptoms	cartilage is functional matrix rather than cartilage swelling alone • Risk of post-marketing withdrawal of regulatory approval for drug if it fails to show benefit for signs/symptoms
Pain-lowering-anabolic-profile	• Candidate which demonstrates durable symptomatic and/or functional benefit in a Phase 3 trial but does not achieve statistical difference on a structural endpoint	• The structural EP might have failed because of short trial duration of one or two years only or the powering of the trial was such that the appropriate number of subjects was not recruited for the structural endpoint; or the	• Traditional approval for a signs/symptoms claim • Post-marketing study to determine DMOAD effect with possible addition of DMOAD claim	• If DMOAD effect shown subsequent to clinical availability of drug, difficulty later changing cost to get return on additional investment required to show DMOAD effect

	despite anabolic properties	recruited subject population did not reflect the concept of rapid progressors so that the change in progression could not be measured in the relatively short time frame of a signs and symptom benefit • The profile is similar to a growth factor with some direct effects on symptoms and/or function		

EP = Endpoint; MCID=minimal clinical important difference; DMOAD=disease modifying OA drug

SCENARIO 1 (FIGURE 1): PROSPECTIVE TRIAL CONTINUATION

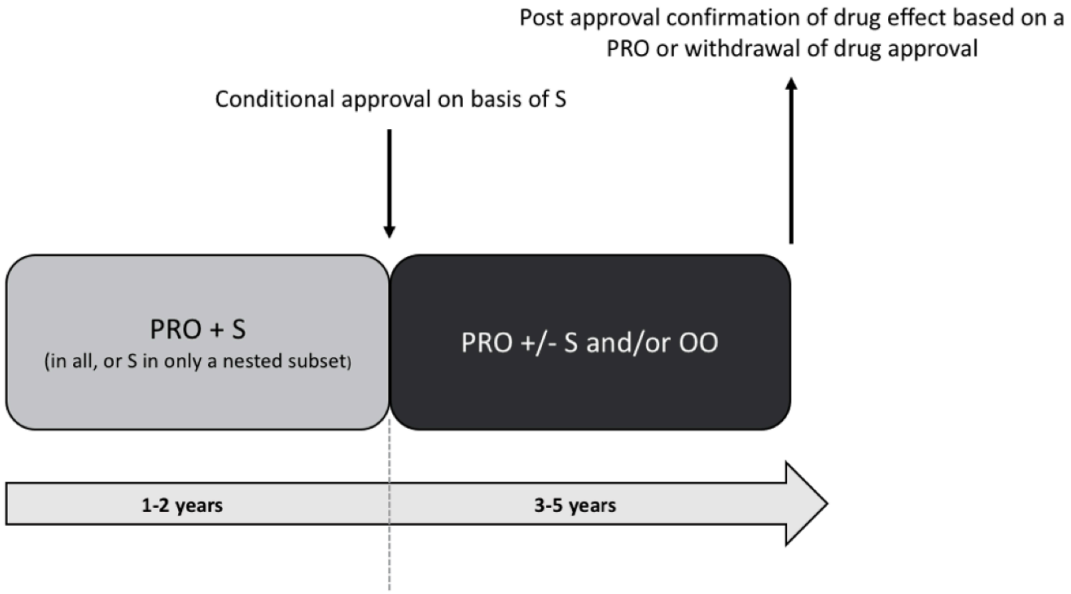
This scenario represents the continuation, post-approval, of the Phase 3, double-blind, placebo-controlled trial. The post approval (approval based on a surrogate) study population contains the same patients as the original trial. The following characteristics and possible variations on this study design are as follows:

- The surrogate (S) in the initial phase may be measured in all or only a subset of the study population (determined based on study power estimates for the S and PRO outcomes);
- Inclusion of the surrogate, as an example cartilage thickness as measured by MRI, in the post marketing approval (PMA) study is optional; it is however valuable to show that the change in the surrogate in the pre-approval study is linked to a PRO or potentially observational outcome (OO) and this would best be shown in the same patients and such evidence accrued post approval would help to determine durability of the DMOAD response;
- Continue all patients on initial drug allocation into the PMA trial until a failure threshold is achieved; this could allow crossover of placebo treated patients to active agent or exit from trial; for placebo patients transitioned to active treatment, their failure to 'catch up' to patients treated with active agent for the entire study duration (throughout the pre-approval and PMA study) would be evidence of drug efficacy and a persistent treatment effect on the disease course; failure

threshold(s) would have to be defined a priori (e.g.,based on a certain amount of rescue medication use, or attainment of a threshold level of pain or disability);

- Alternatively, at the start of the PMA study, re-randomize all patients (placebo and treated) to low and high active treatment and follow rates of OA progression; such a design would facilitate retention of the maximal number of patients from the pre-approval study in the PMA study as no one would be on placebo once the agent is approved and available clinically/commercially; greater numbers of individuals retained from the initial trial would provide a larger patient population in which to monitor for adverse effects in the post-conditional approval phase. Statistical analysis likely would require within prior group (placebo vs treated) comparisons; alternatively, only prior treated patients could be retained in the PMA to avoid this issue;
- An endpoint might be Time-To-Event (TTE) of replacement surgeries or clinically relevant symptom worsening such as pain or function or whatever is first (see discussion below).

Figure 1: Scenario 1 – Prospective Trial Continuation*



Abbreviations:
PRO: (meaningful patient reported outcome (how a patient feels, functions)
S: surrogate (biomarker)
OO: observational outcome (e.g., joint replacement)

*Study Population is the **SAME** as for Original Trial

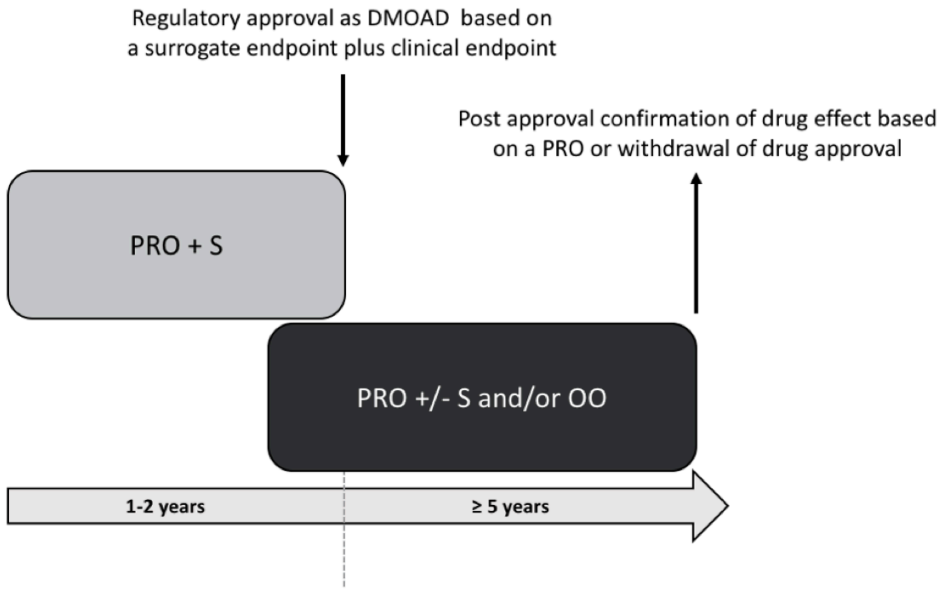
SCENARIO 2 (FIGURE 2): SEPARATE PMA STUDY

There are circumstances in which the Phase 3 study could be amended or adapted to be a PMA study, especially if the demonstration of symptomatic and/or functional benefit is needed and the prolongation

of a placebo-controlled study for one or two years might be appropriate (Scenario 1). Other profiles may need to demonstrate an effect on structure or even joint survival which might be more appropriate in a study population which is enriched for progressors. In this case, the PMA study might be conducted as a separate study as in Scenario 2. A combination of the two scenarios are possible as well. The following characteristics and possible variations on this study design are as follows:

- The PMA study population is different than the population in the original trial (although some patients may be the same);
- Inclusion criteria in this PMA study might be different from the pre-approval or pre-registrational trial;
- All patients may be on active (high vs low dose) treatment in this PMA study;
- An endpoint might be Time-To-Event (TTE) of replacement surgeries or clinically relevant symptom worsening including pain or function or whatever is first.

Figure 2: Scenario 2 – Separate Post-Marketing Approval Study*



Abbreviations:
PRO: (meaningful patient reported outcome (how a patient feels, functions)
S: surrogate (biomarker)
OO: observational outcome (e.g., joint replacement)

*Study Population contains **SOME** or **NONE** of the Original Trial subjects as a nested cohort

USE OF JOINT REPLACEMENT OUTCOMES IN POST-MARKETING CONFIRMATORY TRIALS

Although the ultimate proof of DMOAD activity could be demonstrated by delay (TTE) or eliminating consideration of joint replacement surgery, this outcome poses considerable barriers. While clinical benefit in the case of "joint survival" is clear, this outcome as an endpoint measurement for clinical trials poses challenges due to the need for long study durations, large sample sizes and the impact of non-disease and other factors on the outcome (e.g., level of patient education, cost, physician willingness to operate based on health status, comorbidities, and/or age of the patient). So, although joint replacement can be considered an observational outcome, it is impacted by numerous subjective factors. For knee OA, the time frame for a study using a joint replacement outcome is most likely more than 5 years for the KL2/3 population (7-11 years depending on the sample size).[2] There are no consensus criteria guiding patient recommendations regarding replacement surgery; this results in the obvious problem of differences between countries, regions and even centers within the same region. If these differences are adequately addressed by the study design, (e.g., by randomization per study center), then the TTE of the replacement surgery might represent a feasible primary endpoint. Furthermore, the development of a composite endpoint to include TTE of total knee replacement and symptoms, which in general consensus leads to a clinical determination of the need to recommend replacement, (e.g., extent of pain, presence of night time pain, a measure of pain interference along with both PRO and or measured functional outcomes) might be preferable.

USE OF PLACEBO IN POST-MARKETING CONFIRMATORY TRIALS

The study designs may be different for the first drug to market compared to the second drug to market. For instance, subsequent drugs may be compared to existing drugs on the market rather than placebo, particularly if patient harm is anticipated due to placebo treatment once any effective disease treatment is available. This might require robust non-inferiority margins if that route was chosen or superiority studies which might be difficult to develop and at which to succeed.

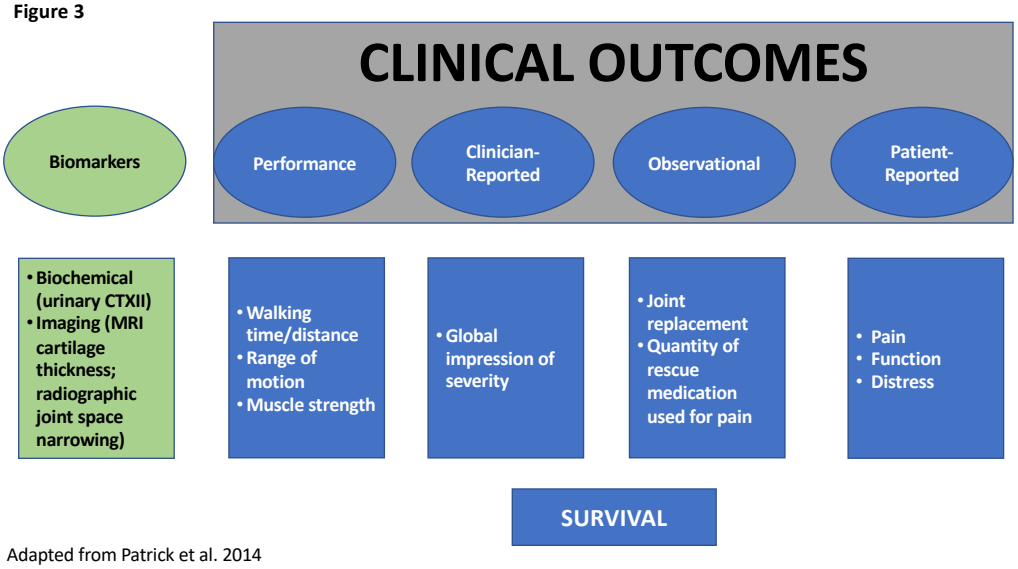
All post approval confirmatory studies must address a fundamental question: How can a patient be kept in the study if the drug is generally available commercially? It is unlikely that a patient would accept the risk of randomization into the placebo or even standard of care arm once the drug is available clinically/commercially, particularly when a prolonged use of placebo in a PMA study would be anticipated. A precedent has been established in the FDA guidance on rheumatoid arthritis (RA) trials for limiting the exposure of patients to placebo or ineffective therapies for a prolonged period of time (i.e., beyond 12 weeks).[3] It is recommended that studies longer than 12-weeks should include an active comparator as the control or provisions for rescue treatment for patients with active disease. Procedures for enabling prolonged PMA studies could therefore possibly maintain blinding until a study participant reaches a failure endpoint; patients on placebo could be offered active treatment at that time; patients on active treatment reaching a failure endpoint would be considered treatment failures and withdrawn from the study, but continued to be followed. This scenario would require the establishment of threshold criteria for failure. Alternatively, the study could be designed to treat all patients with the active agent, comparing high versus low dose levels of the active drug without a placebo arm. This variation might be appropriate for each of the scenarios. Of note, this trial option (high versus low dose without placebo) for symptom and structure claims was embodied in the 1999 draft clinical trial guidance for OA drug

development (withdrawn August 2018), that encouraged "at least one trial showing superiority of the test product to placebo, to a lower dose of the agent, or to an active control".[4] Another pragmatic option would be to offer all patients an exercise (core) treatment representing a high standard of care as "background therapy" and thereby promote their retention in the PMA study, whether on active or placebo treatment.

POSSIBLE OUTCOMES FOR POST-MARKETING APPROVAL STUDY AND USE OF REAL-WORLD EVIDENCE (RWE) IN OA TRIALS

In traditional trials, direct evidence of treatment benefit is derived from clinical trial effectiveness endpoints that measure survival or a meaningful aspect of how a patient feels or functions in daily life. There are four types of clinical outcomes that may support either direct or indirect evidence of a treatment benefit (**Figure 3**).

Figure 3



Adapted from Patrick et al. 2014

The clinical outcome assessments include:

- Patient-reported outcome (PRO) measures (objectively reported symptoms and function such as with WOMAC or KOOS scores in OA that could lead to the derivation of a TTE of clinically relevant symptomatic worsening);

- Clinician-reported outcome (ClinRO) measures (ratings based on specific professional training such as physician global assessment);
- Observer-Reported outcome (ObsRO) measures (items assessing directly reportable behavior without interpretation or interference such as total joint replacement and quantity of rescue medication used for pain);
- Performance outcome (PerfO) measures (objectively measured function such as 6-minute walk test).

The 21st Century Cures Act, approved December 2016, *(docs.house.gov/billsthisweek/20161128/CPRT-114-HPRT-RU00-SAHR34.pdf*) includes a provision for post-approval studies to include clinical evidence, clinical studies, patient registries, or other sources of real-world evidence, such as electronic health records, collection of larger confirmatory datasets or post-approval monitoring of all patients treated prior to approval of the therapy. An electronic medical record based assessment of effectiveness could show paradoxically negative results because of biased loss to follow up (patients return for care when they are faring poorly and stay home when they are doing well).

Conclusion

OARSI has attempted in this response to address two issues. The first is related to the FDA Divisional response to the submitted White Paper demonstrating that for some patients who suffer OA, the disease represents a serious threat to their health, thus allowing for the development and subsequent approval of therapies which might be marketed based on data demonstrating improvements in identified surrogate markers of benefit. The FDA requested that OARSI identify study designs that might be considered under these circumstances. This document describes several scenarios for the FDA to consider. One would be randomized controlled trials to demonstrate benefit of a surrogate outcome with the same patient cohorts being studied post approval to establish the beneficial link between the observed surrogate change and subsequent clinically relevant benefits. Additional scenarios have also been provided.

The second issue is related to the recently released FDA guidance entitled: *Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment Guidance for Industry.* This document stated several important issues to be considered when developing therapies that "inhibit structural damage or target the underlying pathophysiology associated with OA". As outlined in the guidance, these concerns include:

1. That OA is "multifactorial" and has a "complex etiopathogenesis";
2. There is a "well-recognized discordance between structural changes and signs, symptoms, and function";
3. There is a" lack of standard definitions of disease progression";
4. There is an "absence of endpoints to reliably assess the ability of a product to alter OA disease progression";

5. “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)”;
6. “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”;
7. “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.

OARSI acknowledges the present paucity of evidence linking structural endpoints with clinically relevant outcomes; however, OARSI also recognizes the role of the FDA in establishing opportunities to afford progress in this regard. Since the studies which demonstrate this link will be long term, complex and likely very expensive, the community of investigators, sponsors and other stakeholders need to reliably understand and work with the FDA to define the manner in which such work can be begun. The Osteoarthritis Initiative and other observational data, although not yet RCTs, have pointed out linkages between progression of cartilage loss and loss of function over time. This preliminary evidence may help to establish some sense of effect size of measured change which might be considered reliable enough to allow the FDA the to consider studies to be performed prospectively in controlled trials to confirm this possibility. Furthermore, the encouragement of applying changes in MRI measurements by the FDA would be helpful to allow more investment in this effort. Finally, since the guidance clearly states that joint failure and the need for joint replacement is an important fundamental outcome, then time to such an event by a priori defined clinical signs and symptoms should also be encouraged as an outcome.

We thank the FDA for considering these issues and welcome the FDA’s participation in a public private collaborative meeting which OARSI is planning in early 2019 to further address these issues.

SOME QUESTIONS FOR REGULATORY CONSULTATION

- Do the two study design paradigms presented capture the majority of variation possible and feasible in OA?
- Is it necessary to link the PRO in the confirmatory study to the biomarker (surrogate) in the initial approval study? Such a linkage is of course of high interest for potential DMOADs with similar modes of action. However, the clinical benefit is the matter of confirmation in the confirmatory trial and not necessarily the retrospective justification of the surrogate.

- Is it feasible to use real world evidence for the post-approval study? The study has to be well-controlled which can be interpreted that a randomization procedure might be required. However, there are several other conflicting circumstances including the substantial placebo effect in OA, particularly for an intraarticular route of administration, which might end up in an imbalanced comparison. The slow progressive nature of the disease also suggests that studies may be of extended duration, which would hinder participant compliance in placebo-controlled investigations.
- Can function (both patient reported and/or measured) be used as a primary outcome in a PMA study? PRO-function and performance-based function have a lower placebo response rate and higher treatment effect than PRO pain in OA trials.[5]
- Can a Time to Event (TTE) study based on joint survival (time to joint replacement) with or without other composite measured components provide ultimate proof of DMOAD activity and used as a design option for confirmatory PMA trials?
- Can the placebo group be switched to active drug in the PMA study? Other disease paradigms cross placebo to active treatment during the confirmatory study phase with failure to catch up as the metric of success.
- How will the OA clinical trial guidance change when MRI measures are qualified as predictors of long-term patient benefits in delaying or preventing the progression to disability or joint replacement related to OA?

REFERENCES

1. FDA, Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014).

2. Kwoh CK, Guehring H, Hannon MJ, Aydemir A. Clinical Relevance of Structural Measures in Knee Osteoarthritis: Baseline Values and Change from Baseline Discriminate Patients Subsequently Receiving Knee Replacement [1207]. *Arthritis Rheumatol.* 2017; 69 (suppl 10).

3. FDA, Draft Guidance for Industry, Rheumatoid Arthritis: Developing Drug Products for Treatment (May 2013).

4. FDA, Draft Guidance for Industry, Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of Osteoarthritis (July 1999).

5. Huang Z, Chen J, Hu Q-S, Huang Q, Ma J, Pei F-X, Shen B, Kraus V. Based on meta-analysis, placebo responses in osteoarthritis trials are less inflated for function compared to pain measures. Seminars in Arthritis & Rheumatism 2018;in review.