CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ARTHRITIS ADVISORY COMMITTEE

DATE OF MEETING: 02/20/98

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AGENDA

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research
Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD

February 20, 1998

Agenda

Proposed: **Guidance for Industry:** Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of **Osteoarthritis (OA)**

8:00 Call to Order, Introductions: Michelle Petri, M.D., Chair
Arthritis Advisory Committee

Meeting Statement: Kathleen Reedy, Executive Secretary
Arthritis Advisory Committee

Welcome and Introduction: Michael Weintraub, M.D., Acting Director, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

Presentation of Document: Kent R. Johnson, M.D., Medical Officer, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

8:30 **Open Public Hearing**

9:00 **Claims**
Pain
Function
Structure
Durability
Delay in New OA Development
Delay in Surgical Joint Development
Other Claims

12:30 **Lunch**

1:30 **Trial Analyses**
Assembling the Evidence
Risk-Benefit Assessment

3:00 **Questions**

4:30 **Summary and Conclusion**

5:00 Adjourn

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APPEARS THIS WAY

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research
Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD

February 20, 1998

Proposed: **Guidance for Industry:** Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of **Osteoarthritis (OA)**

Open Public Hearing

1. Searle: Dr. Steve Geis, Exec Dir Clin Res.
   Standards for Trials
2. John Beery, MD, linking claims to pain relief

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CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ARTHRITIS ADVISORY COMMITTEE

DATE OF MEETING: 02/20/98

QUESTIONS

Arthritis Advisory Committee
February 20, 1998
OsteoArthritis Guidance Document
Questions for Discussion

1. Is the overall claim structure appropriate?

2. In OA trials of novel new agents, is it worth trying to *capture* under the randomized rubric a broader assessment than suggested above? This might be done, for example, by formally defining outcomes described by the patient to include toxicity considerations and to aim to have an endpoint closer to the full risk/benefit expression.

3. Is there a more elegant way to capture *nonsignal joint* activity? Given its strong rationale, should it matter that there is ***no*** experience using such a measurement?

4. Should time be an explicit requirement for ***any*** claim, or should limitations in the data simply be reflected in labeling?

5. Should *pain improvement* and *function improvement* be combined into one claim?

6. Is it best to leave unspecified ***how much*** clinical evidence of pain or function improvement is needed for a structure claim?

7. Are there insurmountable obstacles, which will make designs for the claims *delay in new OA development* and *delay in surgical joint replacement* fatally flawed?

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ARTHRITIS ADVISORY COMMITTEE

DATE OF MEETING: 02/20/98

SLIDES (HANDOUTS)

[redacted]
APPEARS THIS WAY ON ORIGINAL

NICHOLAS BELLAMY MD,MSc,FRCP(Glas),FRCP(Edin),FRCP(C),FACP
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I have reviewed the document, and find it very interesting, although in some places there are clearly some concepts explored that we might all struggle with a little. I will give my comments in accordance with the sequence of issues presented in the document

I. Introduction:
It is true that studies have tended to be short term and focus on hip or knee OA and that there is very little experience with generalized OA. I would also suggest that there is relatively little experience in the area of hand OA with the respect to the types of interventions you are considering.

The sentence "functional measurements, such as pain on walking...." underscores some of the confusion in the literature. In my own mind pain on walking is a measure of pain not of function. The function question would be phrased by way of "difficulty in walking". I do accept that other lower extremity problems as well as those in the spine might modulate the response to the question, although I do feel in the recent versions of the WOMAC we have attempted to provide attribution as to source. You are correct that the patient global assessments could include other joints than a signal joint. We are currently evaluating different phraseologies of the patient global assessment focusing on a signal joint, osteoarthritis as a whole and the patient as a whole. I hope that these data may be available later in the year. We have not explicitly asked about non-signal joint pain global measurement, but this might be one way to capture all non-signal joints, although I feel that an additional measure of OA joints in their entirety would be a useful alternative. You are correct the Lequesne index does not capture specific effects on non-signal joints. I have not seen any investigation of this with the Lequesne Index. We have applied the WOMAC differentially in signal and non-signal joints, and observed different responses suggesting that the index can be targeted on individual joints.

I agree with the general views expressed in the last paragraph of the introduction. But I am not, certain in my own mind, that it is reasonable to require bone density markers in all future OA trials. This would be a very interesting issue to debate.

II. Claims for the treatment of OA

This is a difficult area, since the relationship between pain, function and structural damage is a complex one. The first sentence of the second paragraph of this section causes me some concern. What is the definition of "no major deterioration"? Furthermore, the requirement that the non signal joint not deteriorate may be problematic if the signal joint selection is based on a radiographic criterion which does not take into account the possibility of more severe disease in the controlateral joint. In other words, a patient with bilateral disease in whom there is bone on bone contact in the right knee but 2.5 mm of interbone distance in the left knee might be allowed to enter the study on the basis of the "good knee" while the controlateral knee may be so severely damaged that it is destined to deteriorate in any case. This will need to be considered in drafting a revised document.

The sentence reading "slowing of structural deterioration will be recognized as a claim, **provided some clinical benefit also is demonstrated**", is problematic in that the time frame over which clinical benefit is derived may be considerably longer than the time frame over which slowing of structural deterioration may be detectable. For example, if the rate of structural deterioration is slowed by 20% over 2 years, it may not be until years 5 or 6 that the clinical consequence of this reduced rate of slowing becomes evident. I presume that this issue can be resolved through cost effectiveness studies, or some similar strategy. I assume that there is an upper limit to the duration of time over which it is reasonable to give a structure modifying drug with out seeing any clinical benefit. The final sentence of the claims sections is as you know problematic. It is difficult to know who does not have OA, because of the disparity of symptoms, plain radiographs, MRI and arthroscopy. It will, therefore, be difficult to know the point at which it can be claimed that OA has <u>not yet</u> developed. By what criterion? Also as you know the time to total joint surgery can be influenced by a number of factors quite remote from the symptoms or the structural status of the joint.

A. Pain

I really think before promoting nonsignal joint patient global measurement that an attempt should be made to understand the clinimetric properties of a standard instrument for measuring this aspect of health, since there is considerable variability in the configuration of joint involvement in OA.

III. Trial Analyses

The method for analyzing clinical trials data has been well described and is perfectly familiar to you. As you will know from the presence of FDA observers at the recent OARS Response Criteria Initiative meeting in Paris last weekend, we are attempting to develop a set of response criteria for future Phase 3 clinical trials in OA of the hip and knee. This may be an additional way of examining the response to treatment. At the present time the initiative does not include consideration of measures of tolerability/safety or of structural progression.

IV. Assembling the Evidence

I am basically in agreement with the contents of this section. I feel that it is important to encourage the collection of candidate surrogates, particularly biologic markers. As recommended at OMERACT III and by the OARS Task Force two years ago, I do subscribe to the view that investigators should be encouraged to use health related quality of life measures in order that this aspect of the effect of interventions can be assessed and some decision made regarding the value of such instruments in future Phase 3 clinical trials.

V. Overall Risk-Benefit Assessment

I am basically in agreement with the contents of this section.

APPEARS THIS WAY
ON ORIGINAL

Questions for Discussion

Kent I would like to make a brief response to these questions, although clearly I would prefer to have been present at the discussion before taking a final position. So my comments are preliminary, but nevertheless, they are as follows:

Question 1. Yes, I believe the claim structure is appropriate. I am concerned, however, that the rate of slowing in structural progression may be so gradual that the benefits may not acrue for several years, and that this may be out with the scope of most studies, and most companies.

Question 2. I feel that individual response criteria, or other composite index of outcome, would encompass clinical efficacy, toxicity/safety, and structural damage into a single end point.

Question 3. You are correct that there is no experience using a measure of nonsignal joint activity. We have some experience in this area, but it is quite limited. In my mind the key issues relate to the phraseology of the question(s), and the scale on which the response will be recorded. I feel that patients do have the capacity to differentiate the effects of one joint from another. Although clearly this is simpler for pain, and that the site of origin can be easily ascertained than for function, since normal lower limb functioning is dependent of the integrity of all lower limb joints. This issue becomes, of course, more complex if one wishes to capture nonsignal joints in the upper extremity or even the spine.

Question 4. I don't know the answer to this question, but perhaps the latter would provide an easy solution, since the time requirement may vary for different interventions.

Question 5. My inclination would be to keep pain, and function separate. In general, they tend to move together, but I have observed improvements in pain with out improvements in function, and also, strangely enough, vice versa.

Question 6. I think that at this stage in our knowledge, I would leave the level of improvement in pain or function unspecified.

Question 7. I do not feel that either of these outcomes (i.e. delay in new OA development and delay in surgical joint replacement) are necessarily valid for aforementioned reasons. That is not to say that they can not be quantitated. However, it is very difficult to know when OA starts in a joint, although an operational definition of this, based on an imaging study could be developed. Of course there are a number of factors which determine whether an individual delays their surgical joint replacement and these factors may be quite independent of the efficacy of the intervention. Paradoxically, both of these end points are extremely important, and, therefore, I would not dismiss them, but I would tend to view them as secondary or tertiary outcomes.

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February 10, 1998

Kathleen Reedy
FDA Arthritis Advisory Committee
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APPEARS THIS WAY
ON ORIGINAL

Dear Ms Reedy:

I will not be able to be at the meeting on February 20th, dealing with guidelines for the development of drugs, devices and biological products intended for the treatment of osteoarthritis. I have had a chance to review the draft provided to us in preparation for the meeting and wanted to provide some thoughts about this document.

First, a revision of the guidelines for osteoarthritis is timely because of the many new therapies being developed. Also, I am struck that this is a very difficult area to lay out a prescription for drug development because, unlike recent efforts in rheumatoid arthritis and lupus, there is a paucity of clinical trial and longitudinal information about the intercorrelation of structure, function and pain and about the sensitivity to change of different instruments. However, based on what we do know about the correlations of some of these measures in osteoarthritis and about what we know in rheumatoid arthritis, I did want to make some suggestions about the draft guidelines presented.

In general, I thought the guidelines were reasonable. I thought that the emphasis on nonsignal joints was perhaps excessive. Based on Framingham and other study data, roughly half of people with knee osteoarthritis have only symptoms in one knee and do not necessarily have other symptomatic joints which need to be followed. Thus, in an attempt to evaluate the effect of the new treatment on nonsignal joints, sponsors might be inappropriately encouraged to recruit only subjects who had multiple joints affected by osteoarthritis and not test their new treatment on those with monoarticular disease. That would be unfortunate. Certainly starting off the osteoarthritis section with a section on signal and nonsignal joints overemphasizes the importance of nonsignal joints.

Although separating pain and function indications is intriguing, evidence suggests that these two outcomes almost never diverge. Work originally done in rheumatoid arthritis suggested that pain was highly correlated with physical disability and more recent observational studies in patients with osteoarthritis show consistently that pain and disability are highly correlated. It is hard to imagine how a patient could experience

improvements in one of these parameters and experience the opposite effect in the other. I wonder why we don't consider a symptoms and signs indications like in rheumatoid arthritis. To achieve approval for symptoms and signs, the sponsor could choose either a function or a pain primary efficacy measure or could devise a measure combining pain and function (the WOMAC and Lequesne indicies already do this). This seems more logical than requiring separate claims for pain and function.

Further, I see no reason why demonstration of functional improvement needs to take six months while pain improvement takes only three. Studies of non-steroidals in osteoarthritis using WOMAC has shown significant improvements in function over a ten week clinical trial (see trials by Bellamy). Further, in rheumatiod arthritis, Meenan showed a number of years ago in the Cooperating Clinics trial of gold that the improvement in function occurred pari passu with the improvements in other symptom parameters such as pain. Functional improvement occurs rapidly when pain improvement occurs, and it could be well documented within three months. Requiring longer trials for the demonstration of function claim may discourage sponsors from going after a function claim which would be unfortunate, since functional improvement is so critical in this disease.

Some treatments for structural change in osteoarthritis may not affect symptoms and signs at all. They may neither ameliorate nor worsen symptoms. In the guidelines proposed here, these treatments would not be eligible for a structure claim. Nonetheless, if this type of efficacy were documentable, we should allow a structure claim. The market could readily decide whether such treatments, which may need to be used for many years without any symptom improvement, would actually be prescribed or used by patients. I believe we should require that treatments demonstrate significant improvements in structure compared to placebo and that they don't cause deterioration in symptoms and signs.

Thus, I believe there should be two different claims for which a treatment could gain approval in osteoarthritis. One claim related to symptoms and signs and the other related to structure.

Powering a study for many of the other claims listed here is currently not very feasible and is awfully expensive. To determine whether a particular treatment delayed surgical joint replacement not only requires many subjects but assumes a joint replacement occurs at the same point in everyone's disease course which is terribly problematic. Being involved in a long-term trial may or may not discourage referral for a total joint replacement. If any discouragement occurred, as part of being in a trial in which one outcome was joint replacement, this would almost certainly be unethical. Thus, I would be loath to consider a claim for treatment that delayed surgical joint replacement.

The other claims listed such as those related to durability and delay in new osteoarthritis development are intriguing and could be secondary claims, although not ones that would garner a new treatment approval.

Let me also comment that the assessment of symptoms and signs in osteoarthritis is often tricky. The WOMAC instrument does not specify whether pain is joint specific or person specific. I believe that we should require that a targeted joint show improvement in symptoms. This is different from an improvement in disability which tends to be a person specific matter and not a joint specific matter. Thus, an injected medication into one involved joint could conceivably leave function unchanged if the person had many joints affected by osteoarthritis only some of which were not treated. Further, one could envision a trial in patients with bilateral disease in which the treatment were randomly given to only one of the bilateral joints. Pain might improve in that joint but function would not.

Lastly, as in these draft guidelines, I think it is important to emphasize that in osteoarthritis, evaluation of symptoms and signs can occur without a physical examination and without performance assessment. Assuming the patients actually have documented osteoarthritis, a therapy should be approvable on the basis of self-reported information on the part of the patient. This is contrast to rheumatoid arthritis. This use of self-reported information to evaluate treatment efficacy will make it easier and less expensive to develop treatments for osteoarthritis and should be encouraged.

Once again, I am sorry I cannot make this meeting and hope my comments are helpful to the group.

Sincerely,

David Felson, MD, MPH
Professor of Medicine and Public Health
Consultant, FDA Arthritis Advisory Committee

APPEARS THIS WAY
ON ORIGINAL

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

London, 29 January 1998
CPMP/EWP/784/97

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS USED IN THE TREATMENT OF OSTEOARTHRITIS

DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	October 1997 December 1997
APPROVAL BY THE CPMP	January 1998
RELEASE FOR CONSULTATION	January 1998
DEADLINE FOR COMMENTS	April 1998

Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document related to Osteoarthritis will be revised in accordance with the scientific advances made in this area.

The CPMP's position on this matter is now released for consultation. Any comments you may have should be sent to Dr. Leng Heng at the EMEA secretariat (fax no +44 171 418 8551) by April 1998.

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CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS USED IN THE TREATMENT OF OSTEOARTHRITIS

INTRODUCTION

Osteoarthritis is a disorder which can potentially affect all synovial joints. It is characterised by degeneration and regeneration of articular cartilage and bone. The pathological changes can be focal or more generalised and these changes often correlate poorly with clinical symptoms and signs. However, it has been suggested that asymptomatic osteoarthritis, diagnosed radiologically, is a precursor of symptomatic disease. Osteoarthritis, particularly of the large joints of the lower limbs - for example, knees and hips- is now widely recognised as a major cause of chronic disability in the population.

Currently, there are inconsistencies in the classification of drugs for the treatment of osteoarthritis and the indications for their use.

1 SUMMARY OF THE BACKGROUND PROBLEMS

1. Scope

This concept paper presents guidance for studies addressing pharmaceutical treatments of osteoarthritis only. Use of topical remedies including iontophoresis and intra-articular injections are not dealt with in this paper. Other rheumatic diseases will require separate guidances.

2. Classification of anti-osteoarthritis therapies

Medications for osteoarthritis may affect symptoms and/or modify structures. The nomenclature currently proposed recognises three classes of drugs acting in osteoarthritis: fast-acting drugs that induce symptomatic relief, slow-acting drugs that induce symptomatic relief and disease-modifying drugs.

Arguments for classifying drugs that induce symptomatic relief into fast and slow subgroups are not compelling. Although drugs that act slowly may have different mechanisms of action from those that act rapidly, there is a range of duration of action of drugs which act on symptoms. The design of trials should adequately take into account the timing and duration of the action of the drug on symptoms and these factors may influence the use of any concomitant treatment which is permitted in a trial.

Based on these considerations, drugs for the treatment of osteoarthritis should be classified into two categories:

a) Symptom-modifying drugs

These act on symptoms with no detectable effect on the structural changes of the disease. Registration of such drugs would require demonstration of a favourable effect on symptoms with no detectable adverse effects on the structural changes of the disease.

b) Structure-modifying drugs

These interfere with the progression of the pathological changes in osteoarthritis. These drugs may or may not have an independent effect on symptoms:

1) Structure modifying, symptom relieving drugs

Registration of such drugs would require demonstration of beneficial effects on both symptoms and structural indices of the disease

2) Structure modifying drugs with no direct effect on symptoms

There is good indirect evidence that, by favourably modifying the natural history of osteoarthritis in terms of structural changes, long-term clinical benefit will occur in a large proportion of patients.

II RECOMMENDED PRIMARY/SECONDARY EFFICACY ENDPOINTS

a) Symptom modifying drugs

Pain attributable to the target joint is recommended as primary endpoint for symptom modifying drugs for osteoarthritis. Functional disability is an important additional endpoint for symptom modifying drugs.

Pain

Pain should be measured by self assessment with validated methods, such as visual analogue or Likert scales. Use related and rest pain should be assessed separately. The period of assessment should be defined - for example, now, today, this week. Frequency of measurements of pain should provide an assessment of the time needed for the onset of pain relief as well as an assessment of the duration of the analgesic effect.

Functional disability

A disease specific and joint specific instrument such as the Western Ontario Mac Master University osteoarthritis index (WOMAC) or the Lequesne index is recommended to assess disability arising from osteoarthritis of the hip or the knee.

Secondary end points include:

- Global rating
- Flares
- Physical signs including range of motion
- Quality of life
- Consumption of medications

b) Structure modifying drugs

Some epidemiological data support a relation between structural changes and a long-term clinical outcome. However, the nature and the magnitude of the structural changes that are likely to be clinically relevant on a long-term basis remain debatable. Therefore, hard clinical endpoints, as necessity of joint replacement, time to surgery and long-term clinical evolution (pain and disability) would be preferable to assess the efficacy of such drugs. On the other hand, the radiographic measurement of joint space width or osteophytes seems to be a promising tool to assess the progression of osteoarthritis, although its validity has not still been fully demonstrated. Consistently, and provided that the applicant gives some data supporting this surrogacy, these changes could be considered as alternatives primary endpoints. In all case, hard clinical endpoints, as mentioned above, should be assessed during the study.

Films should be read centrally. Material collected during trials (radiographs) should be kept available for re-reading because the techniques for assessing structural changes may be improved or changed during the course of the trial. Other technologies for the evaluation of the severity of osteoarthritis: chondroscopy, magnetic resonance imaging, scintigraphy, ultrasonography, biochemical measurements (serum, urine, joint fluids) may be considered as secondary endpoints. Obtaining reproducible X-rays on successive visits is a prerequisite for reliable assessment of progression of osteoarthritis. The sources of variability in joint space width measurement are numerous (patient positioning, radiographic procedure, measurement process, etc). It is essential to standardise radiographic technique based on published, validated data. The method should define the radio-anatomic position of the joint, beam alignment, and should define the anatomic landmarks for measurements. Positioning of the patient should also be based on validated published methods, but in all cases, weight bearing (standing) anteroposterior views should be used in studies involving the hip or the knee. Repositioning of the joint can be facilitated by use of foot maps drawn at the time of the initial examination. Correction for radiographic magnification has been shown to improve accuracy and precision of measurements.

Even though a structure modifying drug may not have an independent effect on symptoms, clinical signs and symptoms (as mentioned on II a) symptoms modifying drugs) need to be assessed.

If both symptoms modifying effect and structure modifying effect are claimed, the requirements under both II a) and II b) should be fulfilled.

Table1: Recommended end-points for structure modifying drugs

Primary End-points	Secondary End-points
Radiographic score Pain Functional Disability	Supportive Imaging Technique (MRI, Chondroscopy, Scintigraphy, Ultrasonography) Biochemical Markers

III MAIN FEATURES OF CLINICAL TRIAL DESIGNS FOR ASSESSING DOSE-FINDING AND THERAPEUTIC COMPARATIVE TRIALS

1. Study population

Osteoarthritis is a heterogeneous disorder. Observing an effect of a treatment for osteoarthritis in a major joint does not necessarily mean that it will be effective in every joint.

It is the responsibility of the applicant to show that a proven therapeutic effect in a major joint can be extrapolated to other joints. Clinical trials aimed at evaluating the effect of drugs in osteoarthritis of the hand are better focused on assessing progression of the disease in proximal and distal interphalangeal joints than in trapezo-metacarpal joint. Although osteoarthritis of the hand is a potential target for assessing evolution of disease in trials, it is less important clinically than hip or knee disease. Osteoarthritis of the hip is a common and disabling disease. Osteoarthritis of the knee is also both very common and a major cause of

disability. Currently, outcome measures for both symptoms and structures are better validated for medial tibiofemoral disease than for lateral or patello-femoral disease. If the spine is used as the target joint it is the responsibility of the applicant to demonstrate the validity of the endpoints chosen and their clinical relevance.

To improve the homogeneity of the patient groups studied, inclusion criteria should limit the target joint to a single site. However, simultaneous assessment of other joints is always possible and such results might generate supportive evidence for « general » efficacy. The presentation and natural history of the condition may be different in younger and older age groups. Therefore the age range of patients to be entered needs to be pre-selected and specified. A narrower age range will increase group homogeneity, possibly at the expense of the generalisability of the data obtained.

To be enrolled in a study, patients should have both symptomatic and structural changes of osteoarthritis in the target joint. Currently, this will mean pain related to use with radiological evidence of joint space narrowing for osteoarthritis of the hip and knee, and the diagnostic criteria of the American College of Rheumatology for hand osteoarthritis.

For studies of structure modifying drugs, the inclusion of phase II studies of special subpopulations of subjects who are at high risk for development of osteoarthritis or rapidly progressive osteoarthritis may be advantageous (i.e., obese women with unilateral radiographical osteoarthritis and men or women who have undergone meniscectomy). However, inclusions of a specific risk group in phase III studies might decrease the potential for generalisation of the results.

It is recommended that patients should be excluded on the basis of secondary osteoarthritis if they have a history or present evidence of any of the following diseases in the potential target joint:

- Septic arthritis
- Inflammatory joint disease
- Gout
- Recurrent episodes of pseudo-gout
- Paget's disease
- Articular fracture
- Ochronosis
- Acromegaly
- Haemochromatosis
- Wilson's disease
- Primary osteochondromatosis
- Heritable disorders (e.g. hypermobility)

Pain and disability at entry need to be recorded. However, the minimum severity of symptoms related to disease in the target joint at entry will depend on the primary outcome measure being assessed, the potential mode of action of the drug, and the joint sites involved. For example, a higher baseline level of pain may be appropriate for entry into a trial of a symptom-modifying drug than a trial of a structure-modifying drug.

The severity of radiological changes in the target joint at entry should be established.

For studies of symptomatic response, the level of symptoms at baseline should be of sufficient severity to permit detection of changes.

For studies of structure-modifying drugs, the following should be considered: Kellgren and Lawrence radiographic entry criteria: grades 2 or 3 (i.e., sufficient remaining interbone distance to permit detection of worsening/progression).

Factors that might affect the rate of evolution of osteoarthritis including age, sex, obesity, major joints injury, types of use, development abnormalities, familiar osteoarthritis must be recorded. These factors should be stratified at entry or adjusted at data analysis.

2. Concomitant interventions

All symptom-oriented studies require discontinuation of prior analgesic and anti-inflammatory medications, including topical agents and steroid injections, prior to initiating treatment with the test drug in order to permit an evaluation of unmodified pain severity. The time of withdrawal should be the time required for the clinical effect to disappear (e.g., 5 half-lives of drug).

Many patients with osteoarthritis who are recruited for trials are likely to have exacerbations of symptoms («flares») which require treatment during the study, irrespective of the type of study design used. Such concomitant treatment may interfere with outcome measures, and should ideally be excluded. However, in long term studies it is neither ethical nor practical to exclude all concomitant treatments. For all trials, concomitant treatments (drugs or interventions) that are likely to affect joint structure should be excluded, and rescue treatment (including physical therapy) should be standardised, carefully recorded, and monitored.

3. Study design

a) Phase II studies

Phase II studies should provide data over a range of doses. The doses selected for these studies should enable the minimum effective dose and the dose-response profile to be determined. Evaluation of at least three doses is recommended. Phase II should be performed in accordance with the EU guidelines EDAR/C/93014 for dose-response information to support product authorisation.

Some agents may have both symptom and structure modifying effects, but the optimal dose for modification of symptoms may be different from that which alters structure.

Modification of Symptoms: The duration of phase II studies for symptom modifying effects will depend on the expected outcome and the mode of action of the drug. Normally, even in the case of a slow acting symptom modifying drug, its effects would be expected to be apparent in several months.

Modification of structures: The duration of phase II studies for a drug with structure modifying effects will also depend on its mode of action, but is likely to be longer than that required to assess modification of symptoms. Studies over a range of doses and of sufficient duration to show meaningful changes in structure are required. The magnitude of these changes should be predetermined.

b) Phase III studies

Because of the heterogeneity of osteoarthritis, limiting the number of different joints investigated also can limit the potential for generalisation of the results. In each trial one joint, preferably the hip or the knee, should be selected as the target joint, although simultaneous assessment of further joints is possible. The primary analysis population should be defined

according to the intention to treat principle. The design and the duration of these studies may differ according to the properties of drug.

Modification of symptoms: Studies should have a randomised, double blind, parallel group design. To establish that a symptom modifying drug does not have deleterious effects on the joint, structural changes should be monitored for at least one year.

Modification of structures: Studies should have a randomised, double blind, parallel group design. As stated in section II b), clinical variables, or alternatively structural changes when their surrogacy value is proven, are required as primary endpoints. When structural changes are chosen as primary endpoint, the magnitude of a clinically relevant effect of a drug on such variable should be predetermined based on data solidly established. Due to the expected mechanism of action of these drugs, long-term studies, no shorter than at least two years, will be requested both for efficacy and safety assessment.

IV USE OF PLACEBO AND CHOICE OF COMPARATORS

1. Phase II studies

Pivotal studies should have a placebo-controlled, randomised, double blind, and parallel group design.

2. Phase III studies

For symptom modifying drugs active controlled studies are necessary with the most favourable comparator. Three-arm, placebo and active controlled studies are recommended. It is possible to show that the beneficial effect is sustained long-term by means of a withdrawal study in which actively treated patients, at the end of the study period, are randomised to discontinue or continue (double-blind) treatment.

For structure modification studies should have a randomised, double blind, placebo controlled, parallel group design.

V SPECIAL SAFETY CONSIDERATIONS

For drugs having their primary target tissue outside the joint, safety data for the primary target tissue should be provided, at the dose selected for osteoarthritis and for a duration similar to the one chosen for the phase III pivotal trials. Safety assessment should be consistent with standard CPMP requirements for safety data for long-term treatments.

REFERENCES

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3. Guidelines for testing slow-acting drugs in osteoarthritis (Lequesne et al), (Journal of Rheumatology, 1994, S41, 21, 65-73)

4. Design and conduct of clinical trials in patients with osteoarthritis (Recommendations from a task force of the Osteoarthritis Research Society), (Osteoarthritis and Cartilage, 1996, 4, 217-243)

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Guidance for Industry

Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA)

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*. Copies of this draft guidance are available on the Internet at http://www.fda.gov/cder/guidance/index.htm. For further information on this draft guidance, contact Chin Koerner, Center for Drug Evaluation and Research (HFD-550), 9201 Corporate Blvd., Rockville, MD 20850, 301-827-2090.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA)

I. INTRODUCTION

Current drug treatment in osteoarthritis (OA) is symptomatic. No data are available on the impact of drug therapy on long-term outcomes. Clinical trial experience in OA has been limited to short-term studies in patients with knee or hip OA, with virtually no trial experience in generalized OA. Knee or hip OA trials traditionally have been done with patients who manifest sufficient OA involvement of at least one hip or knee joint. For the purposes of this document, the specific knee or hip joint that qualifies a patient for entry into a knee or hip OA trial is called the *signal joint*. Traditionally, the signal joint has been the focus of the efficacy assessment.

Patients often experience OA at other sites, but assessing the contribution of drug effects on those sites has always been problematic. Functional measurements, such as *pain on walking,* could incorporate drug effects on the lower extremity and spine. *Patient global* assessments could include other joints, in spite of instructions to limit the claim *patient global* to only the signal joint. Additionally, two contemporary, validated functional assessments (the Lequesne and the WOMAC) were not designed to capture specific effects on nonsignal joints. Because it is considered important to ensure an accurate and reliable assessment of the *nonsignal OA*

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[1]This guidance has been prepared by the Rheumatology Working Group of the Medical Policy Coordinating Committee (MPCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. The working group includes members from the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH). This guidance document represents the Agency's current thinking on osteoarthritis. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For additional copies of this guidance, contact the Drug Information Branch, Division of Communications Management, HFD-210, CDER, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-827-4573).

joints, an explicit *nonsignal joint patient global measurement* is being proposed in this draft guidance: a 10cm VAS measurement, which should focus on all joints, except the signal joint, and should function as a secondary efficacy variable in OA trials.

Historically, OA assessment has been empirical and, to a large degree, patient driven. In deciding whether an OA drug ***works***, simple questions are asked: "How much pain do you have?" and "What can you do?" Pain and function are obvious, important assessments, and since pain and function may not tightly associate in OA short term, and may even diverge long term, both should be measured and analyzed simultaneously in OA trials. When assessing pain, the examiner should ask the patient to consider pain only from the signal joint. OA pain has been validated using a Likert scale, or 10cm VAS, with the latter marginally preferable. Alternatively, the pain subsections of the Lequesne or the WOMAC can be averaged and used as a pain measurement, although this will make the measurement of pain and function mathematically interdependent. OA function has been validated for the Lequesne knee and hip instruments and for the WOMAC, which subsumes both knee and hip disease.

In summary, pain, function, structure, and nonsignal joint patient global measurement all have face validity and should be assessed in OA trials. Novel drug development strategies and trial designs in the treatment of OA will be more complicated if the agent proves to have two separately acting mechanisms for its effects on pain and function, so that the dose-response curve for each is substantially different. Furthermore, an agent affecting the signal joints differently from the nonsignal joints would also be of interest. Additional markers, such as biochemical assays reflecting cartilage metabolism, bone density, newer structural assessments, and even arthroscopic measures (visual or even biomechanical, such as cartilage compliance) will be valuable in facilitating OA drug development strategies and will help define correlations with traditional measurements. Given the incomplete understanding of bone and joint physiology, which novel pharmacologic interventions will be detrimental, rather than beneficial, remains unpredictable. Assessing biochemical and bone density markers in OA trials can provide evidence against this concern.

II. CLAIMS FOR THE TREATMENT OF OA

A number of novel approaches are under study for the treatment of OA, as companies, clinicians, and patients search for more effective therapeutics. The label claims below are intended to facilitate the assessment of therapeutics that may result from these approaches. Although label claims have diverse legal and regulatory ramifications, their central purpose is

to inform prescribers and patients about the documented risks and benefits of the product. The claims discussed in this section represent the current views of Agency rheumatologists about achievable and clinically relevant claims for OA.

An agent that positively affects pain or function will be granted a claim for *improvement in pain* or *improvement in function*, respectively, provided there is no major deterioration in the other measurement and in the nonsignal joint patient global measurement. In other words, to support a claim for improvement in pain, a trial should show success in pain measurement and no major worsening in function and in the nonsignal joint global measurement. Changes in structure, currently validated for x-ray measurement of joint space narrowing (JSN) of the hip or knee OA, are important and probably represent a stronger surrogate than biochemical markers. For this reason, *slowing of structural deterioration* will be recognized as a claim, provided some clinical benefit (e.g., improvement in pain or function) also is demonstrated. How much clinical benefit should be demonstrated is as yet undetermined. A *long-term durability* claim demonstrated in trials lasting 2 to 5 years is proposed (similar to rheumatoid arthritis). Finally, *a delay in new OA* claim (i.e., OA has not developed at sites uninvolved at trial outset) and a *delay in time to total joint surgery* claim also are proposed.

A. Pain

The primary efficacy variable is any validated pain scale; secondary endpoints are function and nonsignal joint patient global measurement. Trial duration should normally be at least 3 months or 6 to 12 weeks if there is a large body of similar drugs in the same class — nonsteroidal anti-inflammatory drugs being the only current example.

B. Function

The primary efficacy variable is any validated knee or hip OA function measurement; secondary endpoints are pain improvement and nonsignal joint patient global measurement. Trial duration should normally be at least 6 months.

C. Structure

The primary efficacy variable is currently a comparison of baseline and final radiographic scores for knee or hip JSN, provided some pain or function improvement is also demonstrated. Trial duration should normally be at least 1 year.

D. Durability

The primary efficacy variable is either pain or function improvement, with the other as the secondary variable, along with nonsignal joint patient global measurement, structure improvement, and health-related quality-of-life assessment. Trial duration should normally be 2 to 5 years.

E. Delay in New OA Development

Survival designs should include *time-to-event* analyses. The Agency is asking for comment on whether a duration should be specified, and if so, what duration is appropriate.

F. Delay in Surgical Joint Replacement

Survival designs should include time-to-event analyses. The Agency is asking for comment on whether a duration should be specified, and if so, what duration is appropriate.

G. Other Claims for Which There Exists Face Validity

FDA is asking for comment on trial designs for other claims for which there may exist face validity.

III. TRIAL ANALYSES

Certain trial designs mandate certain analyses and may preclude others. Because in the end, a trial is only as persuasive as its analysis, it is important at the design stage to decide what statistical tests are to be done and on what endpoints. Endpoints need to be evaluated by how compelling they are to the clinician; statistical tests need to be assessed by how artificial the data assumptions are that they impose. Traditionally, OA trial analyses have used statistical tests comparing mean changes from baseline in various endpoints, with, or without, adjustments for multiplicity. Alternatively, trial analyses done with a by-patient rating (e.g., "better," "unchanged," or "worse") seem understandable to practitioners. However, by-patient response definitions are difficult to define upon analysis of the data in protocols because pilot studies are usually inadequate, leaving the risk that the ratings will prove too skewed one way or another.

In trials for claims of pain, function, structure, and durability improvement, either a comparison of groups (e.g., means) or a predefined by-patient comparison is acceptable. If the former is used, the primary endpoint should be the investigative drug being statistically superior to placebo, or statistically non-inferior (as defined in the ICH draft guidance "Statistical Principles for Clinical Trials" (62 FR 25711, May 9, 1997)) to an active control, by predetermined criteria if an active-controlled equivalence design is used, and the secondary endpoints should not normally worsen compared to control. The claims of prevention of new disease and delay in time to total joint surgery should use a straightforward survival analysis.

IV. ASSEMBLING THE EVIDENCE

More than one claim can be pursued in the same trial, and claims can be submitted singly or together. Because the persuasiveness of trials showing a difference is, in general, much greater than that of equivalence trials, it is highly desirable for a claim to be demonstrated in at least one trial showing superiority of the test agent (compared to placebo, a lower dose of the agent, or an active control). If a claim of superiority over a specific drug is sought, it should be substantiated by usually more than one adequate and well-controlled trial showing superiority, that uses doses, target populations, endpoints, and other design features allowing a

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fair comparison. These studies can also be the basis for demonstration of the product's efficacy. Finally, because the field is evolving, collection of candidate surrogates is strongly encouraged, which, if they correlate with standard clinical measures, may enhance the overall persuasiveness of the assembled evidence.

V. OVERALL RISK-BENEFIT ASSESSMENT

Approval is predicated on controlled evidence demonstrating efficacy and acceptable overall risk-benefit. Database requirements generally follow the ICH guidances, but particular attention should be paid to collecting information systematically on known or suspected pharmacologic effects that might lead to undesirable consequences. Finally, approvals for agents for chronic, long-term use may not detect rare, but serious, adverse drug reactions, which, if concern exists (e.g., from the mechanism of action or from prior experience with similar agents), may need to be addressed in a phase 4 program.