In this brief abbreviated review of regulatory issues regarding the development of drugs and or devices for the treatment of osteoarthritis (OA), the steps that are expected by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are discussed.

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Introduction

In both the US and in Europe, drugs are approved on accumulated clinical and nonclinical data which demonstrates the potential benefits and risk of harm in the appropriate patients studied. The benefit of therapies have to in general, define how a patient feels, functions or survives. The development of new therapeutics, either drugs and devices, for the treatment of osteoarthritis (OA) for improvement in signs and symptoms such as pain or decreased function as well as potentially those treatments which will alter the natural history of the disease as determined by altering structural progression, requires a development company to follow guidances developed to provide a roadmap on best practices considered at the time by the regulatory agencies in both the US and in Europe. Table I outlines the development steps followed by a sponsor developing a drug or biologic therapy while interacting with the regulatory agencies which are expected to assure adequate data collection for justifying approval. Table I outlines the steps that a development company would follow if developing a device within the US.

Device development in the US is handled by a branch of the Food and Drug Administration (FDA), the Center for Device and Radiologic Health (CDRH) and is governed by different requirements than drugs or biologic therapeutics. If a device is being developed which is highly similar to one that already has been on the market then the sponsor of that development program can pursue a “510k” procedure which leads, if successful, to the FDA “clearing” the use of the new device. Alternatively, approval of a new device may require a Pre Market Application (PMA) which is a dossier not dissimilar from a New Drug Application (NDA) or Biologic License Application (BLA) reviewed within the Center for Drug Evaluation and Research (CDER).

The process is quite different in the European Community and is mostly dependent on obtaining a CE mark for use across the European Economic Community. The CE mark represents the manufacturer’s declaration that the product meets the requirements of the applicable European Community directives governing the particular device. This is done thru a different group than European Medicines Agency (EMA).

Both the FDA and EMA have been considering the approach to OA for years and have determined that drugs which are developed to alter structural progression will likely have to concomitantly treat the signs and symptoms of OA. However, the EMA has stated that it is possible that structure modification might at a later date provide symptomatic benefits, but this has yet to be proven. In regulatory terms, that means until proven otherwise, a drug proposed to alter the structural progression of OA will need to concomitantly improve a patient’s signs and symptoms. Furthermore, drugs or devices that might be structure modifying, will need to provide evidence over at least 1 year if not longer, to demonstrate
effectiveness of the intervention. In contrast, drugs or devices developed to treat the signs and symptoms of OA of a specific joint typically require randomized controlled trials lasting 12 weeks with a minimum number of patients studied for up to 1 year, since OA is considered a chronic process. This report will not outline the requirements for drugs or devices developed to treat acute pain of OA.

Overall exposure: number of patients required

The number of patients required to be exposed to a specific drug or biologic therapeutic is governed mostly by international agreements. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), requires 1500 patients exposed at any dose, 300–600 patients exposed to the proposed therapeutic dose for three to 6 months, and at least 100 patients exposed for at least 1 year

What would a typical development program look like?

A typical development program will need to have defined first, in non clinical studies in two species, the maximal tolerated dose in the animal as well as a drug serum level where no safety signals are noted or the no affect level is defined. Then, clinical studies will need to define the minimally effective dose, as well as the no affect level of dose, thus the highest dose tolerated but without safety signals in patients. Furthermore, the optimal dose level and dose duration so that timing of dose is also identified. Once that is done, for the development of a new molecular or chemical entity, whether it be a small molecule or a biologic therapy, the sponsor likely needs to succeed with two replicate and adequate and well controlled randomized controlled trials (not necessarily identical trials).

Since OA is a chronic process and although intermittent therapy might be used to alleviate symptoms, the standard design should last for at least 12 weeks at which time the primary outcome is considered. These patients should also be subsequently enrolled into an extension trial for an understanding of safety with longer term exposure to provide for at least 100 patients exposed for 1 year, as noted previously, although the exact number should be defined by the review divisions in the FDA or the scientific advice committee within EMA depending on the mode of action of the purported therapy. This report is part of a larger number of papers discussing various studies to be considered for different forms of OA, and there are separate papers on specific trial designs and statistical analysis plans to be considered.

What about devices?

In the US, devices are developed and governed by the same OA FDA guidance as are drugs and biologic therapies; whereas, in Europe, devices are predominantly governed by uniform

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Table I

What steps are necessary for drug or biological therapy approvals?

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<th>Step</th>
<th>Details</th>
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<tr>
<td><strong>Non clinical safety</strong></td>
<td>Define dose exposures as related to risk, maximally tolerated dose, no effect level in two species. Timed exposure for drugs for chronic therapy to provide “cover” for first in human studies as well as longer term exposure. Study reports have to be signed to be considered complete.</td>
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<td><strong>Pre IND meeting</strong></td>
<td>Held once enough non clinical data is accumulated to obtain a regulatory picture of what will be generally necessary for the indication sought.</td>
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<td><strong>Clinical studies</strong></td>
<td>Single ascending dose studies mostly in normal human volunteers but depending on the mechanism of action (MOA) of the therapy, if there is risk, this might be done in the appropriate patient. Multiple ascending dose studies sometimes done in normal human volunteers but sometimes performed in patients.</td>
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<td><strong>Phase II</strong></td>
<td>Studies are performed in selected patients to define dose, dosing schedule as well as potentially minimally effective dose. Assessments of primary and other outcomes. Differences in formulations might be tested; however, if telescoping development time is important, then all such trials have to be considered adequate and well controlled, using commercial material, following good laboratory practice, good manufacturing practice and good clinical practice guidelines.</td>
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<tr>
<td><strong>End of Phase II meeting</strong></td>
<td>To determine a path forward including number of patients that will need to be exposed to any dose and dose formulation as well as how patients many need to receive the commercial formulation, dose and dosing schedule. What primary outcomes will allow which indications to be awarded. A preliminary discussion of the planned statistical analysis plans and the analysis of measuring an effect size which will be clinically meaningful.</td>
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<tr>
<td><strong>Phase III</strong></td>
<td>Once an optimal dose or doses is (are) determined, then pivotal trials for regulatory approval can be performed. Usually of larger numbers of patients with a broader demographic footprint is recruited than earlier trials. Inclusion and exclusion criteria are considered. Multicenter trials are required with a representative demographic of patients which reflects the demographic of patients in the US. Enough patients need to be studied, with adequate and well controlled trials to allow for a clinically relevant benefit as opposed to risk due to emerging adverse events assessment to be concluded.</td>
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Table II

What steps are required for device approvals

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<td><strong>Pre Investigational Device Exemption (pre IDE) meeting</strong></td>
<td>At this meeting, clarity is achieved as to whether the sponsor may pursue a “510K” approach (see text) or has to perform a full development program leading to a PMA. Furthermore, the number of patients to be studied with the new device is defined. Safety is a much more important issue within CDRH and efficacy may take a back seat depending on the therapy. However, it is always a useful measure to define the benefit especially if there are unique safety signals observed with the new device.</td>
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<tr>
<td><strong>PMA meeting</strong></td>
<td>If a PMA is required, then typically substantive clinical trials may be required. The guidance document for the Development of Drugs in the Treatment of OA defines the path forward with modifications as determined by the review division within CDRH.</td>
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<tr>
<td><strong>PMA</strong></td>
<td>Submission of the PMA.</td>
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expectations of safe use through the awarding of a "CE" mark. In the US, devices are required to be proven safe when used as therapeutics and are cleared by the FDA if they are proven similar to other devices, or they can be approved for use by submission of a PMA for review. The evidence to support a PMA for the treatment of OA is similar to the requirements that the CDER at the FDA requires.

If a new therapy is approved, what are the present indications for OA?

In the US, there are two different possible indications awarded at approval for a new therapy for signs or symptoms of OA. The first is to be awarded an indication for the treatment of the signs and symptoms of OA. This threshold for approval requires the sponsor to demonstrate that the therapy is statistically better than placebo with an effect size that is clinically relevant in terms of pain, some functional assessment (typically Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function) and some form of question to determine the patient global response to the therapy. The patient global question usually encompasses both a sense of benefit and presence of adverse events noted by the patient while being treated with the new putative therapy. However, in the US, the other possible indication is the treatment of the "pain of OA of the knee" or whatever specific joint has been studied. This would require clinical studies designed to prove that the study drug was better than placebo statistically and the effect size was also clinically relevant in terms of pain relief with both a functional outcome and a patient global question as secondary outcomes which do not need to be statistically significantly better than placebo, but also cannot worsen. In Europe, EMA likely will require an active comparator as well. This serves two purposes. By using an approved drug as an active comparator provides a positive control to allow more confidence in the completion of an adequate and well controlled trial with noted success of the active comparator. The second issue, is that the presence of an active comparator in the same trial, provides for European regulators a sense of comparative effectiveness comparing the study drug to the effect of a known active therapeutic. As of yet, this is not required in the US.

If a topical drug is being developed, then the overall approach is similar; however, the specific joint treated is the one the product is labeled for and is for either the treatment of the signs and symptoms of OA or the treatment of pain of OA, (e.g., treatment of OA of the knee, or the treatment of pain of OA of the knee). Replicate trials are still required and systemic exposure is also important to define. Depending on the efficiency of absorption of the product as well as the bioavailability there may be more studies necessary to further understand the safety issues when the product is used. Both in the US and in Europe, a sponsor could prove that the study drug is better than placebo in at least three different sites (for a topical to obtain the pain of OA or the treatment of OA and not of a specific joint), or in the case of a systemic therapy, achieving the broader indication for the treatment of musculoskeletal pain, the sponsor would need to succeed in studies of at least three models of musculoskeletal pain. For example, duloxetine was awarded such an indication after successfully demonstrating benefit in the treatment of OA, low back pain, and fibromyalgia.

Unique aspects of a structure modifying development program

To obtain a structure modifying indication, thus proving that the therapy slows, retards, or stops OA progression, the study should be long enough to allow for a clinically relevant change to be measurable. Presently, joint space narrowing measurement by X-ray is the anchor evidence, but much data has been accumulated to suggest that magnetic resonance imaging (MRI) is now a generally accepted technique. Both the FDA and EMA acknowledge this; however, there has been little data presented to either regulatory body in a drug development program which has succeeded with either an MRI outcome or an X-ray outcome. Recommendations from OMERACT and OARSI have presented supporting evidence for this to the FDA.

Is there a way to enhance likelihood of success?

An enrichment guidance was developed by the FDA to define the process of increasing success in carrying out clinical trials which will be used for approval in indications such as OA which are characterized by significant patient heterogeneity. This allows recruitment of patients with manifestations of OA which are more likely to demonstrate responsiveness in such clinical trials.

Author contributions

Lee Simon conceived researched and wrote the manuscript.

Conflict of interest

I have no conflicts of interest.

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References