Expanded Access Program Manual
- Single Patient Use Requests to the U.S.FDA
:JointStem

Version: 1.0 (2025.04.02)

CONFIDENTIAL

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1. Purpose

This manual aims to clearly outline standardized procedures for providing "JointStem" through the Expanded Access Program (single patient use requests) of the U.S. FDA to patients with severe knee osteoarthritis (K-L grade 3), who are unable to participate in clinical trials or have exhausted other therapeutic options. The goal is to ensure consistent and efficient execution of related tasks by all involved parties.

2. Scope

This applies to the supply process for a single patient Expanded Access Program for severe knee osteoarthritis patients in the United States.

1) Medical practitioners (e.g., physicians, Advanced Practice Registered Nurses (APRNs), Nurse Practitioners (NPs), Physician Assistants (PAs)):
   Managing Expanded Access Program (FDA applications, reporting, patient care)
2) NatureCell representatives and department heads:
   Reviewing Expanded Access requests, preparing and submitting necessary documentation to the U.S. FDA, and post-submission monitoring
3) Departments responsible for production, quality control, and quality assurance:
   Manufacturing, supervising quality control, and quality assurance of JointStem in accordance with Expanded Access requests

3. Procedures

The Expanded Access process consists of four primary steps: Identification, Application, Treatment, and Follow-up (Fig. 1).

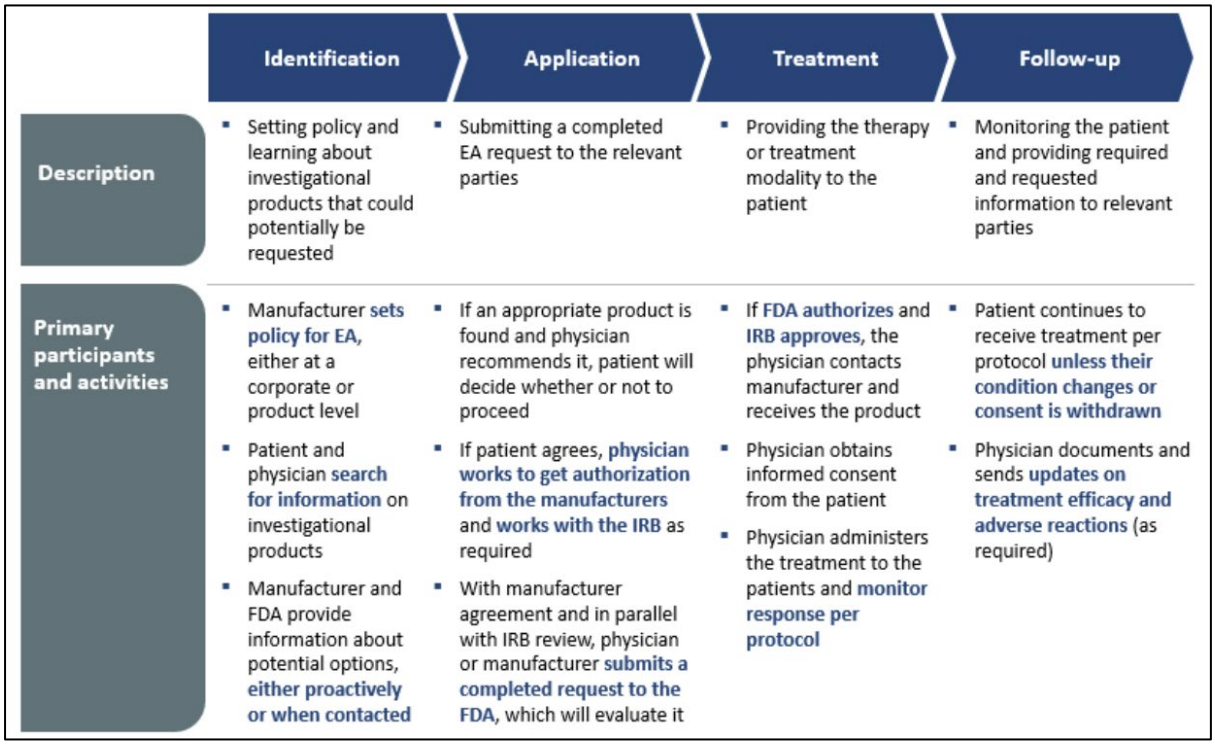

Figure 1. The EA process
Ref.: FDA. Expanded Access Program Report. May 2018.

Step 1: Identification

1) NatureCell representatives provide information about JointStem from ClinicalTrials.gov or published literature upon receiving inquiries from medical practitioners or patients regarding Expanded Access.

: Inquiries regarding the Expanded Access Program may be received by the company through the following three channels.

- Industry Policy
- Online searches or through the Reagan-Udall Foundation's Expanded Access Navigator External Link Disclaimer website.
- Patient Advocacy Organizations

2) When a request for access to an Expanded Access Investigational Product (IP) is received, representatives will conduct a preliminary review, taking into consideration the following company policy-related factors.

■ Patient Eligibility Criteria

Representatives will review whether the patient meets the inclusion/exclusion criteria. If necessary, the responsible medical practitioner may be asked to provide documentation regarding the patient's diagnosis, treatment history, current condition, and the need for treatment. This information will help determine whether JointStem may be a potentially appropriate product for the patient.

・Inclusion criteria

: The following criteria ① and ② may be reviewed using an and/or approach, while criterion ③ is subject to an and condition.

① K-L grade 3 patients with persistent symptoms despite standard of care

- Refractory Patients : Patients whose symptoms (e.g., pain) persist despite treatment with oral medications and/or intra-articular injections (e.g., steroids, hyaluronic acid, etc.)
- Relapsed Patients : Patients whose pain level returns to the pre-treatment state despite the administration of oral medications and/or intra-articular injections (e.g., steroids, hyaluronic acid, etc.)

② Patients whose pain cannot be adequately managed even with the use of opioid painkillers.

③ Patients who are unable to participate in clinical trials.

- When patients are unable to participate due to the absence of an ongoing clinical trial, lack of information, geographic or time constraints, or failure to meet eligibility criteria for trial enrollment.

・Exclusion criteria

① Patients deemed inappropriate according to JointStem clinical trial eligibility criteria

■ Plan for the quantity of the Expanded Access IP to be provided

- The Expanded Access IP, JointStem, is derived from autologous adipose tissue and requires patient-specific manufacturing. Considering the current manufacturing facility's CAPA (Capacity and Production Ability), the supply of the Expanded Access IP will be gradually increased to ensure stable and efficient distribution.

  Accordingly, at the initial stage of this program, the number of patients will be limited to five per month.

Step 2: Application

1) If representatives determine through 'Step 1: Identification' that the patient is eligible and the company is willing to provide the product, they will inform the medical practitioner accordingly.

2) The medical practitioner shall provide the patient with a thorough explanation of the treatment with JointStem. If the patient decides to proceed with the treatment, the practitioner must obtain written consent using the consent form provided by the company. A signed copy of the consent form should then be submitted to the representatives.

3) Representatives shall follow the company's internal approval process for providing the IP. Once approved, a copy of the "Letter of Intent to Provide" shall be sent to the medical practitioner via email or other appropriate means.

4) Representatives shall provide the medical practitioner with the necessary documents required for the Expanded Access application to the U.S. FDA. These documents include the protocol, questionnaires, paper CRFs, and the informed consent form, among others.

5) The medical practitioner may submit the required documents for the Expanded Access application—including those provided by the company—to both the U.S. FDA and the IRB simultaneously.
When applying to the U.S. FDA, Form 3926 may be used (a simplified form for single patient requests), or alternatively, Form 1571 and Form 1572—typically used for IND submissions—may also be used (see Figure 2).

6) The U.S. FDA will evaluate the submitted application documents and determine whether to approve or deny the request. As part of the review process, the FDA may request additional information or documentation if needed.

At this stage, representatives will discuss the FDA's feedback with the medical practitioner and, if necessary, revise and resubmit the relevant documents.
FDA Review Timeline: For non-emergency use, the review typically takes 30 days.
[For emergency use, the FDA reviews the request immediately and usually grants verbal authorization first, followed by a written submission.]

7) Upon receiving Expanded Access approval from the U.S. FDA, the company, the medical practitioner, and the patient shall ensure that the approval notification is shared among all parties.

Step 3: Treatment

1) Upon receiving Expanded Access approval from the U.S. FDA, representatives shall share the approval details with the manufacturing center as well as the Quality Control (QC) and Quality Assurance (QA) departments to initiate product manufacturing.

2) The medical practitioner coordinates and finalizes the adipose tissue collection schedule with the patient and notifies the responsible company representative. At the same time, the company representative provides the necessary supplies for adipose tissue and blood collection to the designated hospital where the procedure will take place.

3) In accordance with the scheduled adipose tissue and blood collection, the company representative arranges for a delivery service (e.g., an in-house logistics team or a transportation provider such as World Courier) to visit the hospital. The collected adipose tissue and blood are placed in temperature-controlled (refrigerated) containers and transported to the company’s manufacturing facility.

4) The manufacturing facility will inform the responsible company representative and the department head of the expected supply date for the IP (JointStem), based on the U.S. FDA-registered manufacturing process. The confirmed schedule will then be

communicated to the hospital.

5) The hospital schedules the patient to visit in accordance with the confirmed administration date. Using the delivered JointStem product, the patient is treated according to the protocol approved by the U.S. FDA.

Step 4: Follow up

1) After a single administration of JointStem, the medical practitioner shall follow up with the patient according to the protocol, evaluating treatment effectiveness and monitoring for any adverse events using the protocol's questionnaires and other tools. All observations and data must be documented using the paper Case Report Form (CRF).

2) In the event of a serious adverse drug reaction in the patient, the medical practitioner must promptly report the incident to the responsible company representative and the department head.

3) The medical practitioner shall submit an Annual Report to the U.S. FDA or IRB regarding the patient's post-treatment condition, in accordance with follow-up requirements. The responsible company representative and their department head are responsible for regularly monitoring the process to ensure that the reports are submitted without omission.

4) The patient must comply with the physician's instructions for follow-up in accordance with the protocol until the treatment is completed or the patient voluntarily withdraws from the program.

5) Upon termination by the medical practitioner (including in cases where the IND is withdrawn), a follow-up report must be submitted to the FDA in advance and shared with the responsible company representative.

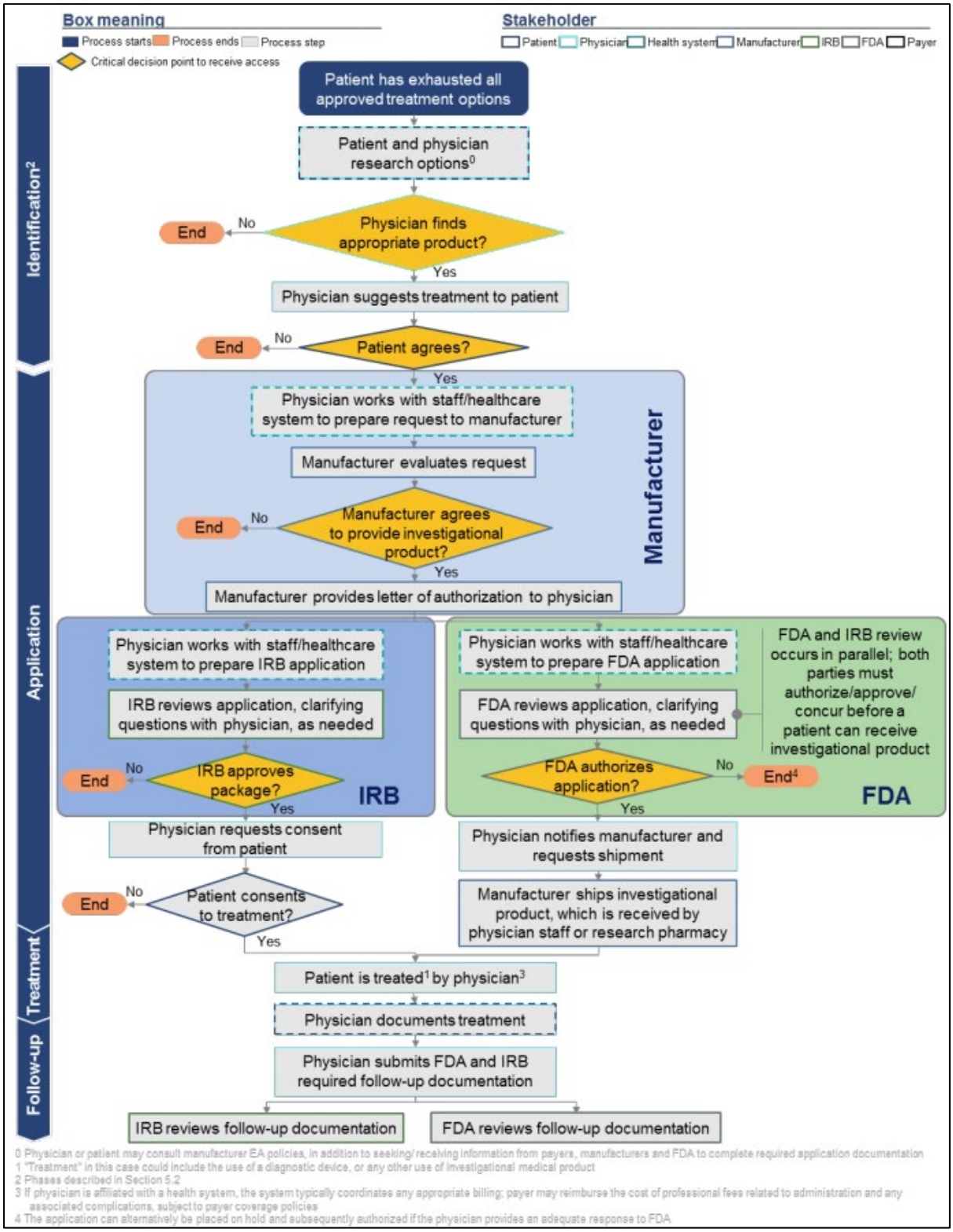

Figure 2. The flow chart for a typical single patient EA request.
Ref.: FDA. Expanded Access Program Report. May 2018.

4. Reference

1) FDA. Expanded Access Program Report. May 2018.
2) 21 CFR 312 section I
3) Food and Drug Administration Safety and Innovation Act (FDASIA) section 902
4) Food and Drug Administration Safety and Innovation Act (FDASIA) 561A(f)(2)

Revision History

Version	Revision Contents	Date
1.0	enactment	2025.04.02

Signature Page

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