Osteoarthritis:
CBER Regulatory Perspective

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Examples of Products for Osteoarthritis

Biological Products

Autologous

& Allogeneic

Common Routes of Administration: Intra-articular, Intravenous

Cellular Therapies

from different sources

- Bone marrow
- Umbilical cord blood, amnion
- Human chondrocytes
- Adipose tissue / Stromal Vascular Fraction

Gene Therapies

- Genetically modified cells
- Viral vector-based therapies
- Plasmid-based therapies

Devices with Biologic Output

Regulatory Requirements

- Drugs & Biologics
  - Approval must be based on **substantial evidence of effectiveness** and evidence of safety
  - Evidence of effectiveness should be obtained from **adequate and well-controlled studies**
- Devices
  - **Valid scientific evidence** to determine whether there is **reasonable assurance** that the device is safe & effective

Evaluating
Cellular & Gene Therapies

- Favorable Benefit-Risk
  - Understanding benefits & durability of clinical effect
  - Understanding short-term & long-term risks
  - Taking into account patient preferences

Study Design Considerations for Osteoarthritis (OA)

- Two adequate & well-controlled studies
  - Randomized Controlled Trials
  - Blinded (at least subjects & raters)
  - Appropriate control group (based on study population & treatment regimen)
- Study population targeted to product & mechanism
  - Adequate exposure given chronic condition & prevalence of osteoarthritis
  - Consider risks and anticipated benefits at different stages of OA and with different joints involved

Primary Efficacy Endpoints

- Pain & Function
  - Use validated scales
    - Examples: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), 100mm Visual Analog Scale (VAS)
  - For the treatment of OA: co-primary endpoints measuring pain & function
  - For a product developed for analgesic effects: pain as primary endpoint & function as secondary (strong consistent trend in improvement of function)

Efficacy Considerations: Structural Endpoints

- Structural endpoints are not currently used as primary endpoints
- Imaging studies for structural endpoints should be rigorously performed & analyzed
  - Appropriate imaging charter
- Must have confidence that structural endpoint correlates with clinical outcome(s) of interest and delays disease progression
  - Evidence may be developed in individual product programs or via Drug Development Tool Qualification Program

Timing of Efficacy Assessments

- Timing depends on anticipated product effects & setting of administration
  - Often up to 1 year
- Durability of effect
  - Consistency of treatment effect over time

Safety Considerations

- Adequate safety database
- Long-term follow-up
  - Duration depends upon product characteristics
- Sufficient monitoring for potential safety signals
  - Short-term: inflammatory and immunogenic reactions, contamination/ infections
  - Long-term: ectopic tissue formation, acceleration of cartilage degradation, tumorigenicity

Relevant FDA Guidances

- Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological Products for Treatment; Guidance for Industry (Draft 2018)
- Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (Final 2011)
- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry (Final 2015)
- Long-Term Follow-up after Administration of Human Gene Therapy Products: Guidance for Industry (Final 2020)

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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