Osteoarthritis: CBER Regulatory Perspective

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Examples of Products for Osteoarthritis

Biological Products

& 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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