The Creation of rhBMP-2

Identification

Recombination and Replication

Cell Bank Creation and Storage

Purification and Sterility

Cell Culture and Production

rhBMP-2
The rhBMP-2 patients included in this analysis exhibited excellent fusion rates and improved clinical outcomes without the need for autogenous iliac crest bone graft.

INFUSE® Bone Graft has more Level-1 clinical evidence than any other bone grafting material.

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“INFUSE® Bone Graft has more Level-1 clinical evidence than any other bone grafting material.”

Marshall R. Urist, MD, 1997

“BMP is destined to bring osteogenesis under the control of surgeons...”
The preferred method for obtaining BMP is to manufacture a recombinant version of a naturally occurring BMP using well-established molecular biology technique (e.g., recombinant insulin). This production method results in pure solutions of a single BMP. Recombinant production offers the advantage of tightly controlled manufacturing processes to ensure purity, consistency and sterility.

Using recombinant technology to develop and manufacture rhBMP-2 involves two phases:

**Phase 1: Identifying, Replicating, and Storing the Human Gene for BMP-2**

**Phase 2: Producing, Purifying, Sterilizing and Validating rhBMP-2**

Scientific breakthroughs at the Genetics Institute have led to the identification and isolation of the specific gene that carries the code for making Bone Morphogenetic Protein-2.

A vial of rhBMP-2 production cells is brought into the production room and placed into a glass “spinner flask.” The spinner flask contains nutrients that the production cells need to grow and produce rhBMP-2. These nutrients, or “medium,” contain a combination of vitamins, amino acids, minerals, and sugar, but they do not contain any human or animal components.
Once the gene was isolated, it was spliced and recombined into the DNA of a commonly used mammalian cell. “Recombinant” refers to the insertion, or recombination, of the gene into the production cell.

As the recombined cells grow and multiply, they include the new gene in their DNA. This replication process results in the development of a homogeneous population of cells capable of producing recombinant human Bone Morphogenetic Protein-2—rhBMP-2.

To foster cellular replication and production of rhBMP-2, they are transferred to a bioreactor, a computer-controlled, closed-system environment where large-scale production of rhBMP-2 begins. After a growth period of about three days, the recombined cells are filtered away from the rhBMP-2 containing medium and discarded. The rhBMP-2 moves on to the purification process.

The purification process involves a series of four chromatography columns.
To safely maintain the cells until they are needed for rhBMP-2 production, the small vials are frozen at -135°C and stored in secure, monitored, temperature-controlled freezers. Because only a few recombined cells are needed to make many millions of rhBMP-2 units and future cell banks, the isolation and cloning process will not need to be repeated.

Throughout the production process, quality control testing is done to assess the safety, consistency and purity of all materials. A large number of tests are completed during the manufacture of rhBMP-2. Quality-checked liquid rhBMP-2 is filtered and freeze-dried in vials and then further tested for purity and consistency.
Advantages of the Recombinant Process to make rhBMP-2

» Sterile product
» >98% pure protein
» Constant supply
» Controlled production process
» Quality assurance, highly regulated
» Excellent safety profile
» Reproducible bioactivity

The purified rhBMP-2 is freeze-dried in vials. The vials are assembled into INFUSE® Bone Graft Kits.

Availability of rhBMP-2 Technologies

INFUSE® Bone Graft – Kit Components

<table>
<thead>
<tr>
<th>Part Number/ Size</th>
<th>7510050 XX Small Kit</th>
<th>7510100 X Small Kit</th>
<th>7510200 Small Kit</th>
<th>7510400 Medium Kit</th>
<th>7510600 Large Kit</th>
<th>7510800 Large II Kit</th>
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<tbody>
<tr>
<td>INFUSE® Bone Graft Kit</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<td><img src="image5.png" alt="Image" /></td>
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<tr>
<td>Total Graft Volume</td>
<td>0.7cc</td>
<td>1.4cc</td>
<td>2.8cc</td>
<td>5.6cc</td>
<td>8.0cc</td>
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<tr>
<td>Total mg rhBMP-2</td>
<td>1.05mg</td>
<td>2.1mg</td>
<td>4.2mg</td>
<td>8.4mg</td>
<td>12.0mg</td>
<td>12.0mg</td>
</tr>
<tr>
<td>Sterile Water for Injection</td>
<td>(1) 5mL Vial</td>
<td>(2) 5mL Vials</td>
<td>(1) 5mL Vial</td>
<td>(2) 5mL Vials</td>
<td>(1) 10mL Vial</td>
<td>(1) 10mL Vial</td>
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<tr>
<td>Sterile rhBMP-2</td>
<td>(1) 1.05mg Vial</td>
<td>(2) 1.05mg Vials</td>
<td>(1) 4.2mg Vial</td>
<td>(2) 4.2mg Vials</td>
<td>(1) 12mg Vial</td>
<td>(1) 12mg Vial</td>
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<tr>
<td>Sterile Absorbable Collagen Sponge (ACS)</td>
<td>(1) ½” x 2” Sponge</td>
<td>(1) 1” x 2” Sponge</td>
<td>(2) 1” x 2” Sponges</td>
<td>(4) 1” x 2” Sponges</td>
<td>(6) 1” x 2” Sponges</td>
<td>(1) 3” x 4” Sponge</td>
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<td>PMA Approved Indication</td>
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<td>Spine* Dental</td>
<td>Spine* Dental</td>
<td>Spine* Dental</td>
<td>Spine* Dental</td>
<td>Spine* Trauma Dental</td>
</tr>
</tbody>
</table>

*Must be used with a Medtronic Titanium Threaded Interbody Fusion Device.
INFUSE® BONE GRAFT
CONTAINS THE PROVEN, PREDICTABLE BONE-FUSING POWER OF rhBMP-2

THE HISTORY OF rhBMP-2

The history of rhBMP-2 stretches back for decades, providing a wealth of research and studies to support its ability to induce new bone formation.

1965

Dr. Marshall R. Urist discovers that demineralized bone matrix stimulates the formation of new bone tissue in lower-order animal muscle. This led to the isolation of bone morphogenetic proteins (BMP), the only proteins known to induce new bone formation (osteoinduction).

2002

As a result of a prospective, randomized, clinical trial of 279 patients that proved rhBMP-2 to be equivalent to autograft, the U.S. Food and Drug Administration (FDA) approves INFUSE® Bone Graft/Medtronic Threaded Titanium Interbody Fusion Device for use in anterior lumbar spine fusion with certain interbody devices.

2004

After a prospective, randomized, clinical trial encompassing 299 patients, proving the healing power of rhBMP-2, INFUSE® Bone Graft gains FDA approval for open tibial fractures with intramedullary (IM) nail fixation.

2007

The FDA approves INFUSE® Bone Graft as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets. This approval was based on data from 312 patients enrolled in a total of 5 clinical studies.
INFUSE® BONE GRAFT/INTER FIX™ THREADED FUSION DEVICE
INFUSE® BONE GRAFT/INTER FIX™ RP THREADED FUSION DEVICE

BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, AND WARNINGS FOR: INFUSE® BONE GRAFT

INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations, and for local and skeletal ridge augmentations for defects associated with osteonecrosis.

The INFUSE® Bone Graft consists of two components – recombinant human Bone Morphogenetic Protein-2 (rhBMP-2), in a bovine Type I collagen carrier/scaffold. These components must be used as a system for the procedures indicated in this document. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document.

The INFUSE® Bone Graft component must not be used without the Medtronic Titanium Threaded Interbody Fusion Device component.

NOTE: The INTER FIX™ Threaded Interbody Fusion Device and the INTER FIX™ RP Threaded Fusion Device may be used together to treat a spinal level. The INTER FIX™ Threaded Fusion Device implants are not to be used in conjunction with either the INTER FIX™ or INTER FIX™ RP implants to treat a spinal level.

The INFUSE® Bone Graft/INTER FIX™ Threading Interbody Fusion Device is contraindicated for patients who are skeletally immature, in patients with an inadequate neurovascular status, in patients with an active malignancy, and in patients undergoing treatment for a malignancy. INFUSE® Bone Graft should also not be used in patients who are skeletally immature, in patients with an active malignancy or patients undergoing treatment for a malignancy. INFUSE® Bone Graft should also not be used by patients who are skeletally immature, in patients with an active malignancy, or in patients with compartment syndrome of the affected limb, in pregnant women, or in patients with an active infection at the operative site.

There are no adequate and well controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of childbearing potential should be advised to use other contraceptive methods of birth control until at least 1 year following treatment with this device.

Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, and all other important medical information.

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