

CANADIAN COUNCIL FOR  
DONATION AND TRANSPLANTATION



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# **Market Evaluation of Demineralized Bone Matrix Products in Canada**

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Research Highlights

**June 2006**

**Market Evaluation of  
Demineralized Bone Matrix Products in Canada:  
Research Highlights**

**Prepared for the Canadian Council for Donation and Transplantation**

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## **Glossary**

### **Advanced DBM Products**

DBM that has been manipulated into specialized product forms such as injectable pastes or machined blocks.

### **Basic DBM Products**

Not more than minimally manipulated bone tissue such as cancellous blocks, chips or powders.

### **Bone Morphogenic Proteins**

A group of proteins that promote bone growth. BMPs may be used as part of products that also use DBM or with other synthetic products. Osteogenic Protein 1 (OP-1) is a current BMP product used in spinal and orthopaedic surgery.

### **Demineralized Bone**

Allograft bone that has been demineralized leaving only the collagen component. Demineralized bone can be developed into basic minimally manipulated (e.g., powder) and advanced DBM products (e.g., injectables and putties).

### **Tissue Recovery Organizations (TROs)**

Companies or organizations that offer donor referral, screening and tissue recovery services that then provide tissue to tissue banks or advanced tissue processing companies.

## 1.0 Introduction

Demineralized bone matrix (DBM) is an advanced bone tissue product used for a wide range of bone grafting procedures. DBM is used by a number of end user physician groups including orthopaedic surgeons, oral and maxillofacial surgeons, neurosurgeons, periodontists and dentists. DBM products are currently available to Canadian end users from over 30 international tissue banks and private companies. There is no Canadian manufacturing source of DBM products. Development and purchasing of DBM products occur outside of Canadian tissue bank operations. The extent of the utilization of DBM products in Canada is not published in current tissue related literature.

The Canadian Council for Donation and Transplantation (CCDT) initiated a study to characterize the use of DBM products in Canada through quantitative market research.

The study methodology consisted of two main components:

- 1) An end user survey of dentists, periodontists, oral and maxillofacial surgeons and hospital or operating room managers at hospitals with orthopaedic surgeons and neurosurgeons to obtain primary data on DBM utilization and purchasing; and
- 2) An industry analysis to characterize the types of organizations producing DBM products, the range of product types, how DBM products are entering the Canadian market, utilization of DBM products by end users, and a Canadian market size estimate.

A review of DBM substitute products was also provided.

## 1.1 Types of DBM Products

DBM products come in basic and advanced forms. Basic DBM products include demineralized large grafts (e.g., tibia), cancellous chips and powders. The distinction between basic and advanced DBM is in the addition of additives to produce various forms of products, including carriers to produce injectable products, addition of advanced proteins, combination with machined scaffolds and inclusion in other medical device combination products.

A wide range of DBM products are available. Basic DBM product forms include:

- Cortical and cancellous powders,
- Cortical and cancellous chips,
- Cortical and cancellous granules, and
- Cancellous cubes or “sponges”.

Once the basic demineralization process occurs, a wide range of products is afforded, including:

- Putty for void filling,
- Injectables and paste,
- Gels,

- Specially machined blocks and forms,
- Flexible strips,
- Pellets, and
- Fibres.

## 2.0 End User Survey

Three hundred and sixty-seven (367) physicians and operating room managers were contacted to participate in a DBM utilization survey conducted from November 2005 to March 2006. A total of 202 responses were received. All participants were contacted at random from comprehensive lists of all physicians practicing in Canada for each profession or hospital in the case of orthopaedic and neurosurgical operating rooms. Key findings for each physician group or hospital are discussed below. The total numbers of respondents from each group are provided in Table 1 and Table 2 below.

The key findings for each group include:

### **Dentists:**

- Approximately 11% of dentists in Canada are using DBM products.
- Majority of DBM use in dental implant procedures (~80%).
- Several dentists reported performing periodontal and oral and maxillofacial procedures, in particular sinus lifts and guided tissue regeneration.

### **Oral & Maxillofacial Surgeons:**

- Approximately 89% of oral and maxillofacial surgeons are using DBM products.
- Primary procedures that utilize DBM include sinus ridge augmentation, socket preservation, implant preparation and defect repair.

### **Periodontists:**

- Approximately 81% of periodontists in Canada are using DBM products.
- Primary procedures that utilize DBM are sinus lifts, alveolar augmentation, implant placement, socket preservation and guided tissue regeneration.

### **Orthopaedic Surgeons & Neurosurgeons:**

- 13 of 20 hospitals with orthopaedic surgeons and neurosurgeons reported purchasing DBM products.
- Major orthopaedic procedures that use DBM include revision total hip replacement, revision total knee replacement, non-union repair and ankle repair and replacements.
- The major neurosurgical procedure that utilized DBM is cervical fusions.

**Table 1: Use of DBM Products by Physician Groups in Canada**

	<b>Dentists</b>	<b>Oral &amp; Maxillofacial Surgeons</b>	<b>Periodontists</b>	<b>Orthopaedic Departments</b>	<b>Neurosurgical Departments</b>
Number of Respondents	92	56	26	20 (rep. 119 surgeons)	10 (rep. 35 surgeons)
Use DBM % (count)	10.9% (10)	89.3% (50)	80.8% (21)	65.0% (13)	60.0% (6)
Margin of Error	±6.4%	±8.2%	±15.1%	±8.6%	±16.2%
95% Confidence Interval	4.6% to 17.7%	80.8% to 97.2%	65.9% to 96.1%	56.4% to 73.6%	43.8% to 76.2%

**Table 2: Estimated Total Use of DBM Products by Physician Group**

	<b>Dentists</b>	<b>Oral &amp; Maxillofacial Surgeons</b>	<b>Periodontists</b>	<b>Orthopaedic departments</b>	<b>Neurosurgical departments</b>
Physician Population	17,000	310	228	1150	250
National Estimate of DBM Use	1870 ± 1088	276 ± 25	185 ± 34	748 ± 99	150 ± 41

## 2.1 Overarching Issues Identified by End Users

The following issues were indicated from all physician groups:

- Eighteen of 50 physicians who use DBM also reported using synthetic bone substitute products.
- A Canadian source of DBM alone may not be enough to change purchasing habits – quality standards, product literature and clinical data are considered critical.
- A large range of product types and forms was identified.
- A high number (18) of procedure groups that use DBM were identified.
- Twenty-eight (28) sources of DBM products (manufacturers, distributors and tissue banks) were identified as selling products in Canada.
- The major reason provided by physicians not using DBM was that they did not perform any procedures that could use DBM (84 of 96 cases).
- Only two physicians (of 202 respondents represented) indicated concerns over safety of DBM products.

### **3.0 DBM Industry**

All DBM products utilized in Canada come primarily from the U.S., with a small number of products from other international sources. As such, the U.S. is the primary focus of the industry analysis. The U.S. market for DBM use in oral reconstructions, joint replacement/revision and spinal fusions has been estimated to range from US\$240 to \$270 million.

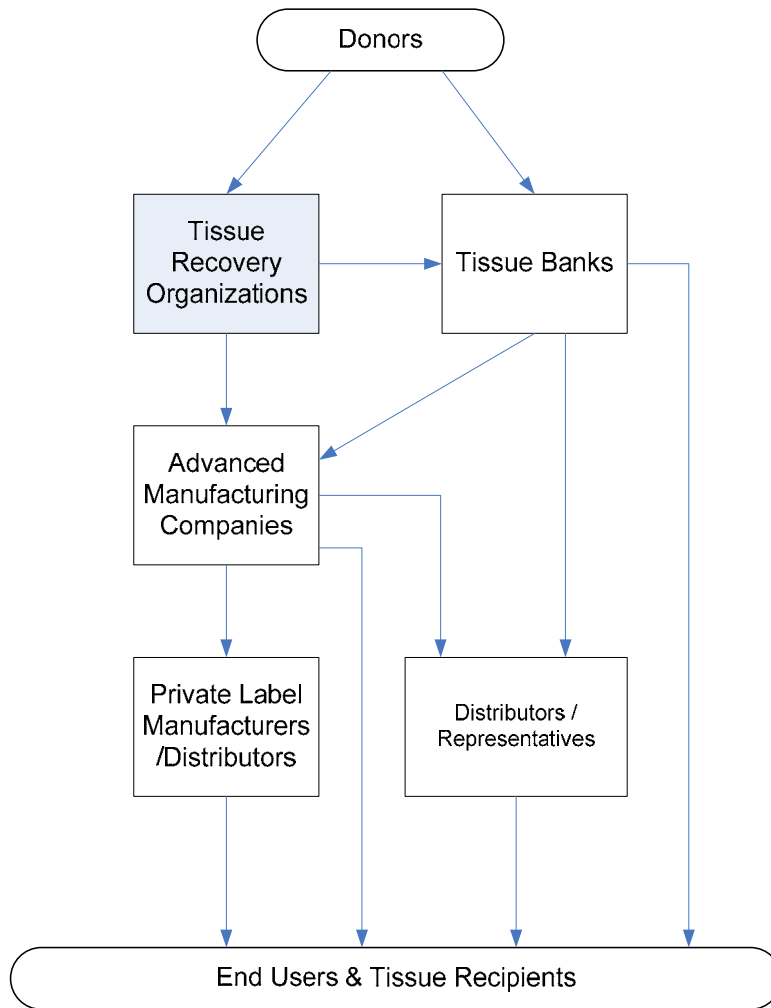
#### **3.1 Distribution Channels**

The majority of DBM products are produced by not-for-profit tissue banks or private for-profit corporations. All for-profit corporations distributing DBM products are reliant on not-for-profit tissue banks or tissue recovery organizations (TROs) for access to basic allograft material and/or basic demineralized bone products for the production of advanced DBM products. This includes all DBM products that are sold in to Canada. Advanced products are distributed through large distribution networks of the public for-profit companies. While all of the DBM allograft material is obtained originally through the not-for-profit companies, the majority of end users obtain DBM products from public medical device companies. Figure 1 below outlines the possible routes that DBM products can enter the Canadian market from U.S. distribution channels.

TROs and tissue banks may provide bone tissue directly to advanced processors (e.g., Regeneration Technologies) or to not-for-profit tissue banks (e.g., MTF) with the capability of producing advanced DBM products. Tissue banks also provide DBM directly to end users or through distributors (some do both, e.g., Pacific Coast Tissue Bank).

Advanced manufacturers provide DBM products through distributors or company representatives, through private label products (e.g., Osteotech Inc. providing DBM for Aesculap Inc. orthopaedic products) or directly to end users (e.g., hospital purchasing departments).





**Figure 1: DBM Distribution Links**

### 3.2 Processing and Cost Recovery Partnerships

Advanced DBM product manufacturers also assist in distribution of DBM products on behalf of the tissue banks that obtained the original tissue. Tissue banks and TROs receive cost recovery fees related to procurement of the original tissue. A cost recovery partnership with a U.S. advanced product manufacture is possible for a Canadian tissue bank.

### 3.3 DBM Manufacturers and Distributors

Appendix 2 lists the major sources of DBM products available in Canada from the U.S. DBM industry. There are at least 34 different sources of DBM products available to Canadian end users, 28 of which were identified in end user surveys. There at least 10 major distributors of DBM products in Canada. DBM products can be purchased through catalogues, on-line or though distributor representatives. Several DBM products are sold under the distributors' name (e.g., "ACE DBM") rather than the original manufacturers' name (e.g., Pacific Coast Tissue Bank).

## **4.0 Canadian Medical Device Licenses**

Advanced or “more than minimally manipulated products” that contain human tissue are classified and regulated as Class IV medical devices. There are at least five (5) DBM product manufacturers that hold medical device licenses in Canada: IsoTis, Musculoskeletal Transplant Foundation (MTF), Regeneration Technologies Inc, Tutogen Medical Inc. and Wright Medical Inc. The majority of advanced DBM products used in Canada are obtained either directly from these companies or through one or more of their distributors. Only one of these companies, MTF, is a not-for-profit tissue bank. Interestingly, one major DBM manufacturer, Osteotech, has not renewed its Canadian medical device license since 2004.

Basic DBM products are also available from companies that do not hold Canadian medical device licenses. Basic or “not more than minimally manipulated” DBM products are not classed as medical devices and are not tracked as medical devices by Health Canada; rather they are regulated under the Food and Drugs Act. These products are required to have a transplant record maintained for adverse event and recall procedures.

## **5.0 Canadian Market Analysis**

The total Canadian market size for DBM products is estimated to be between 36,000 to 89,000 cc's, representing a market potential of US\$7.7 million to \$18 million. Given that the low market estimates are based on 2003 utilization data that did not include verifiable estimates for spinal fusion, plastic surgery and onlay grafting procedures, a current market size of US\$13 to \$18 million is considered to be the most probable current market size for DBM products in 2005-2006.

The Canadian market for DBM products was estimated by:

- 1) Identifying the most common procedures that utilize DBM products,
- 2) Estimating the utilization of DBM per procedure (i.e., the type of DBM product and amount used),
- 3) Estimating the total number of procedures performed per year in Canada, and
- 4) Multiplying the utilization and procedure frequency by the average price per product to arrive at a market size estimate.

### **5.1 Canadian DBM Market Characterization**

There are several key characteristics of the DBM market in Canada:

- 1) Utilization by physician group,
- 2) Spending by physician group,
- 3) Use of basic vs. advanced DBM products, and
- 4) In-hospital vs. private practice demand.

Table 2 below describes the total utilization by volume, percentage of total spending and use of basic and advanced products by physician group. The data in Table 3 is based on the mid-range market estimates.

Orthopaedic, periodontal and neurosurgical procedures each utilize approximately 25% of the total volume of DBM products used. Oral and maxillofacial surgeons and private dental procedures utilize 11 to 14% of the total volume of DBM products used in Canada. In-hospital dental use of DBM products is comparatively low, at approximately 3.5%.

**Table 3: DBM Utilization and Spending by Physician Group**

<b>Physician Group</b>	<b>Utilization (% of total volume of DBM used in Canada)</b>	<b>Spending (% of total DBM market annually)</b>	<b>Use of Basic DBM Products (% of total DBM market annually)</b>	<b>Use of Advanced DBM Products (% of total DBM market annually)</b>
Dental, in-hospital	3.5	1.0	6.8	2.4
Dental, private	13.6	3.2	34.5	6.2
Neurosurgical	22.3	14.6	Not reported	30.1
Oral & Maxillofacial	10.7	7.5	Not reported	14.4
Orthopaedic	26.7	68.2	Not reported	36.3
Periodontal	23.2	5.5	58.7	10.6
Mid-range Estimate	64,000 cc's	\$12.9 million (U.S.)	<\$1.0 million (U.S.)	~\$12 million (U.S.)

When viewing the DBM market by current spending, orthopaedic procedures account for the majority of spending on DBM products in Canada, estimated at approximately US\$8.8 million annually. Dental, oral and maxillofacial and periodontal procedure spending is relatively lower due to higher use of basic forms of DBM products like powders and chips and lower use per procedures; e.g., dental procedures typically use less than 1cc of low cost powders, while orthopaedic procedures commonly use up to 5cc of DBM pastes or putty that can be up to 10 times the cost of the same volume of basic DBM products. Neurosurgical spending is also comparatively lower, due to the use of DBM as a graft extender with non-demineralized cortical and cancellous chips in spinal fusion procedures. The dental and periodontal market for DBM in Canada utilizes the majority of powder forms of DBM products, with a relative low use of advanced DBM products compared with orthopaedic and neurosurgical procedures.

Three basic market segments appear to be functioning in Canada:

- 1) A private basic DBM market segment, used primarily by private dentists and periodontists,
- 2) A private advanced DBM market segment, used primarily by private dentists and periodontists, and

3) An in-hospital advanced DBM market segment, used primarily by orthopaedic surgeons, neurosurgeons and oral and maxillofacial surgeons.

## **6.0 Use of Non-DBM Bone Substitutes**

The use of bone substitutes is expected to continue to increase as viable alternatives to traditional bone allografts as a wide array of products continues to emerge. In the tissue substitute market, there are currently over 50 products that are alternatives to demineralized bone matrix products. A number of products are in development that are claiming to be close to emulating traditional human allografts.

Of interest to tissue banks is estimating the effect of increased use of DBM and non-DBM bone substitutes on the demand for traditional allografts. The market for bone graft substitutes is projected to increase by 7 to 10% per year up to 2012. In 2001, the total global demand for bone tissue and substitutes combined was US\$732 million, of which DBM and non-DBM substitutes encompassed 40% of the market. Demineralized bone matrix products were estimated at US\$154 million, and non-DBM products were estimated at US\$138 million in 2001.

Over the next five years, there is increasing demand projected for more complex products that mimic human bone to greater degrees; the demand will likely not be for “DBM vs. non-DBM” products, rather the next generation of products will likely combine synthetics, DBM, bone morphogenesis proteins (BMPs) and cellular technologies in to single products as direct replacements of traditional human allografts, for example, in the current use of osteogenic proteins (OP-1) combined with autograft tissue for spinal fusion.

### **6.1 Future Trends**

If the trend toward greater use of synthetic-human tissue combination products continues the demand for traditional allografts will decrease; however, the need for human tissue for these combination products will still place a continuing demand on tissue banks to provide human tissue.

## **7.0 Conclusion: Market Drivers and the Future of DBM Use in Canada**

Will the market for DBM products increase or decrease? Two questions need to be asked to determine if the DBM market will be increasing or decreasing:

- 1) Will the market for bone grafts increase or decrease, and
- 2) Will DBM remain a preferred bone graft material?

Looking at the key market drivers of demographics, technological changes and changes in clinical practice, it is expected that the demand for bone allografts or bone substitutes will increase.

## **7.1 Demographics**

Approximately 2.5 million more Canadians will be over the age 65 in the next 15 years than there are now. The largest increase in the population of this cohort will start to occur five years from now and continue to increase between 2011 and 2021. Two procedures in particular, revision total hip surgery and edentulous conditions (precipitating the need for dentures or implants), will increase with this cohort creating a higher demand for bone graft or bone graft substitute products. Cancer rates are higher in this cohort as well, which will also increase the need for bone grafts.

The percentage increase in population over 65 will be approximately 2.7% between 2006 and 2011. However, the percentage increase in population over the age of 65 will increase significantly between 2011 and 2021, averaging over 4.0% per year over the 10-year period. It is expected that the number of in-hospital procedures related to this age cohort that use bone grafts or bone graft substitutes will similarly increase by at least 4.0% per year between 2011 and 2021.

## **7.2 Technological Changes**

As discussed above, bone grafts and bone graft substitutes are becoming highly complex materials, possibly on the verge of being able to truly mimic human bone tissue. Dozens of forms of products are available to suit any bone void filling requirement, making ease of use of these products high. These products are also easily obtainable through a number of distribution networks, including on-line purchasing. Given the ease of use, range of products, broad clinical applicability and relative affordability, it is expected that these products will see continued increased use with the demographic group described above.

## **7.3 Clinical Practice Changes**

Dentists have access to a number of advanced training courses in oral implantology for implants and bone grafting (particularly sinus lift procedures). While the actual percentage of dentists currently performing implants is low (~10%), the increasing ease of use of new products, access to training and a growing demand for dental implants it is expected that the number of dentists performing implants will increase. There are currently fewer than 300 periodontists in Canada versus over 17,000 dentists – dentists have the potential to reach a much larger market of patients.

If the costs of implant and bone graft technology decreases over time and make implants more affordable, and if dentists make the technology available to a wider range of patients, the use of bone graft materials could increase significantly.

Dental implant procedures account for 80% of bone graft materials used in the dental market – any increase in the use of implants will see a corresponding rise in the use of grafting products. A recent Cochrane review found over 1200 different implants are available on the market; however, there was little clinical evidence for superiority of any particular product.

#### **7.4 Will DBM remain a preferred bone graft material?**

For DBM to remain a preferred grafting material in the medium to long term, given the current substitutes available on the market, it will most likely have to outperform bone morphogenic protein based products in clinical effectiveness and price (e.g., BMPs combined with cancellous chips).

Given that DBM has a clinical history typically as a bone graft extender and the current high cost of BMP products, the use of DBM in the short term (one to five years) will likely increase at least 3-4% per year for in-hospital procedures, based on population increases of people over 65 discussed above, and may increase further depending on the number of dentists that begin to offer bone grafting services over the next 15 years, as well as with increased adoption and use among orthopaedic, oral and maxillofacial and neurosurgeons. For comparison, the oral and maxillofacial hardware market (e.g., plates and screws for bone fixation) has been projected to also grow at a rate of 4.8 percent to 2007.

Mid to long term demand (5 to 15 years) will depend on the adoption of non-DBM based substitutes, particularly clinical adoption of BMPs and improvements in calcium-phosphate products used in conjunction with patient blood or bone marrow or other platelet or gene therapy technologies.

At least one orthopaedic hospital surveyed in Canada is currently purchasing BMPs and there appears to be growing support in peer-reviewed literature and in the non-DBM bone substitute market for alternate products to DBM.

If BMPs continue to show clinical effectiveness and the cost becomes competitive with DBM, the relative percentage of DBM products used will likely decrease.

The use of bone grafts that utilize DBM will likely increase in the short term (1 to 5 years). DBM products will likely have to be competitive with BMPs and other substitutes to see continued growth in the medium and long term (5-15 years).

#### **8.0 Recommendation and Next Steps**

DBM and non-DBM bone substitutes will likely not replace traditional bone grafts in the next five years. However, there will be increased demand for grafting products and continued development of new products over the next 15 years. Tissue banks in Canada do have the potential to begin to develop, or form partnerships to develop, DBM products. There are also several segments to the Canadian DBM market that allow for different product types, ranging from basic demineralized chips and powders to injectables and putties.

If certain Canadian tissue banks are interested in developing DBM products from bone tissue donated in Canada, it is recommended that:

- 1) The capacity for producing basic DBM products, primarily demineralized chips and powder, be developed first and marketed to the dental and periodontal market,
- 2) An advanced processing relationship with a U.S. or other international processor be pursued for the development of a Canadian private label advanced DBM product line, and
- 3) Research and development linkages are pursued with an orthopaedic training hospital for the development of new DBM and/or DBM-substitute products.

Starting with the production of basic DBM products is the lowest cost option to begin DBM product development, i.e., there will be few, if any, intellectual property barriers and the least infrastructure burden<sup>i</sup>. Given the potential emergence of competitive products in the 5-15 year horizon, the high cost of maintaining distributor and promotional networks, and the high number of manufacturers and distributors currently selling DBM in Canada, a formal business case analysis is needed to assess the feasibility of both basic and advanced DBM production in Canada.

Unless a tissue bank can develop a business plan that can capture a large enough portion of the Canadian DBM market to support the financing, infrastructure, operations and distribution network required, it is not recommended that a Canadian tissue bank invest in advanced DBM production capability to serve the Canadian market alone.

## **8.1 Final Consideration: Impact of Sole Reliance on U.S. Sources of Tissue**

One of the attributes of DBM utilization in Canada that stands out from the interviews and analysis of the Canadian market is the almost complete reliance on U.S. sources of tissue for advanced bone graft products. This may not be a familiar scenario to all tissue banks in Canada as the purchasing of DBM typically occurs outside of tissue banks, usually through hospital or private clinic purchasing departments..

Reliance on U.S. manufacturers is commonplace in many areas of the Canadian health care system, however, the extent of reliance on foreign sources of advanced tissue products may not be well known.

As part of future meetings or initiatives, CCDT may want to consider promoting a discussion regarding possible implications – positive, negative or otherwise – on the nearly sole reliance on foreign sources of advanced tissue products. These discussions may benefit from exploring possible development of Canadian capabilities, partnerships and contingencies that may be required due to the reliance on foreign sources of tissue.

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<sup>i</sup> Methods for the production of basic DBM products are available publicly[e.g., in expired patents (US Pat. # 4,394,370 *Bone graft material for osseous defects and method of making same*)] and in the literature (e.g., von Versen, et. al. 1989).