TABLE E-1 Bone Morphogenetic Protein (BMP) Commercialization Timeline*

1965	• Discovery of osteoinductive effect of BMP by Marshall Urist, MD
1988	• Discovery of method to make recombinant human BMP (rhBMP)
1991	• Stryker starts IDE clinical trial on nonunions treated with rhBMP-7 (OP-1)
1994	• Genetics Institute starts IDE clinical trial on open tibial fractures and oral/maxillofacial augmentation treated with rhBMP-2
1997	• Genetics Institute (now Wyeth) starts large clinical trial in Europe on open tibial fractures treated with rhBMP-2 • Medtronic Sofamor Danek starts IDE clinical trial of interbody spine fusion treated with rhBMP-2
1998	• Sulzer starts IDE clinical trials in periodontal disease and spine fusion treated with a bovine BMP extract (Ne-Osteo)
1999	• Stryker starts IDE clinical trial on posterolateral spine fusion with OP-1 • Medtronic Sofamor Danek starts IDE clinical trial of posterolateral spine fusion treated with rhBMP-2
2001	• Stryker receives a 'not approvable' letter from the FDA on their nonunion PMA submission with OP-1 • Centerpulse (formerly Sulzer) shuts down development of its Ne-Osteo bovine BMP product • Stryker receives approval of their HDE for long bone nonunions
2002	• Medtronic Sofamor Danek receives PMA approval from the FDA for rhBMP-2 in interbody spine fusion
2004	• Stryker receives approval of their HDE for revision spine fusion • Medtronic Sofamor Danek receives PMA approval from the FDA for rhBMP-2 in open tibial fractures
Note: Institutional review board approval is required to use an HDE product. OP-1 is a registered trademark of Stryker Corporation and Ne-Osteo is a trademark of Sulzer Medica.	

*IDE = investigational device exemption, HDE = humanitarian device exemption, PMA = premarket application, and FDA = Food and Drug Administration.

TABLE E-2 Treatment Costs of Various Recombinant Proteins

Company	Protein	Treatment	Treatment Cost
Approved as Drugs			
Amylin, Novo Nordisk, Eli Lilly	Insulin and insulin-like factors	Diabetes	$1,000 to $2,000
Novo Nordisk, Wyeth	Plasma activated factor VII or IX	Hemostasis	$3,000 to $4,000
Johnson & Johnson, Amgen, Ortho Biotech	Erythropoietin	Anemia	$6,000 to $10,000
Eli Lilly	Activated protein C (rhAPC)	Sepsis	$7,000 to $10,000
Eli Lilly	Parathyroid hormone (PTH)	Osteoporosis	$7,000 to $8,000
Abbott, Centocor, Amgen, Wyeth	Tumor necrosis factor (TNF) inhibitor or TNF-alpha antibody	Arthritis	$14,000 to $15,000
Eli Lilly, Genentech, Pfizer, Tercica, Teva	Growth hormone or insulin-like growth factor (IGF)	Hormone deficiency	$10,000 to $12,000
Biogen, Schering-Plough, Berlex	Interferon beta-1b	Multiple sclerosis	$14,000 to $15,000
Amgen	Granulocyte-colony stimulating factor (G-CSF)	Prevent infection	$13,000 to $18,000
Biogen Idec, Genentech, ImClone	Synthetic antibodies	Cancer treatment	$17,000 to $109,000
Approved as Devices			
Medtronic	Bone morphogenetic protein-2 (rhBMP-2)	Spine fusion and open tibial fractures	$4,000 to $5,000
Stryker Biotech	Osteogenic protein-1 (OP-1)	Long bone nonunion and revision spine fusion*	$5,000 to $10,500

*Note: Humanitarian device exemption (HDE) approval requires institutional review board approval before use; HDE price cannot make a profit.

TABLE E-3 Examples of Platelet Concentrator Systems and Their FDA Indications

Platelet Concentrate System	FDA 510(k) Indication
SmartPRep (Harvest Technologies, Plymouth, MA, distributed by DePuy, Warsaw, IN, as Symphony)	K991430: "… used in the clinical laboratory or intraoperatively at point-of-care for the safe and rapid preparation of platelet poor plasma and platelet concentrate from a small sample of blood."
Ultraconcentrator System (Interpore Cross, Irvine, CA, distributed as the AGF system)	K011148: "… indicated for use as a ultrafiltrator for the selective removal of undesirable plasma water and small dissolved solutes from blood plasma proteins …"
Platelet Concentrate Separation Kit (Biomet, Warsaw, IN)	K021927: "… designed for use in the clinical laboratory or intra-operatively at point of care, for the safe and effective preparation of platelet poor plasma and platelet concentrate from a small sample (50-60 ml) of whole blood."
Harvest PRP Separation System (Harvest Technologies, Plymouth, MA)	BK000037: "… used for the safe and rapid preparation of autologous platelet-rich-plasma (PRP) from a small sample of blood at the patient's point of care. The PRP can be mixed with autograft and allograft bone prior to application to an orthopedic surgical site as deemed necessary by the clinical use requirements."