

CHAPTER ONE: INTRODUCTION.....	1
STUDY GOALS AND OBJECTIVES.....	1
REASONS FOR DOING THE STUDY	1
SCOPE OF REPORT	1
INTENDED AUDIENCE.....	2
INFORMATION SOURCES.....	2
ANALYST CREDENTIALS.....	2
RELATED REPORTS.....	2
BCC ONLINE SERVICES.....	3
DISCLAIMER	3
 CHAPTER TWO: SUMMARY.....	 4
<i>SUMMARY TABLE GLOBAL MARKET FOR PROTEIN</i>	
<i>THERAPEUTICS, THROUGH 2013 (\$ MILLIONS)</i>	4
<i>SUMMARY TABLE (CONTINUED)</i>	5
<i>SUMMARY FIGURE GLOBAL MARKET FOR PROTEIN</i>	
<i>THERAPEUTICS, 2007-2013 (\$ MILLIONS)</i>	5
 CHAPTER THREE: OVERVIEW	 6
DEFINING THE TERMS: PROTEINS AND PEPTIDES.....	6
PROTEIN DRUGS: THEN AND NOW.....	7
<i>TABLE 1 NEW DRUGS ENTERING CLINICAL TRIALS, BY TYPE, 2007</i>	8
DRUG ADMINISTRATION: MILESTONES AND CHALLENGES	9
PEGYLATION.....	10
PEPTIDE-MEDIATED RECEPTOR TARGETING.....	11
PATIENT COMPLIANCE	11
Patient Compliance (Continued).....	12
 CHAPTER FOUR: MARKETS BY PRODUCTS	 13
<i>TABLE 2 GLOBAL SIZE OF PROTEIN DRUGS MARKET BY</i>	
<i>PRODUCTS, THROUGH 2013 (\$ MILLIONS)</i>	13
<i>FIGURE 1 GLOBAL SIZE OF PROTEIN DRUGS MARKET BY</i>	
<i>PRODUCTS, 2008 AND 2013 (\$ MILLIONS)</i>	14
<i>FIGURE 2 GLOBAL SHARE OF PROTEIN DRUGS MARKET BY</i>	
<i>PRODUCT, 2008 (%)</i>	14
<i>FIGURE 2 (CONTINUED)</i>	15
<i>FIGURE 3 GLOBAL SHARE OF PROTEIN DRUGS MARKET BY</i>	
<i>PRODUCT, 2013 (%)</i>	15
ANTIBODY DRUGS	16
PRODUCTION OF ANTIBODIES FOR THERAPY.....	16
Murine Monoclonal Antibodies	17
Chimeric and Humanized Monoclonal Antibodies.....	17
Human Monoclonal Antibodies.....	18
Antibody-directed Enzyme Prodrug Therapy (ADEPT).....	18

HOW ANTIBODY DRUGS WORK.....	18
How Antibody Drugs Work (Continued).....	19
TABLE 3 FDA-APPROVED MONOCLONAL ANTIBODIES, 2008.....	20
THE ANTIBODY DRUG MARKET	21
TABLE 4 GLOBAL MARKET FORECAST FOR ANTIBODY DRUG	
PRODUCTS, THROUGH 2013 (\$ MILLIONS).....	21
FIGURE 4 GLOBAL MARKET FOR ANTIBODY DRUGS, 2008 (%).....	21
FIGURE 4 (CONTINUED)	22
FIGURE 5 GLOBAL MARKET FOR ANTIBODY DRUGS, 2013 (%).....	22
FIGURE 5 (CONTINUED)	23
CHANGES IN A DYNAMIC MARKET.....	23
Possible new indications for Campath.....	23
EGF-R Antibodies: Still Investigational Therapies	24
Side Effects Could Affect Tysabri's Future	25
TABLE 5 FDA-APPROVED MONOCLONAL ANTIBODIES FOR	
CANCER TREATMENT, 2008.....	26
CYTOKINES	27
THE CYTOKINE MARKET	28
Granulocyte-colony Stimulating Factors	28
Interferon β	28
Interferon α	28
Interferon γ	29
Interleukins	29
TABLE 6 GLOBAL MARKET FORECAST FOR CYTOKINE PRODUCTS,	
THROUGH 2013 (\$ MILLIONS).....	30
FIGURE 6 GLOBAL MARKET FOR CYTOKINE DRUGS, 2008 (%).....	30
FIGURE 7 FORECAST GLOBAL MARKET FOR CYTOKINE DRUGS,	
2013 (%).....	31
PEPTIDE HORMONES.....	32
TABLE 7 GLOBAL MARKET FORECAST FOR PEPTIDE HORMONES,	
THROUGH 2013 (\$ MILLIONS).....	33
FIGURE 8 GLOBAL MARKET FORECAST FOR PEPTIDE	
HORMONES, 2008 AND 2013 (\$ MILLIONS)	33
FIGURE 9 GLOBAL MARKET FORECAST FOR PEPTIDE	
HORMONES, 2008 (%).....	34
VACCINES	34
KINDS OF VACCINES.....	35
Killed Whole Organisms.....	36
Attenuated Organisms	36
Toxoids	36
Surface Proteins.....	36
Inactivated Virus	37
Attenuated Virus	37
TABLE 8 VACCINE PREPARATIONS, BY DISEASE.....	37

<i>TABLE 9 VACCINE-PREVENTABLE DISEASE IN THE U.S., PRE- AND POST- VACCINATION PROGRAMS</i>	38
THE GLOBAL PROTEIN VACCINE MARKET.....	39
<i>TABLE 10 GLOBAL MARKET FORECAST FOR VACCINES, THROUGH 2013 (\$ MILLIONS)</i>	39
<i>FIGURE 10 GLOBAL MARKET FORECAST FOR VACCINES, 2008 AND 2013 (\$ MILLIONS)</i>	40
<i>TABLE 11 NEW AND EMERGING VACCINE PRODUCTS</i>	41
BLOOD PRODUCTS.....	42
WHAT DRIVES DEMAND FOR BLOOD PRODUCTS.....	42
THE GLOBAL MARKET FOR BLOOD PRODUCTS.....	43
<i>TABLE 12 GLOBAL MARKET FORECAST FOR BLOOD PRODUCTS, THROUGH 2013 (\$ MILLIONS)</i>	44
<i>FIGURE 11 GLOBAL MARKET FORECAST FOR BLOOD PRODUCTS, 2008 AND 2013 (\$ MILLIONS)</i>	44
<i>FIGURE 12 GLOBAL MARKET FOR BLOOD PRODUCTS, 2008 (%)</i>	45
Recombinant Albumin.....	45
Factor VIII.....	46
<i>TABLE 13 COMPANIES INVOLVED IN FACTOR VIII DEVELOPMENT</i>	46
Factor IX.....	46
Hemoglobin.....	47
Second Generation Hemoglobins in Development.....	48
<i>TABLE 14 COMPANIES INVOLVED IN RECOMBINANT HEMOGLOBIN MANUFACTURE</i>	49
Protein C.....	49
PEPTIDE ANTIBIOTICS.....	50
TYPES OF PEPTIDE ANTIBIOTICS.....	50
<i>TABLE 15 GLOBAL MARKET FORECAST FOR PEPTIDE ANTIBIOTICS, THROUGH 2013</i>	51
THE RESISTANCE PROBLEM.....	51
THERAPEUTIC ENZYMES.....	52
Glucocerebrosidase.....	52
Tissue Plasminogen Activator.....	53
Pancreatin.....	53
Thrombin.....	53
<i>TABLE 16 GLOBAL MARKET FORECAST FOR THERAPEUTIC ENZYMES, THROUGH 2013</i>	54
CHAPTER FIVE: MANUFACTURING TECHNOLOGY.....	55
NATURAL SOURCING AND EXTRACTION.....	55
HUMAN SOURCING.....	56
SPECIAL FEATURES OF HUMAN-SOURCING MANUFACTURE.....	56
<i>TABLE 17 PROTEIN DRUGS MADE BY HUMAN-SOURCE EXTRACTION</i>	56

SPECIAL FEATURES OF ANIMAL SOURCING	
MANUFACTURE.....	57
TABLE 18 PROTEIN DRUGS MADE BY NATURAL ANIMAL-SOURCE	
EXTRACTION.....	58
TABLE 19 PROTEIN DRUGS MANUFACTURED BY NATURAL	
SOURCING AND EXTRACTION, BY PRODUCT, THROUGH 2013	
(\$ MILLIONS).....	58
FIGURE 13 PROTEIN DRUGS MANUFACTURED BY NATURAL	
SOURCING AND EXTRACTION, BY PRODUCT, 2008 AND 2013	
(\$ MILLIONS).....	59
FIGURE 14 PROTEIN DRUGS MANUFACTURED BY NATURAL	
SOURCING AND EXTRACTION, BY PRODUCT 2008 (%).....	59
FIGURE 15 PROTEIN DRUGS MANUFACTURED BY NATURAL	
SOURCING AND EXTRACTION, BY PRODUCT, 2013 (%).....	60
MICROBIAL FERMENTATION.....	60
TABLE 20 PROTEIN DRUGS MANUFACTURED BY MICROBIAL	
FERMENTATION, BY PRODUCT, THROUGH 2013 (\$ MILLIONS).....	61
FIGURE 16 PROTEIN DRUGS MANUFACTURED BY MICROBIAL	
FERMENTATION, BY PRODUCT, 2008 AND 2013 (\$ MILLIONS).....	62
FIGURE 17 PROTEIN DRUGS MANUFACTURED BY MICROBIAL	
FERMENTATION, BY PRODUCT, 2008 (%).....	62
FIGURE 18 PROTEIN DRUGS MANUFACTURED BY MICROBIAL	
FERMENTATION, BY PRODUCT, 2013 (%).....	63
MAMMALIAN CELL CULTURE.....	63
BIOREACTORS.....	64
TABLE 21 TYPES OF BIOREACTORS.....	64
Bioreactors (Continued)	65
OTHER CELL CULTURE SYSTEMS: INSECT CELLS	66
TABLE 22 PROTEIN DRUGS MANUFACTURED BY CELL CULTURE,	
BY PRODUCT, THROUGH 2013 (\$ MILLIONS).....	66
FIGURE 19 PROTEIN DRUGS MANUFACTURED BY CELL	
CULTURE, BY PRODUCT, 2008 AND 2013 (\$ MILLIONS).....	67
FIGURE 20 PROTEIN DRUGS MANUFACTURED BY CELL	
CULTURE, 2008 (%).....	67
FIGURE 21 PROJECTED PROTEIN DRUGS MANUFACTURED BY	
CELL CULTURE, 2013 (%).....	68
TRANSGENICS: PLANTS AND ANIMALS	68
TRANSGENIC PLANTS PHARMING.....	68
TABLE 23 TRANSGENIC PLANT PHARMACEUTICALS UNDER	
DEVELOPMENT.....	69
TRANSGENIC ANIMALS	70
Founder Animal Production.....	70
History in the Making: the First Transgenic Drugs	71

<i>TABLE 24 PROTEIN DRUGS MANUFACTURED BY TRANSGENICS, BY PRODUCT, THROUGH 2013 (\$ MILLIONS)</i>	72
<i>FIGURE 22 PROTEIN DRUGS MANUFACTURED BY TRANSGENICS, BY PRODUCT, THROUGH 2013</i>	73
<i>FIGURE 23 PROTEIN DRUGS MANUFACTURED BY TRANSGENICS, BY PRODUCT, 2013 (%)</i>	73
<i>TABLE 25 PROTEIN DRUGS DERIVED FROM TRANSGENIC ANIMALS, 2008</i>	74
On the Horizon: Gene Therapy with Transgenics?	74
CHEMICAL SYNTHESIS	75
HOW IT WORKS.....	75
COST AND SCALING- UP	76
<i>TABLE 26 PEPTIDE PHARMACEUTICALS MANUFACTURED BY CHEMICAL SYNTHESIS</i>	77
<i>TABLE 27 PROTEIN DRUGS MANUFACTURED BY CHEMICAL SYNTHESIS, BY PRODUCT TYPE, THROUGH 2013 (\$ MILLIONS)</i>	77
<i>FIGURE 24 PROTEIN DRUGS MANUFACTURED BY CHEMICAL SYNTHESIS, BY PRODUCT TYPE, THROUGH 2013 (\$ MILLIONS)</i>	78
<i>FIGURE 25 PROTEIN DRUGS MANUFACTURED BY CHEMICAL SYNTHESIS, BY PRODUCT TYPE, 2008</i>	78
<i>FIGURE 26 PROTEIN DRUGS MANUFACTURED BY CHEMICAL SYNTHESIS, BY PRODUCT TYPE, 2013</i>	79
CHAPTER SIX: TECHNOLOGY	80
MANUFACTURING, PROCESSING AND FORMULATION.....	80
<i>FIGURE 27 MANUFACTURING PROCESS FLOW CHART</i>	80
PROCESSING AND DOWNSTREAM.....	81
PROTEIN AGGREGATION HAS CLINICAL RAMIFICATIONS.....	82
FOCUS ON FORMULATION	83
FREEZE-THAW	83
Challenges in the Freezing Process	84
Thawing	85
Freeze-Thaw Technologies	85
FORMULATION STEP.....	86
Formulation Step (Continued)	87
FILTRATION	88
DRUG PRODUCT FILLING.....	88
LYOPHILIZATION	89
Lyophilization (Continued)	90
Lyophilization (Continued)	91
INSPECTION AND PACKAGING	92
DRUG STORAGE, TRANSPORT AND DELIVERY	92
Protein-Silicone Oil Interactions	92
Leachables and Extractables	93
TRANSPORTATION.....	94

PHOTOSTABILITY	95
CHAPTER SEVEN: PATENT ANALYSIS	96
PATENTS BY PRODUCT TYPE.....	96
<i>TABLE 28 PROTEIN PHARMACEUTICALS, ISSUED PATENTS BY TECHNOLOGY, AUGUST 2005 TO AUGUST 2008.....</i>	<i>96</i>
<i>FIGURE 28 PROTEIN PHARMACEUTICALS, ISSUED PATENTS BY PRODUCT, AUGUST 2005 TO AUGUST 2008.....</i>	<i>97</i>
PATENTS BY REGION.....	97
<i>TABLE 29 PROTEIN PHARMACEUTICALS, ISSUED PATENTS BY REGION, AUGUST 2005 TO AUGUST 2008</i>	<i>97</i>
<i>TABLE 29 (CONTINUED).....</i>	<i>98</i>
<i>TABLE 30 PROTEIN PHARMACEUTICALS, ISSUED PATENTS BY TECHNOLOGY, AUGUST 2005 TO AUGUST 2008.....</i>	<i>98</i>
<i>FIGURE 29 PROTEIN PHARMACEUTICALS, ISSUED PATENTS BY TECHNOLOGY, AUGUST 2005 TO AUGUST 2008 (%)</i>	<i>99</i>
IMPORTANT PATENT ISSUES FOR FOLLOW-ON BIOLOGICS.....	99
PATENTS OF INTEREST IN THE PROTEIN DRUGS FIELD	100
TREATMENTS USING TRANSGENIC GOAT PRODUCED ANTITHROMBIN III.....	100
HIGHLY PHOSPHORYLATED AND SULFATED RECOMBINANT FACTOR IX	101
HEPATITIS C RECEPTOR PROTEIN CD81	101
PURIFICATION OF POLYPEPTIDES.....	102
Purification of Polypeptides (Continued).....	103
CHAPTER EIGHT: INTERNATIONAL ASPECTS	104
<i>TABLE 31 GLOBAL PROTEIN THERAPEUTIC MARKET PRODUCTION BY REGION, 2008 (\$ MILLIONS)</i>	<i>104</i>
UNITED STATES.....	105
WESTERN EUROPE.....	105
JAPAN.....	105
CHINA.....	106
CHAPTER NINE: MARKET SHARE.....	107
<i>TABLE 32 MARKET SHARE OF COMPANIES INVOLVED IN ANTIBODY DRUGS, 2008 (UNIT, %).....</i>	<i>107</i>
<i>TABLE 33 MARKET SHARE OF COMPANIES INVOLVED IN CYTOKINES, 2008 (UNIT, %).....</i>	<i>108</i>
<i>TABLE 34 MARKET SHARE OF COMPANIES INVOLVED IN PEPTIDE HORMONES, 2008 (UNIT, %).....</i>	<i>108</i>
<i>TABLE 35 MARKET SHARE OF COMPANIES INVOLVED IN VACCINES, 2008 (UNIT, %).....</i>	<i>108</i>
<i>TABLE 36 MARKET SHARE OF COMPANIES INVOLVED IN BLOOD PRODUCTS, 2008 (UNIT, %).....</i>	<i>109</i>

<i>TABLE 37 MARKET SHARE OF COMPANIES INVOLVED PEPTIDE ANTIBIOTICS, 2008 (UNIT, %)</i>	109
<i>TABLE 38 MARKET SHARE OF COMPANIES INVOLVED ENZYMES, 2008 (UNIT, %)</i>	109
CHAPTER TEN: COMPANY PROFILES	110
ABBOTT LABORATORIES.....	110
<i>TABLE 39 ABBOTT LABS PROTEIN DRUGS</i>	111
AEGIS THERAPEUTICS	111
ALEXION PHARMACEUTICALS	112
AMGEN	113
<i>TABLE 40 AMGEN'S PROTEIN DRUGS</i>	114
BAYER DIAGNOSTICS	114
BIOGEN IDEC, INC.	115
<i>TABLE 41 BIOGEN IDEC'S PROTEIN DRUGS</i>	116
CENTOCOR	116
ELI LILLY & CO.....	117
<i>TABLE 42 LILLY'S PROTEIN DRUGS</i>	118
GENENTECH, INC.	118
<i>TABLE 43 GENENTECH'S PROTEIN DRUGS</i>	119
GENZYME CORP.	119
<i>TABLE 44 GENZYME CORPORATION PROTEIN DRUGS</i>	120
<i>TABLE 44 (CONTINUED)</i>	121
JOHNSON & JOHNSON INC.	121
MEDIMMUNE, INC.	122
MEDAREX	122
<i>TABLE 45 MEDAREX'S PIPELINE PROTEIN DRUGS</i>	123
MERCK & CO., INC.	124
<i>TABLE 46 MERCK'S PROTEIN DRUGS</i>	124
MERCK SERONO.....	125
<i>TABLE 47 MERCK-SERONO'S PROTEIN DRUGS</i>	126
NOVARTIS PHARMA AG	126
<i>TABLE 48 NOVARTIS' PROTEIN DRUGS</i>	127
NOVO NORDISK A/S	127
NOVO NORDISK A/S (CONTINUED).....	128
ROCHE HOLDINGS, LTD.	129
<i>TABLE 49 ROCHE'S PROTEIN DRUGS</i>	130
SANGART	131
SANOFI-AVENTIS	131
UNIGENE LABORATORIES, INC.....	132
UNIGENE LABORATORIES, INC. (CONTINUED)	133
VACCINOGEN INC.....	134
WYETH	135
WYETH (CONTINUED)	136
<i>TABLE 50 WYETH' PROTEIN DRUGS</i>	137

APPENDIX: WEB RESOURCES FOR PROTEIN DRUG DESIGN	138
THE NATIONAL CANCER INSTITUTE 3D STRUCTURE DATABASE.....	138
KIBANK	138
COMBINATORIAL CHEMISTRY REVIEW	138
GDB: STRUCTURES.....	139