

**NOVEL ANTIBODIES & THERAPEUTIC
PROTEINS: TECHNOLOGICAL CHALLENGES &
FUTURE PROSPECTS**

By

Dr Cheryl L Barton

Pharmavision

Published by

SELECT
BIOSCIENCES
Delivering the Difference

SelectBiosciences.com

Legal Disclaimer

This Market Report is Copyright Protected by Select Biosciences Ltd. All rights reserved. Neither this Market Report nor its contents (in whole or in part) may be reproduced in any form without the written consent of Select Biosciences.

For More Information, Please Contact Select Biosciences at:

Telephone: +44 (0) 1787 314954

E-mail: Kathy.Gray@Selectbiosciences.com

Terms of Use Governing This Market Report:

Select Biosciences has exercised commercially-reasonable efforts in the preparation of this market report ("Report"), which is based on information available to the public, proprietary technology/market analyses, and information submitted to Select Biosciences by companies and institutions. This Report is intended solely for internal use by the purchaser ("Purchaser") for specific informational, research, or other business purposes. The Purchaser shall not reproduce, distribute, or provide to any third-party this Report (in whole or in part) without the prior written permission of Select Biosciences.

SELECT BIOSCIENCES MAKES NO REPRESENTATIONS OR WARRANTIES AND EXPRESSLY DISCLAIMS ANY FURTHER REPRESENTATIONS OR WARRANTIES, EXPRESS, IMPLIED, OR STATUTORY, REGARDING THE REPORT, INCLUDING BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NONINFRINGEMENT. SELECT BIOSCIENCES SHALL NOT BE LIABLE TO THE PURCHASER FOR ANY CLAIM REGARDING THE ACCURACY OR COMPLETENESS OF THE INFORMATION CONTAINED IN THE REPORT.

Under no circumstances shall Select Biosciences be liable for incidental, special, indirect, direct or consequential damages or loss of profits, interruption of business, or related expenses that may arise from use of this Report, including but not limited to those resulting from inaccuracy of the data therein. Due to the content nature of this market analysis Report, **no returns or refunds of any kind** are issued by Select Biosciences after shipment of this Report to the Purchaser either in electronic format or in hard-copy format.

Cheryl Barton

Dr Cheryl L Barton is an independent consultant with over 16 years research and business analysis experience. Following her senior research positions in academia and seven years with Merck, in which she was responsible for a variety of CNS research projects. Dr Barton joined Dutch investment bank ABN Amro NV as a senior equity analyst to provide coverage on pan-European companies, and assessed the potential impact of new drug development on European Stocks. In 2002, Dr Barton founded a consulting business (Pharmavision) to provide independent, tailor-made, pharmaceutical thematic research to investment houses and pharmaceutical companies

Table of Contents

Novel Antibodies & Therapeutic Proteins: Technological Challenges & Future Prospects

Key Findings 2

Introduction: Historical Milestones & Impact on the Pharma Industry	2
Monoclonal Antibodies: Market Segmentation, Size & Trends	3
Therapeutic Proteins: Market Segmentation, Size & Trends	3
Challenges & Advances in Discovery, Development & Commercialization of TPs	4
Regulation, IP & Reimbursement Issues	6
Industry Perspective & Future Prospects	7

Chapter 1 Introduction: Historical Milestones & Impact on the Pharma Industry 10

Key Findings	10
Overview, definitions, and historical milestones	11
Monoclonal antibodies	11
<i>Therapeutic Uses of mAbs</i>	15
Therapeutic proteins	15
Impact of biopharmacy on the pharma industry	17
<i>R&D</i>	17
<i>Product formulation & marketing</i>	18
<i>Pharma-biopharma alliances</i>	18
<i>Pharma majors</i>	19
Overall Conclusions	20
Report Structure	23

Chapter 2 Monoclonal Antibodies: Market Segmentation, Size & Trends 25

Key Findings	25
--------------	----

Monoclonal Antibodies: Types	26
Murine	26
Chimeric & humanized antibodies	27
<i>Chimeric</i>	27
<i>Humanized</i>	28
<i>Fully human</i>	29
<i>Antibody fragments</i>	29
Monoclonal Antibodies: Uses	31
Cancer	31
<i>Naked antibodies</i>	31
Conjugated antibodies	32
<i>Radiolabelled antibodies</i>	32
<i>Chemolabelled antibodies</i>	33
<i>Immunotoxins</i>	33
Anti-TNF	33
Other indications	34
Autoimmune diseases	34
Bacterial infections	34
Bone disorders	35
Cardiovascular disease	35
CNS disorders	35
Pain	36
Monoclonal Antibodies: The Market	37
Front Runners: Products	37
Front Runners: Companies	38
Abbott Laboratories	38
Biogen Idec	39
Bristol-Myers Squibb	39
Genentech	40
Johnson & Johnson	40
Other mAbs	41
Monoclonal Antibodies: The Future	42
Ones to Watch: Pipeline Products	43
Oncology	43
<i>Head and Neck</i>	43
<i>Ovarian</i>	43
<i>Melanoma</i>	44
<i>Renal cell</i>	44
Immuno-inflammatory related diseases	45
<i>Rheumatoid arthritis</i>	45
<i>Eosinophilic esophagitis</i>	45
Other Indications	46
Autoimmune diseases	46
<i>Systemic lupus erythematosus</i>	46
<i>Type 1 diabetes</i>	47
CNS disorders	48
<i>Alzheimer's disease</i>	48

Infectious diseases	48
<i>Bacterial infections</i>	48
Pain	49
Ones to Watch: Companies	49
Amgen	49
Bioinvent International AB	49
Celldex Therapeutics Inc	50
Genmab A/S	51
Glycotope GmbH	51
ImmunoGen	51
Pfizer	52
Seattle Genetics	53
Tolerx	53
Wilex AG	54
Conclusions	54

Chapter 3 Therapeutic Proteins: Market Segmentation, Size & Trends 57

Key Findings	57
Therapeutic Proteins	58
Therapeutic Proteins: Classes	58
Insulin	58
Growth hormone	59
Haemopoietic growth factors	60
<i>Erythropoietin</i>	60
<i>Colony-stimulating factors</i>	61
Cytokines	61
Interleukins	61
Coagulation factors	63
Therapeutic Proteins: The Market	65
Front Runners: Products	66
Insulin products	66
EPO products	66
Coagulation factor products	66
Ones to Watch: Pipeline Products	67
Early stage	67
Cytokines	67
Haemopoietic growth factors	69
Late stage	69
Front Runners: Companies	70
Specialist companies	70
Amgen	70

Biogen Idec	71
Genentech	71
Major pharmaceutical companies	72
Baxter International	72
CSL Behring	73
Eli Lilly	73
Ipsen	74
Merck Serono	74
Novo Nordisk	75
Sanofi Aventis	75
M&A Activity	76
Ones to Watch: Companies	79
Agennix AG	79
Akebia Therapeutics, Inc.	79
Biovitrum AB	79
Cytheris SA	80
Dyax	80
ERYtech	81
H. Lundbeck A/S	81
Helix BioPharma	81
Human Genome Sciences	82
Immutep SA	82
Octapharma AG	83
Phosphagenics	84
Proteon Therapeutics	84
Shire	84
Teva Pharmaceuticals	84
ThromboGenics NV	85
ZymoGenetics	86
Conclusions	87

Chapter 4 Challenges & Advances in Discovery, Development & Commercialization of TPs 89

Key Findings	89
Phage display	92
High-throughput screening	95
New Classes of Therapeutic Proteins	97
Major histocompatibility complex proteins	97
<i>Phage display of MHCs</i>	97
<i>Yeast cell surface display of MHCs</i>	98
T cell receptors	98
Protein fusions & rational design	99
<i>Phage display of TCRs</i>	100
<i>Yeast surface display of TCRs</i>	100
TCR -like antibodies	100

Targets for New Monoclonal Antibodies	101
Production Challenges	104
Making New Therapeutic Proteins “Fit For Purpose”	104
Improving Pharmacokinetics	105
Fusion	105
Glycosylation	106
Pegylation	106
Reducing Immunogenicity	107
Genetic Engineering	108
Display technologies	109
Phage display	109
Cell surface display	109
Cell free display	109
Commercial Production	110
Manufacturing capabilities	112
Mammalian cell culture—still the most widely-used system	112
Therapeutic Proteins: Production Challenges	113
PTM glycosylation	113
PTM misfolded proteins	114
Protein aggregation	115
Oxidation	115
Deamidation	115
Plant-based Protein Production	116
Case Study: Protalix ProCellEx™ plant cell system	117
Case Study: Biorex Therapeutics LEX system	118
Non-invasive Protein Delivery	118
Proteins & peptides: nature vs. pharmaceuticals	119
Advanced Injection Technologies	120
Conclusions	121

Chapter 5 Regulation, IP & Reimbursement Issues 123

Key Findings	123
Towards regulatory harmonisation	125
Data requirements	126
Local partners	127
GMP compliance	128
Inspections	129
Suppliers’ compliance	130
Communicating with the regulators	131
Regulation of biosimilars	132
Intellectual Property Issues	134
Recombinant DNA technology	136

Monoclonal antibody technology	137
<i>Evolution of mAb technology</i>	138
Current status of technology	139
Cost & Reimbursement Issues	140
Conclusions	142

Chapter 6 Industry Perspective & Future Prospects 146

Key Findings	146
Market size	148
Product trends	149
Industry trends	152
Market Trends	154
Production & manufacturing	154
R&D & product development	155
Monoclonal antibodies	155
<i>Cancers</i>	155
<i>Immuno-inflammatory related diseases</i>	157
<i>CNS diseases</i>	157
<i>Infectious diseases</i>	158
Therapeutic proteins	158
Trends in personalised medicine	159
Commercial relevance	161
Delivery trends	162
Inhalation	163
Transdermals	163
Therapeutic Growth	163
Patient & disease demographics	163
Personalised medicine	164
Companion diagnostics	164
The Biosimilar Market	165
Opportunities & threats	165
The US market: the ‘biggest biosimilar prize’	167
Future Prospects	168
Acknowledgments	171
Bibliography & Endnotes	172

List of Figures

Figure 1:	Schematic of mAb	13
Figure 2:	Molecular structure of Campath	28
Figure 3:	Production strategies for antibody fragment therapeutics	30
Figure 4:	Schematic of a bacteriophage structure	93
Figure 5:	Production of a phage library	94
Figure 6:	HTS microtitre plates	96
Figure 7:	Rational design of fusion proteins	99
Figure 8:	Biologics today & the future	148
Figure 9:	New cancer therapeutics and vaccine entering clinical study 1993-2006	156

List of Tables

Table 1:	Leading marketed antibodies	41
Table 2:	Leading marketed therapeutic proteins	42
Table 3:	Leading cytokine products	63
Table 4:	Leading coagulation factor products	64
Table 5:	Leading insulin products	66
Table 6:	Leading EPO products	66
Table 7:	Leading coagulation factor products	67
Table 8:	Late stage therapeutic proteins	70
Table 9:	Specialist companies	70
Table 10:	Molecular targets of leading mAbs	101
Table 11:	Molecular targets of developmental mAbs	102
Table 12:	Cost biosimilars vs. brands	142