Development and Licensing of Biopharmaceuticals

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Master of Philosophy

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SUMMARY

Biopharmaceutical products now represent a very important fraction of the total pharmaceutical market. The aim of this thesis is to provide an overview of biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004, and to highlight trends in the development of the biopharmaceutical industry. Interferon beta is used as a case example to illustrate problems and opportunities in the licensing process, evaluation and marketing of a biopharmaceutical drug. Interferon also demonstrates the impact of the United States (US) government's orphan drug incentive scheme on pharmaceutical drug development.

Biopharmaceuticals approved in the US and the EU over the last 10 years were searched within publicly accessible sources. These searches identified 147 biopharmaceuticals that were approved including 30 monoclonal antibodies, 32 vaccines and one antisense oligonucleotide. No gene therapy product was approved by either the Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) during this period. Biopharmaceuticals account for 28% of all medicines approved in the US between 1998 and 2004 and 36% in the EU between 1995 and 2004. The biopharmaceutical industry is still small or medium sized. Biopharmaceuticals approved thus far are mainly protein-based agents for the treatment of life-threatening, chronic or rare diseases, e.g. cancer, severe infection, diabetes, autoimmune diseases and blood-related diseases.

Several biopharmaceuticals have been advantaged by being licensed under the Orphan Drug Act; the Orphan Drug Act states that a rare disease needs to be either affects less than 200,000 persons or the cost of develop such a drug cannot be recovered from the sales. The evaluation of interferon beta products in this thesis shows that the market for an orphan product can be large and an orphan drug is not equal to non-profitable drug. Interferon beta was introduced in 1993 under the US Orphan Drugs Act. By 2003, worldwide sales of three branded formulations exceeded $2.87 billions. However, no direct comparison of efficacy is available between all currently marketed interferon beta products. Pre-marketing clinical trials submitted to the FDA for interferon beta products were searched. Odds ratios and 95% CIs were chosen as evaluation tools for comparison of efficacy between orphan products. The result shows that whilst demonstration of only one aspect of clinical superiority (that is, either safety or efficacy) is enough for the licensing of another orphan product, such a newly licensed drug may not offer superiority using different clinical endpoints.

The financial risks linked with biopharmaceutical drug development are significant although the reward is huge. Biopharmaceutical companies should address how to assure the quality, safety and efficacy of new products in order to deal with new challenges in the near future, such as biogenerics.

Keywords: biopharmaceutical, regulation, interferon beta, orphan drug regulations

Dedication

I would like to dedicate this thesis to my family, especially my parents, with love and thanks for all their support, guidance and encouragement.

I am also grateful to my husband, Di Li, for his full support during my study abroad.

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Chapter I: General Introduction

The biopharmaceutical industry is an essential and growing component of the global, knowledge-based economy. The 1980's have been called the "modern biotechnology era". The first recombinant protein, an insulin (Humulin, Lilly) was launched in 1982; the first recombinant vaccine against hepatitis B was approved by the FDA (Recombivax HB, Merck) in 1986 and the first therapeutic monoclonal antibody (Orthoclone OKT3, kidney transplant rejection, Ortho Biotech) was approved also in 1986 (Fig 1.1). With the continuing rapid progress in genomics, proteomics, bioinformatics, and other basic sciences, the biopharmaceutical industry is entering into an exciting era. Over 150 biopharmaceuticals are currently approved for sale worldwide.

This chapter provides a general introduction to biopharmaceuticals, the aim and objectives of this project.

1.1 Definition of biopharmaceuticals

The traditional meaning of biological products, as used in the United States, the major global market, encompasses a wide range of categories such as vaccines, blood and blood components, allergenics, gene therapy, tissues, and recombinant therapeutic proteins (FDA CBER: What is a biological product? Available from: http://www.fda.gov/cber/faq.htm). Biopharmaceuticals differ from the traditional biological products and include some, but not all of those agents above. The industry has yet to come up with a consensus definition, however a recent report contrasts the difference between traditional pharmaceuticals and biopharmaceuticals in the following way 'unlike chemically synthesized small molecule drugs that have long underpinned the traditional pharmaceutical industry, biopharmaceuticals are complex macromolecules created through the genetic manipulation of living organisms using gene cloning, recombinant DNA (gene splicing) or cell fusion technologies. In terms

of product type, these include recombinant proteins, recombinant antigen vaccines and vaccines derived from genetic material such as DNA, therapeutic monoclonal antibodies and oligonucleotides.' (Anon, 2001).

The definition of biopharmaceutical used by the European Commission is: 'recombinant protein drugs, recombinant vaccines and monoclonal antibodies (for therapeutic roles)', available from: http://europa.eu.int/comm/research/biosociety/library/glossarylist_en.cfm?Init=B .

The definition of biopharmaceutical used by the Tufts Center for the Study of Drug Development is: 'any therapeutic biological compound, including recombinant proteins, monoclonal and polyclonal antibodies, antisense oligonucleotides, therapeutic genes, and recombinant and DNA vaccines', available from: http://csdd.tufts.edu/InfoServices/Glossary.asp .

The other accepted definition of a biopharmaceutical is "a protein or nucleic acid based pharmaceutical substance used for the therapeutic or in vivo diagnostic purposes which is produced by means other than direct extraction from a native (non-engineered) biological source." (Walsh 2002).

In this thesis biopharmaceuticals will include gene therapy products; monoclonal antibodies; antisense oligonucleotides (manufactured by direct chemical synthesis and by enzymatic synthesis); recombinant vaccines and other proteins intended for therapeutic use, including therapeutic proteins derived from plants, animals, or microorganisms, and recombinant versions of these products.

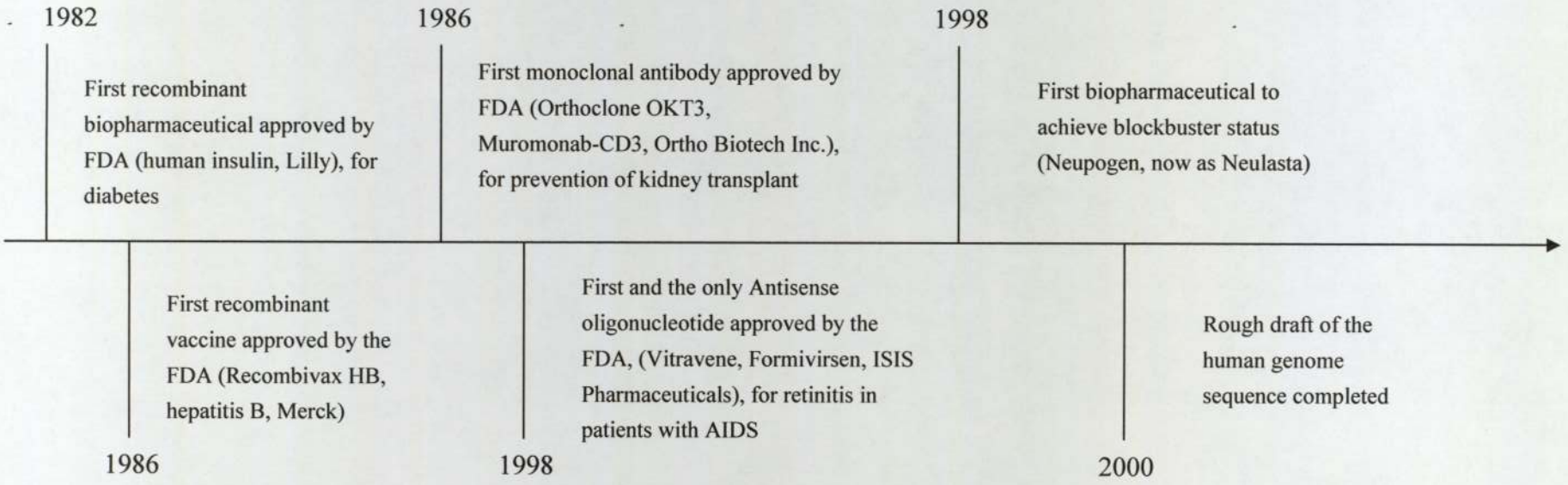


Fig 1.1 Milestones of biopharmaceuticals developed for human use (Source: Bibby 2003)

1.2 Aim and organisation of this thesis

The aim of this thesis is to provide a summary overview of biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004, highlight the trends of biopharmaceutical industry thus far and take interferon beta products as a case example to investigate further the licensing process, pre-marketing clinical trials evidence, and post-marketing sales in the United States to see how the regulators and the drug companies balance the orphan drug incentive, the risk and the benefit to be derived from treatment of patients required the orphan drugs.

This thesis is organised into four chapters:

Chapter 1: General introduction;

Chapter 2: Comprehensive review of biopharmaceuticals approved in the United States and the European Union between 1995 and 2004;

Chapter 3: Case study of biopharmaceutical development: Interferon beta products and The Orphan Drug Act;

Chapter 4: General conclusion and future work

Chapter 2 Comprehensive review of biopharmaceuticals approved in the United States and the European Union between 1995 and 2004

Several research articles have published during these recent years (Reichert 2000; Reichert et al., 2001; Reichert 2004; Walsh 2003) discussing biopharmaceuticals approved in the EU and US. However, this chapter aims to provide a summary overview and assess the drug development trends to date and to explore why they may have happened within the biopharmaceutical industry thus far, using information on biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004.

2.1 Introduction

2.1.1 The licensing procedure of biopharmaceuticals in the United States

The US is the largest and most rapidly growing pharmaceutical market in the world. Before 2003, almost all the biological products were reviewed by CBER (Center for Biologics Evaluation and Research). In order to increase the efficiency and consistency of reviews, the FDA began to transfer the review of protein-based therapeutic agents from CBER to CDER (Center for Drug Evaluation and Research) from June 30, 2003. CDER is responsible for co-ordinating the pre-market review and supervision of these products. All the products transferred to CDER are classified as biological therapeutic products and will continue to be regulated as licensed biologics. (FDA: Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, available from: http://www.fda.gov/cber/transfer/transfer.htm).

According to the FDA's information, the categories of therapeutic biological products reviewed by CDER include: "

- Monoclonal antibodies for in vivo use.

- Proteins intended for therapeutic use, including cytokines (e.g. interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, or microorganisms, and recombinant versions of these products.
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response).
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo. "

The categories of therapeutic biological products still to be reviewed by CBER include: "

- Cellular products, including products composed of human, bacterial or animal cells (such as pancreatic islet cells for transplantation), or from physical parts of those cells (such as whole cells, cell fragments, or other components intended for use as preventative or therapeutic vaccines).
- Gene therapy products. Human gene therapy/gene transfer is the administration of nucleic acids, viruses, or genetically engineered microorganisms that mediate their effect by transcription and/or translation of the transferred genetic material, and/or by integrating into the host genome. Cells may be modified in these ways ex vivo for subsequent administration to the recipient, or altered in vivo by gene therapy products administered directly to the recipient.
- Vaccines (products intended to induce or increase an antigen specific immune response for prophylactic or therapeutic immunization, regardless of the composition or method of manufacture).
- Allergenic extracts used for the diagnosis and treatment of allergic diseases and allergen patch tests.

- Antitoxins, antivenins, and venoms
- Blood, blood components, plasma derived products (for example, albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors), including recombinant and transgenic versions of plasma derivatives, (for example clotting factors), blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations including radiolabeled or conjugated forms, and certain fibrinolytics such as plasma-derived plasmin, and red cell reagents."

(FDA: Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, available from: http://www.fda.gov/cber/transfer/transfer.htm).

Hence, biopharmaceuticals studied defined in this thesis have been reviewed at either of two FDA centers, the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER) in the US.

Biopharmaceutical product evaluation follows a similar general pathway to that used for conventional drugs (Reichert et al., 2001). The review procedure of biopharmaceutical products is shown in Fig 2.1. Receipt of an original product application by the FDA can be viewed as the first day of the whole application process. A first action letter will be issued after the application has been reviewed by the appropriate evaluation center. The letter will state that either the application has been approved or some deficiencies exist. The applicant must resubmit the application if there are some deficiencies until the application has been approved.

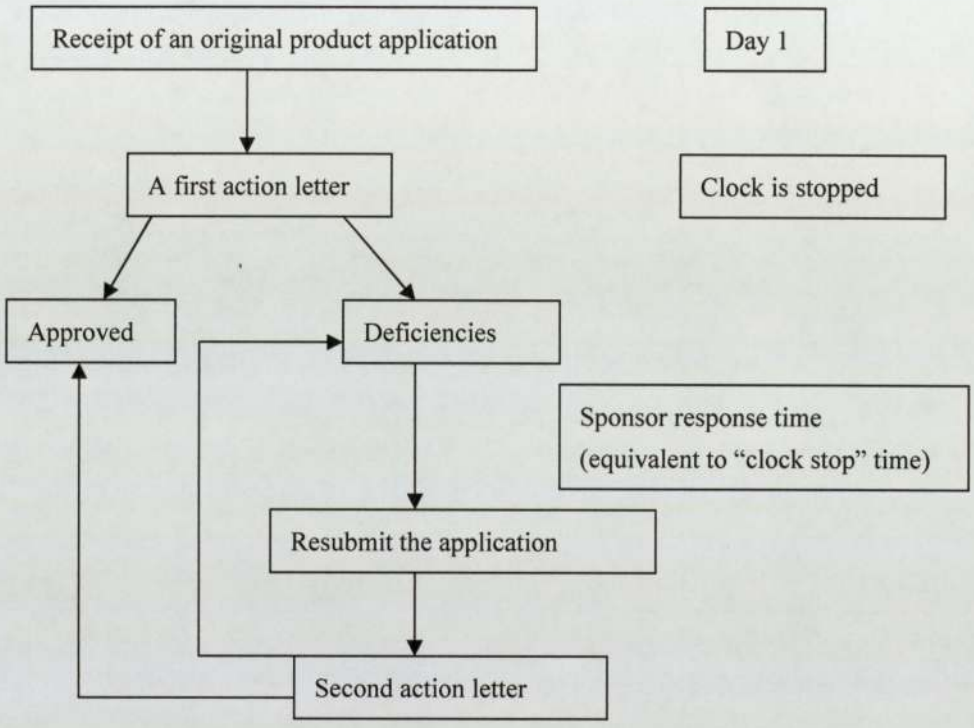


Fig 2.1 FDA biopharmaceutical product review procedure
(Source: Reichert et al., 2001)

2.1.2 The licensing procedure for biopharmaceuticals in the European Union

As one of the world's major players in the drug markets, the licensing process of biopharmaceutical products in the European Union (EU) has changed dramatically during the last 40 years.

Prior to the establishment of the EMEA in 1995, pharmaceutical companies had to go through a time-consuming and expensive process of review and approval in each EU country separately. In order to facilitate the simultaneous introduction of a specific agent to two or more Member States, the European Union had to streamline the licensing procedure. The establishment of the European Medicines Evaluation Agency (EMEA) by Council Regulation (EEC) No. 2309/93 on 22 July of 1993 and, which changed its name to European Medicines Agency in 2004, marked the most important milestone in standardising product review in the EU.

There are two routes for authorization of medicinal products by the EU system (Davis 2003): a centralized procedure (Council Regulation 2309/93) or a decentralized procedure (or mutual recognition procedure, Directive 93/39/EEC).

The EMEA categorizes medicinal products as either List A or List B. List A products are high technology medicinal products especially those derived from biotechnology; the others are classified as List B products (Council Regulation (EEC) No 2309/93). A complete description of List A and List B product categories is provided in Appendix 1.

All the List A products must be reviewed by the centralized procedure while manufacturers of List B products can choose to have these products reviewed by either the centralized procedure or the decentralized procedure (Healy et al., 1999). Hence, nearly all biopharmaceutical products approved in the EU since 1995 have been reviewed under the

centralized procedure. Applications are submitted directly to the EMEA, reviewed by the Committee for Proprietary Medicinal Product (CPMP) and lead to single marketing authorizations for all the 25 EU member countries.

As shown in Fig 2.2 (Reichert et al., 2001), the centralized procedure has strict timetable. EMEA's total time to review a product application is 240 days. The final marketing authorization is granted by the European Commission (EC) within 60-80 days after receipt of the assessment report from the CPMP. The marketing authorization is valid initially for 5 years. Licence renewal is required after 5 years. The marketing authorization is usually of unlimited time validity after renewal. In addition, the marketing authorization is normally considered invalid if any authorization is not used for 3 years.

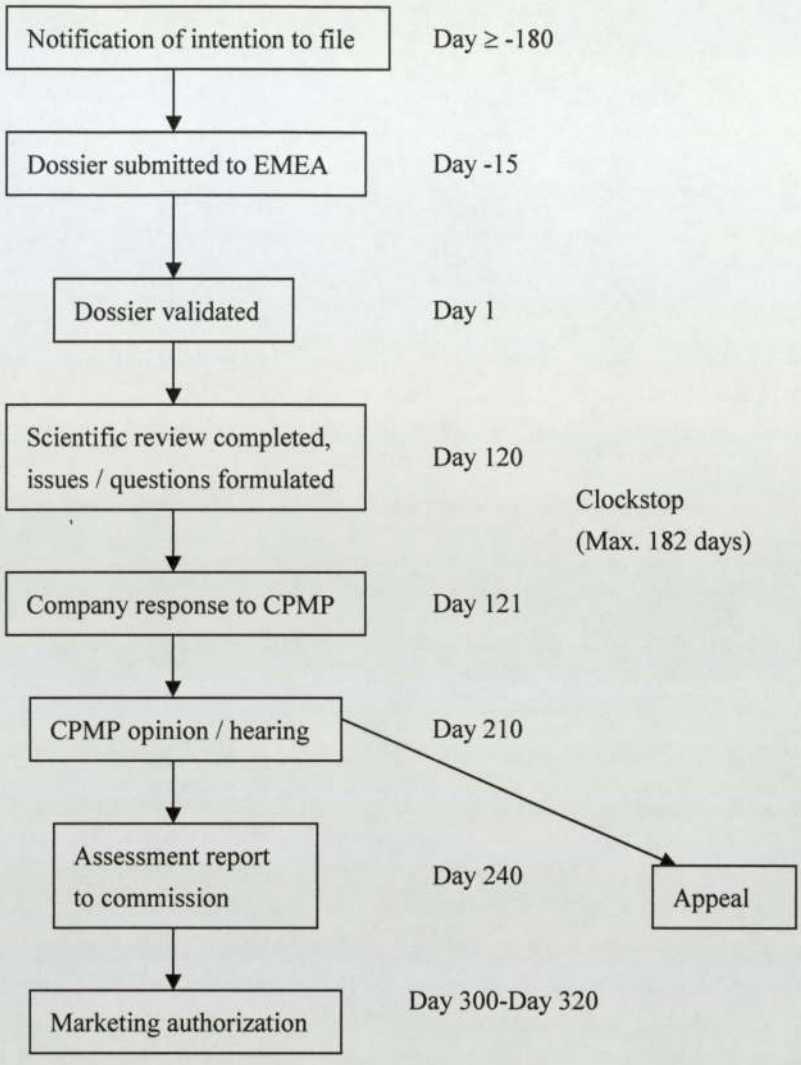


Fig 2.2 EMEA biopharmaceutical product review procedure
(Source: Reichert et al., 2001)

2.2 Objectives

Biopharmaceutical products are making an increasing contribution to the output of the pharmaceutical industry. In order to speed up the approval process, and provide safe and effective medicines, the regulations have changed dramatically in the EU and U.S. The objective of this chapter is to provide an overview and highlight the market trends of the biopharmaceutical industry; this chapter describes a comprehensive review of the biopharmaceuticals, which have been approved in the United States and the European Union between 1995 and 2004.

2.3 Methods

Using publicly available websites, data were collected on biopharmaceutical products which have been approved by the FDA and EMEA. The results have been updated to 20th Feb. 2005.

FDA database

- http://www.fda.gov/cber/transfer/transfprods.htm. [Accessed: 25/02/2004] This list identifies specific products transfered from CBER to CDER as defined in Chapter 1. The list includes proteins intended for therapeutic use, including proteins derived from plants, animal, or microorganisms and recombinant versions (such as monoclonal antibodies) of these products;

- http://www.fda.gov/cber/products.htm This FDA CBER product approval webpage describes recombinant vaccines and recombinant proteins of blood derived products;
- http://www.fda.gov/cder/biologics/biologics_table.htm [Updated: 12/12/2004]. This is the FDA therapeutic biologicals approval webpage which provides supplementary information;

- http://www.fda.gov/cder/rdmt/default.htm [Updated: 30/11/2004]. This details the CDER New Drug and Biologic Approval Reports;
- The sponsor companies' websites and other public domain websites;
- The companies' annual reports for year 2003;
- http://www.biopharma.com/cgi/results2004.lasso [Updated:15/11/2004] A BIOPHARMA products database.

EMEA database:

- http://www.emea.eu.int/pdfs/general/direct/listprod/tableofproducts.pdf This list includes medicinal products with a community marketing authorization by Human Medicines Evaluation Unit of EMEA from 1995 to May 2004;
- http://pharmacos.eudra.org/F2/register/register.htm#h285 [Updated: 17/02/2005]. This is the European Commission's website including a community register of medicinal products for human use;
- www.emea.eu.int. This website links to EMEA Annual Reports, European Public Assessment Reports (EPARs) and CPMP press releases;
- Sponsor companies' websites and other public domain websites;
- Companies' annual reports for year 2003;

Data were derived from the above websites to develop a biopharmaceutical database (Appendix 2), which was reorganized in various ways:

- The total number of biopharmaceutical products approved by the FDA and EMEA from 1995 and 2004 and sub-analysis of the data by different geographic region (US and EU);
- Biopharmaceuticals approved by the FDA and EMEA presented by approval year respectively;
- The number of biopharmaceuticals according to different therapeutic categories;
- The sales data for all biopharmaceutical products in the database in 2003 and identification of biopharmaceuticals with sales of more than US$1 billion per annum

(blockbuster) based on the sponsoring companies' sales data;

- Biopharmaceutical products that have been withdrawn from the market and the reasons for withdrawal;

2.4 Results

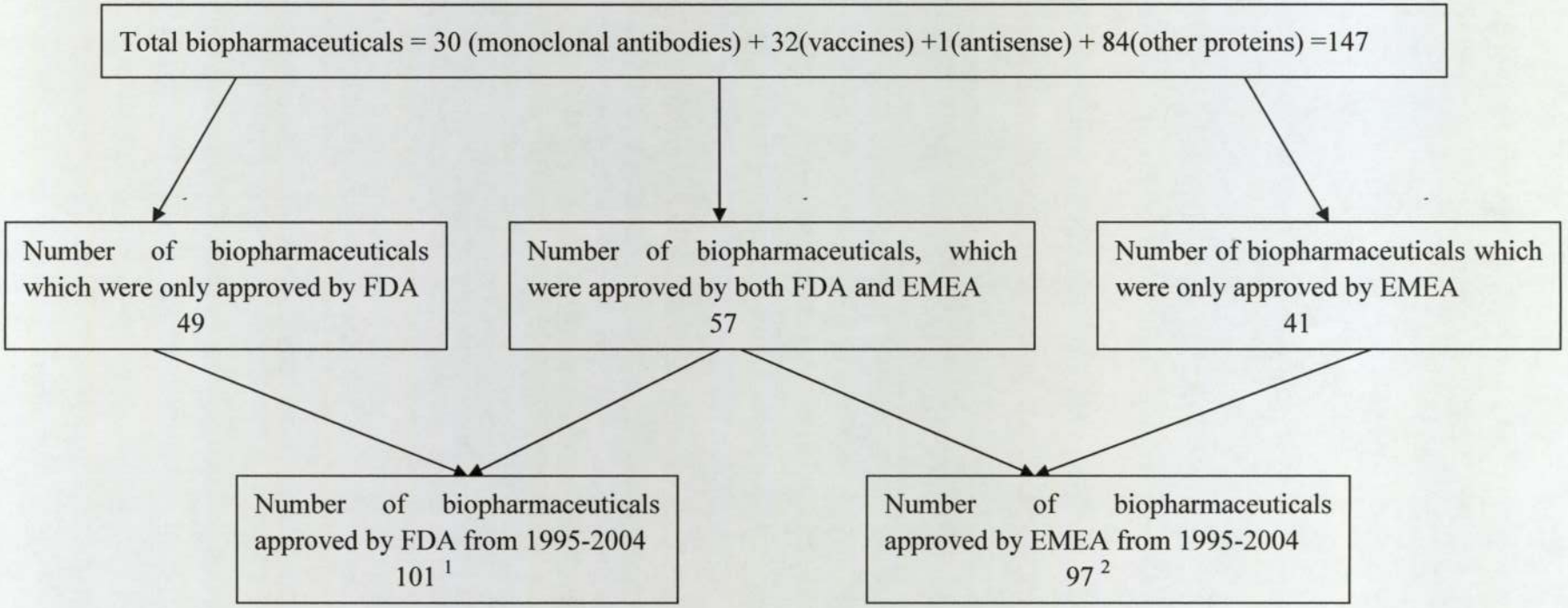
The database contains 147 biopharmaceuticals approved by the FDA and EMEA in the 10 years between 1995 and 2004. Neither the FDA nor the EMEA has approved any gene therapy products yet. Also, only one oligonucleotide antisense product was licensed over this period. All the other biopharmaceuticals are protein-based which includes 30 monoclonal antibodies (therapeutic use and diagnostic use), 32 vaccines and 84 other proteins.

2.4.1 Regional analysis of biopharmaceuticals approved by the FDA and EMEA

Fig 2.3 shows that 101 biopharmaceuticals were approved by the FDA between 1995 and 2004. These 101 biopharmaceuticals do not include betaferon, cerezyme, nutropin AQ, alfatronol and kogenate, which were approved by the FDA before 1995. There are 97 such biopharmaceuticals approved by the EMEA between 1995 and 2004. These 97 biopharmaceuticals do not include glucagon, whose approval date is not available.

This database was further analysed for restricted licensing agreements across regions, there are 49 (33%) biopharmaceuticals, which were approved only by the FDA, 41 (28%) biopharmaceuticals only approved by the EMEA and 57 (39%) biopharmaceuticals approved by both agencies.

The total number of biopharmaceuticals approved by the FDA and EMEA in these 10 years is similar and the total number worldwide, excluding overlapping compounds, is 147.



Note: 1.Biopharmaceuticals approved by the FDA between 1995 and 2004 do not include Betaferon (1993),Cerezyme (1994),Nutropin AQ(1994),Alfatronol (1983) and Kogenate (1993) which were approved before 1995;

2. Biopharmaceuticals approved by the EMEA between 1995 and 2004 do not include

Fig 2.3 Biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004

The licensing time differences between biopharmaceuticals approved by the FDA and EMEA (approval date of the EMEA minus approval date of the FDA) were calculated, see Table 2.1. Of the 57 biopharmaceuticals approved by both the FDA and EMEA, 68% (39 biopharmaceuticals) were approved by the FDA first, and then were approved by the EMEA agency. The average additional time taken for the 39 biopharmaceuticals to be approved by the EMEA was 572 days.

The EMEA approval date for GlucaGen was not available. Of the 57 biopharmaceuticals approved by both the FDA and EMEA, 18 products were approved by the EMEA first. The average additional time taken for the 17 biopharmaceuticals to be approved by the FDA was 588 days. The time needed for compounds developed in Europe get into the market of the United States is similar to those compounds developed in the United States getting into the market of Europe.

Further analysis revealed that of the 57 biopharmaceuticals approved by the FDA and EMEA, 34 (60%) products were approved in at least the US or EU in the five-year period from 2000 compared with 40% of product approvals between 1995 and 2000.

Table 2.1 Biopharmaceuticals approved by both the FDA and EMEA between 1995 and 2004

Trade name	Generic name	EMEA Approval Date	FDA Approval Date	Interval (Day)
Actrapid/ Velosulin/ Monotard/Insulatard/ Protaphane/ mixtard/ actraphane/ ultratard	Insulin human	07/10/2002	Velosulin 19/07/1999	1176
Advate	Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method	04/03/2004	25/07/2003	223
Aldurazyme	Laronidase	10/06/2003	30/04/2003	41
Alfatronol	Interferon alfa-2b	09/03/2000	04/10/1983	5027
Apidra	Insulin Glulisine	27/09/2004	16/04/2004	164
Aranesp	Darbepoetin alfa	08/06/2001	17/09/2001	-101
Avastin	Bevacizumab	12/01/2005	26/02/2004	321
Avonex	Interferon beta-1a	13/03/1997	17/05/1996	300
Benefix	Nonacog alfa (coagulation fator IX)	27/08/1997	11/02/1997	197
Betaferon	Interferon beta-1b	30/11/1995	23/07/1993	860
Campath	Alemtuzumab	06/07/2001	07/05/2001	60
CEA Scan	Arcitumomab	04/10/1996	28/06/1996	98
Cerezyme	Imiglucerase	17/11/1997	23/05/1994	1274
Ecokinase	Reteplase	29/08/1996	30/10/1996	-62
Elitek	Rasburicase	23/02/2001	12/07/2002	-504
Enbrel	Etanercept	03/02/2000	02/11/1998	458
Erbitux	Cetuximab	29/06/2004	12/02/2004	138
Fabrazyme	Agalsidase beta	03/08/2001	24/04/2003	-629
Foresteo	Teriparatide	10/06/2003	26/11/2002	196
GlucaGen	rhGlucagon	NA	22/06/1998	NA
Gonal F	Follitropin alfa	20/10/1995	29/09/1997	-710
Herceptin	Trastuzumab	28/08/2000	25/09/1998	703
Humalog	Insulin lispro	30/04/1996	14/06/1996	-45
Humira	Adalimumab	08/09/2003	31/12/2002	251
Infergen	Interferon alfacon-1	01/02/1999	06/10/1997	483
Kineret	Anakinra	08/03/2002	14/11/2001	114
Kogenate Bayer	Octocog alfa	04/08/2000	25/02/1993	2717
InductOs	Dibotermin alfa	09/09/2002	02/07/2002	99
Lantus	Insulin glargine	09/06/2000	20/04/2000	47
Luveris	Lutropin alfa	29/11/2000	10/08/2004	-1350
Metalyse	Tenecteplase	23/02/2001	02/06/2000	266
Neulasta	Pegfilgrastim	22/08/2002	31/01/2002	203

Novorapid	Insulin aspart	07/09/1999	07/06/2000	-274
NovoSeven	Eptacog alfa (activated) (coagulation factor VIIa)	23/02/1996	25/03/1999	-1126
Nutropin AQ	Somatropin	16/02/2001	09/03/1994	2536
Ovitrelle	Choriogonadotropin alfa	02/02/2001	27/09/2000	128
Pegasys	Peginterferon alfa-2a	20/06/2002	16/10/2002	-118
PEG-Intron	Peginterferon alfa-2b	25/05/2000	19/01/2001	-239
Puregon	Follitropin beta	03/05/1996	29/09/1997	-514
Rebif	Interferon beta-1a	04/05/1998	07/03/2002	-1403
Refacto	Moroctocog alfa	13/04/1999	06/03/2000	-328
Refludan	Lepirudin	13/03/1997	06/03/1998	-358
Regranex	Becaplermin	29/03/1999	16/12/1997	468
Remicade	Infliximab	13/08/1999	24/08/1998	354
Revasc	Desirudin	09/07/1997	04/04/2003	-2095
Rituxan	Rituximab	02/06/1998	26/11/1997	188
Simulect	Basiliximab	09/10/1998	12/05/1998	150
Somavert	Pegvisomant	13/11/2002	25/03/2003	-132
Synagis	Palivizumab	13/08/1999	19/06/1998	420
Thyrogen	Thyrotrophin alfa	09/03/1999	30/11/1998	99
Xigris	Drotrecogin alfa(activated)	22/08/2002	21/11/2001	274
Zenapax	Daclizumab	26/02/1999	10/12/1997	443
Zevalin	Ibritumomab tiuxetan	16/01/2004	19/02/2002	696
Vaccines				
Infanrix	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine	30/07/1997	29/01/1997	182
Prevenar	Pneumococcal conjugate vaccine	02/02/2001	17/02/2000	351
RotaShield	Rotovarus Vaccine, Live, Oral, Tetravalent	14/05/1999	31/08/1998	256
Antisense oligonucleotide				
Vitravene	Formivirsen	29/07/1999	26/08/1998	337

*Note: Approval interval is the approval date of the EMEA minus the approval date of the FDA.

Table 2.2 shows that of the 17 biopharmaceuticals approved by the EMEA first, only Aranesp (Amgen Europe B.V.), Fabrazyme (Genzyme Europe B.V.), Humalog (Lilly Netherlands B.V.), PEG-Intron (Schering-Plough Europe) and Somavert (Pfizer) were developed by the European division of US-based companies.

All the other 12 biopharmaceutical products were developed by EU-based companies. It is very reasonable that the EU-based companies would like to license their products in the EU first, and then seek licensing in the US market.

Table 2.2 Biopharmaceuticals approved first by the EMEA and subsequently by the FDA

Brand Name	Generic Name	Sponsoring Company	EU-based or US-based	Note
Aranesp	Darbepoetin alfa	Amgen Europe B.V.	US-based	The European division of Amgen developed this compound.
Ecokinase	Reteplase	Galenus-Mannheim	EU-based	
Elitek	Rasburicase	Sanofi-Synthelabo Inc.	EU-based	
Fabrazyme	Agalsidase beta	Genzyme Europe B.V.	US-based	The European division of Genzyme developed this compound.
Gonal F	Follitropin alfa	Serono	EU-based	
Humalog	Insulin lispro	Lilly Netherlands B.V.	US-based	The European division of Lilly developed this compound.
Luveris	Lutropin alfa	Serono	EU-based	
Novorapid	Insulin aspart	Novo Nordisk	EU-based	
Novoseven	Eptacog alfa	Novo Nordisk	EU-based	
Pegasys	Peginterferon alfa-2a	Roche	EU-based	
PEG-Intron	Peginterferon alfa-2a	Schering-Plough Europe	US-based.	The European division of Schering-Plough developed this compound.
Puregon	Follitropin beta	Organon	EU-based	
Rebif	Interferon beta-1a	Serono	EU-based	
Refacto	Moroctocog alfa	Genetics	EU-based	
Refludan	Lepirudin	Schering AG	EU-based	
Revasc	Desirudin	Aventis	EU-based	
Somavert	Pegvisomant	Pfizer Limited UK	US-based	The UK division developed this compound.

Most vaccines were approved by either the FDA or the EMEA independently, with only 3 vaccines (Infanrix, Prevenar and RotaShield) being approved by both the FDA and EMEA. The only oligonucleotide antisense product (Vitravene) was approved by both the FDA and EMEA.

Table 2.3 shows that there are 12 monoclonal antibodies which were approved by both the FDA and EMEA and which account for 21% of the 57 biopharmaceuticals both approved by the FDA and EMEA. Eleven of these monoclonal antibodies are for therapeutic use.

Table 2.3 Monoclonal antibodies approved by both the FDA and EMEA between 1995 and 2004

Trade Name	**Generic Name**	**Indication**
Avastin	Bevacizumab	Metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy.
Campath MabCampath [TR in EU]	Alemtuzumab	B-cell chronic lymphocytic leukemia (B-CLL)
CEA Scan	Arcitumomab	As an adjunct to standard non-invasive imaging techniques of carcinoma of the colon or rectum for imaging of recurrence and/or metastases
Erbitux	Cetuximab	EGFR-expressing, metastatic colorectal carcinoma.
Herceptin	Trastuzumab	Metastatic breast cancer
Humira	Adalimumab	Moderately to severely active rheumatoid arthritis
Remicade	Infliximab	Rheumatoid Arthritis; Crohn's disease
Rituxan MabThera [TR outside of U.S. and Japan]	Rituximab	Relapsed or refractory low-grade or follicular, B-cell non-Hodgkin's lymphoma.
Simulect	Basiliximab	Prophylaxis of acute organ rejection in patients receiving renal transplantation
Synagis	Palivizumab	Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease.
Zenapax	Daclizumab	Prophylaxis of acute organ rejection in patients receiving renal transplants
Zevalin	Ibritumomab tiuxetan	Relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma

2.4.2 Trends in biopharmaceutical approval over time

Of the biopharmaceuticals approved by the FDA, monoclonal antibodies account for 24% of the total number of products and vaccines account for 14% of all the products. In contrast, of all the biopharmaceuticals approved by the EMEA, monoclonal antibodies account for 18% of the total number of products and vaccines account for 21% of all products (see Table 2.4 and Table 2.5).

The number of biopharmaceuticals approved by the FDA and EMEA each year (Table 2.4, Table 2.5 and Fig 2.4, Fig 2.5, Fig 2.6) did not show a consistent relationship between the FDA and EMEA. However, the EMEA had the highest number of biopharmaceuticals approved during the consecutive three years between 1999 and 2001: 14, 17 and 16 respectively. The FDA had the highest number of biopharmaceuticals approved in 1998 (15 biopharmaceuticals were approved in this year). The lowest number of biopharmaceutical approvals by the EMEA was in 1995 with only 2 biopharmaceuticals being approved.

Table 2.4. Biopharmaceuticals approved by the FDA by approval year

	Monoclonal antibodies	Vaccines	Antisense	Other proteins	Total
1995	0	2	0	3	5
1996	4	2	0	6	12
1997	2	2	0	7	11
1998	4	3	1	7	15
1999	0	0	0	6	6
2000	4	1	0	8	13
2001	1	1	0	6	8
2002	2	2	0	7	11
2003	3	1	0	7	11
2004	4	0	0	5	9
Total	24	14	1	62	101
%	24	14	1	61	

Table 2.5. Biopharmaceuticals approved by the EMEA by approval year

	Monoclonal antibodies	Vaccines	Antisense	Other proteins	Total
1995	0	0	0	2	2
1996	3	3	0	5	11
1997	1	2	0	8	11
1998	3	1	0	1	5
1999	3	3	1	7	14
2000	1	6	0	10	17
2001	1	3	0	12	16
2002	0	1	0	8	9
2003	2	0	0	3	5
2004	3	1	0	3	7
Total	17	20	1	59	97
%	18	21	1	61	

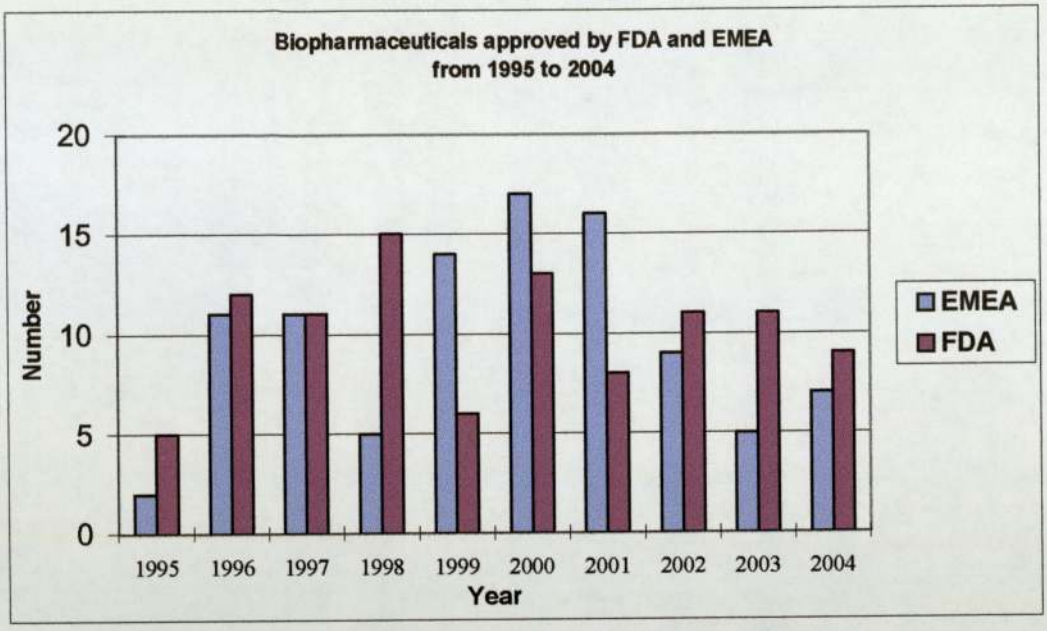


Fig 2.4 Biopharmaceuticals approved by approval year

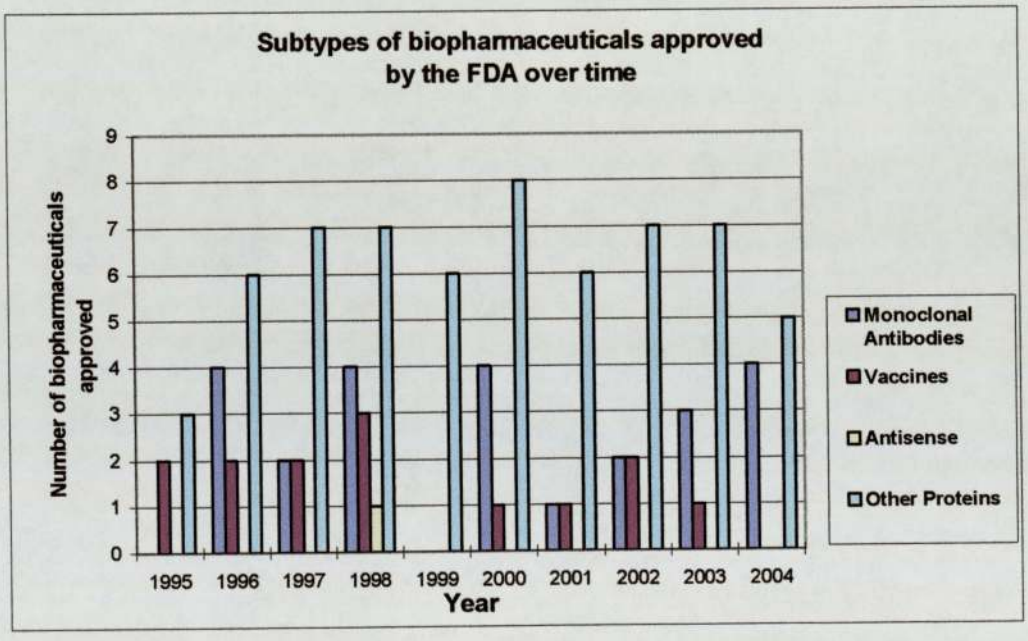


Fig 2.5 Subtypes of biopharmaceuticals approved by the FDA between 1995 and 2004

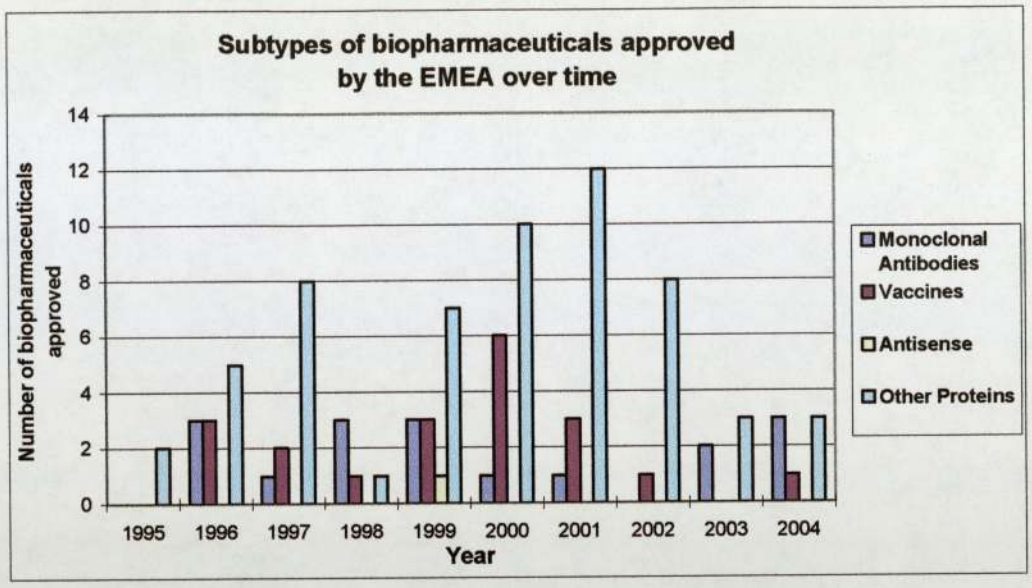


Fig 2.6 Subtypes of biopharmaceuticals approved by the EMEA between 1995 and 2004

The number of biopharmaceutical drugs developed over two four year periods between 1997 and 2004 was collated to examine a longer trend (Table 2.6, Table 2.7). Between 1997 and 2000, the number of biopharmaceuticals approved by the FDA was 45; the number of biopharmaceuticals approved by the EMEA was 47. In contrast, between 2001 and 2004, the number of biopharmaceuticals approved by the FDA and by the EMEA was 39 and 37 respectively. The number of biopharmaceuticals approved by the FDA or EMEA in the recent four years (2001-2004) has decreased compared with the former four years.

Table 2.6 Comparison of Biopharmaceuticals approved by the FDA over time

Year	Monoclonal Antibodies	Vaccines	Antisense	Other proteins	Total Number
1997-2000	10	6	1	28	45
2001-2004	10	4	0	25	39

Table 2.7 Comparison of Biopharmaceuticals approved by the EMEA over time

Year	Monoclonal Antibodies	Vaccines	Antisense	Other proteins	Total Number
1997-2000	8	12	1	26	47
2001-2004	6	5	0	26	37

For the biopharmaceuticals approved by the FDA, the number of monoclonal antibodies (10 products) approved between 1997 and 2000 is identical to the number of monoclonal antibodies approved between 2001 and 2004. The only oligonucleotide antisense was approved in 1998 by the FDA. The FDA approved 28 other proteins between 1997 and 2000 compared with 25 other proteins being approved between 2001 and 2004. Six vaccines were approved by the FDA between 1997 and 2000 versus four vaccines approved by the FDA between 2001 and 2004.

As far as the biopharmaceuticals approved by the EMEA are concerned, the approval number of vaccines has been decreased significantly, from 12 vaccines between 1997 and 2000 to only 5 vaccines between 2001 and 2004. The only oligonucleotide antisense was approved in 1999 by the EMEA. Eight monoclonal antibodies were approved by the EMEA between 1997 and 2000 versus six monoclonal antibodies were approved between 2001 and 2004. For the biopharmaceuticals approved by the EMEA, the number of other proteins (26 products) approved between 1997 and 2000 is identical to the number of other proteins approved between 2001 and 2004.

2.4.3 Review of the range of biopharmaceuticals approved for different therapeutic categories

All biopharmaceutical products were also analysed by therapeutic application and include products approved in the US and/or EU, (see Table 2.8).

For some of the biopharmaceuticals, several different indications have been approved. The indication of Alfatronol (Interferon alfa-2b) is for the treatment of hepatitis B, C, and various cancers. GlucaGen and Glucagon are indicated for hypoglycaemia and for diagnostic aid used during radiologic examinations to temporarily inhibit the movement of the gastrointestinal tract. Remicade (Infliximab) is used for Crohn's disease and rheumatoid arthritis. Enbrel (Etanercept) is indicated for treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis. Humira is for treatment of rheumatoid arthritis and psoriatic arthritis.

Fourteen products were approved for the treatment of 14 unique diseases or conditions, which are defined as "others" therapeutic indications in this chapter.

All the biopharmaceuticals were separated as approved for treatment of blood disease (Table 2.9), which includes anaemia, haemophilia, thrombocytopenia and neutropenia; bone disease (Table 2.10), which includes tibia-related disease and others; cancer (Table 2.11) which includes leukemia, lymphoma and others; enzyme deficiency (Table 2.12) disease which includes Fabry's disease and others; infectious disease (Table 2.13) which includes hepatitis, lower respiratory tract infection, cytomegalovirus retinitis infection and sepsis; diabetes (Table 2.14); growth failure (Table 2.15); hypoglycemia (Table 2.16); infertility (Table 2.17); multiple sclerosis (Table 2.18); myocardial infarction (Table 2.19); organ rejection (Table 2.20); psoriasis (Table 2.21); rheumatoid arthritis (Table 2.22); diagnostics (Table 2.23); vaccines (Table 2.25); and others (Table 2.24) which means the indication is unique.

As far as therapeutic indication is concerned, between 1995 and 2004, the most frequently approved biopharmaceuticals were blood disease-related products (13 biopharmaceuticals), infection treatment products (12 biopharmaceuticals), diabetes treatment products (10 biopharmaceuticals) and cancer treatment products (10 biopharmaceuticals). All of them are focused on the treatment of life-threatening and chronic diseases.

Table 2.8: Biopharmaceutical categories approved by the FDA and EMEA between 1995 and 2004

	Disease	Number of compounds	Note
Blood	Anaemia	4	
	Haemophilia	6	
	Thrombocytopenia	2	
	Neutropenia	1	
Bone	Tibia related disease	3	
	Others	1	
Cancer	Leukemia	2	
	Lymphoma	4	
	Others	4	Alfatronol is indicated for various cancers and Hepatitis B, C.
Enzyme	Fabry's disease	2	
	Others	4	
Infection	Hepatitis	8	Alfatronol is indicated for Hepatitis B, C and various cancers.
	Infection, Lower Respiratory Tract	2	
	Infection, Cytomegalovirus retinitis Antisense oligonucleotide	1	
	Sepsis	1	
	Diabetes	10	
	Growth failure	6	
	Hypoglycemia	2	GlugaGen and Glucagon are indicated for hypoglycemia and for diagnostic aid.
	Infertility	4	
	Multiple Sclerosis	4	
	Myocardial Infarction	4	
	Organ rejection	3	
	Psoriasis	2	
	Rheumatoid Arthritis	5	Remicade (infliximab) is used for rheumatoid arthritis, Crohn's disease, psoriatic arthritis and ulcerative colitis; Enbrel is indicated for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis; Humira is for the treatment of rheumatoid arthritis and

			psoriatic arthritis.
	Diagnostic	17	
	Vaccines	32	
	Others *	14	
Total		147	

Note: * This group includes single product categories.

2.4.3.1 Biopharmaceuticals approved for treatment of blood diseases

Table 2.9 shows that totally there are 13 biopharmaceuticals developed for treatment of blood-related diseases, which account for 9% of all the biopharmaceuticals. After further analysis of these 13 products, 4 products (Neorecormon, Eprex, Aranesp and Dynepo) are for treatment of anaemia; 6 products (NovoSeven, Kogenate Bayer, Benefix, Refacto, Nonafact and Advate) are for treatment of haemophilia; 2 products (Refludan and Neumega) are for treatment of thrombocytopenia; Neulasta is for treatment of neutropenia.

Table 2.9: Biopharmaceuticals approved for treatment of blood disease

Sub-categories	Brand name	Generic name	First Approval Year
Anaemia			
	Neorecormon	Epoetin beta	1997
	Eprex	Epoetin alfa	1999
	Aranesp Nespo [TR in EU]	Darbepoetin alfa	2001
	Dynepo	Epoetin delta	2002
Haemophilia			
	NovoSeven	Eptacog alfa (activated) (coagulation factor VIIa)	1996
	Kogenate Bayer Helixate NexGen [Other Name]	Octocog alfa	1993
	Benefix	Nonacog alfa (coagulation fator IX)	1997
	Refacto	Moroctocog alfa	1999
	Nonafact	Human coagulation factor IX	2001
	Advate	Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method	2003
Thrombocytopenia			
	Refludan	Lepirudin	1997
	Neumega	Oprelvekin	1997
Neutropenia			
	Neulasta Neupopeg [TR in EU]	Pegfilgrastim	2002

2.4.3.2 Biopharmaceuticals approved for treatment of bone disease

Table 2.10 shows that four biopharmaceutical products approved between 1995 and 2004 are indicated for bone-related disease.

Osteogenic protein1, Osigraft and InductOs are indicated for tibia related disease. The definition of the tibia is the large bone between the knee and foot that supports 5/6 of the body weight. The fibula supports 1/6 of the body weight (Available from: http://www.biology-online.org/dictionary/tibia). The indication of InductOs (Dibotermin alfa) is treatment of acute tibia fractures. The indication of Osteogenic protein1 (rhOsteogenic protein 1) and Osigraft (Eptotermin alfa) is the treatment of non-union of tibia. Another product, Foresteo (Teriparatide) is indicated for the treatment of postmenopausal women with osteoporosis and can increase bone mass in men with primary or hypogonadal osteoporosis. All the four products were approved after 2000.

Table 2.10: Biopharmaceuticals approved for treatment of bone disease

Sub-categories	Brand name	Generic name	First Approval Year
Tibia related disease			
	Osteogenic protein 1	rhOsteogenic Protein -1	2000
	Osigraft	Eptotermin alfa	2001
	InductOs	Dibotermin alfa	2002
Others			
	Foresteo	Teriparatide	2002

2.4.3.3 Biopharmaceuticals approved for treatment of cancer

Ten biopharmaceuticals are indicated for cancer (Table 2.11); eight of them are monoclonal antibodies. One product, Ontak (Denileukin diftitox) is a recombinant cytotoxic protein, which is indicated for T-cell lymphoma. Alfatronol is interferon alfa.

Among the ten cancer products approved, two products (Mylotarg for acute myeloid leukaemia and Campath for B-cell chronic lymphocytic leukaemia) are indicated for leukaemia; four products (Bexxar, Rituxan and Zevalin for B-cell non-Hodgkin's lymphoma, Ontak for T-cell Lymphoma) are indicated for lymphoma; Herceptin (Trastuzumab) is indicated for breast cancer; Avastin (Bevacizumab) is indicated for the colon or rectum carcinoma; Erbitux (Cetuximab) is indicated for the treatment of colorectal carcinoma and Alfatronol (interferon alfa-2b) is indicated for the treatment of hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, malignant melanoma, condylomata acuminate, AIDS-related Kaposi's sarcoma, hepatitis B&C.

Again, monoclonal antibodies comprise the majority of anti-cancer biopharmaceutical treatments.

Table 2.11: Biopharmaceuticals approved for treatment of cancer

Sub-categories	Brand name	Generic name	First Approval Year
Leukemia			
	Mylotarg	Gemtuzumab ozogamicin, CD33 immunotoxin, rDNA	2000
	Campath MabCampath[TR in EU]	Alemtuzumab	2001
Lymphoma			
	Rituxan	Rituximab	1997
	Ontak	Denileukin diftitox	1999
	Zevalin	Ibritumomab tiuxetan	2002

	Bexxar	Tositumomab and Iodine I 131 Tositumomab	2003
Others			
	Herceptin	Trastuzumab	1998
	Avastin	Bevacizumab	2004
	Erbitux	Cetuximab	2004
	Alfatronol	Interferon alfa-2b	1983

Note: Alfatronol is indicated for the treatment of hairy cell leukaemia, chronic myelogenous leukaemia, multiple myeloma, follicular lymphoma, carcinoid tumour, malignant melanoma, condylomata acuminate, AIDS-related Kaposi's sarcoma, hepatitis B&C.

2.4.3.4 Biopharmaceuticals approved for treatment of enzyme deficiency disease

Six products are indicated for enzyme deficiency-related diseases (Table 2.12).

Both Fabrazyme (Agalsidase beta) and Replagal (Agalsidase alfa) are used for the long-term enzyme replacement therapy in patients with confirmed Fabry's disease. Fabry's disease is a kind of rare disease according to ORPHANET's rare disease list (Available from: http://www.orpha.net/consor/cgi-bin/pat_index.php?Lng=GB). The cause of Fabry's disease is deficiency in the lysosomal enzyme α-galactosidase A and is genetically inherited (FDA approved label).

Cerezyme (Imiglucerase) is indicated for long-term enzyme replacement therapy of Type I Gaucher disease, which is a rare disease according to ORPHANET's rare disease list (Available from: http://www.orpha.net/consor/cgi-bin/pat_index.php?Lng=GB). Sucraid (Sacrosidase) is a replacement treatment for patients who do not have the enzymes needed to properly breakdown and absorb sucrose (table sugar) and isomaltose (a type of starch) in the intestines, which is also a rare disease. Elitek (Rasburicase) is approved for the management of plasma uric acid levels. Elitek catalyses enzymatic oxidation of uric acid into an inactive and soluble metabolite (allantoin) (FDA label). Aldurazyme (Laronidase) is another long-term enzyme replacement therapy for Mucopolysaccharidosis I, which is a rare disease according to ORPHANET rare disease list.

Hence, five (Fabrazyme, Replagal, Cerezyme, Sucraid and Aldurazyme) of the six enzyme-related biopharmaceuticals are long-term enzyme replacement therapies and are indicated for the treatment of rare diseases.

Table 2.12: Biopharmaceuticals approved for treatment of enzyme deficiency disease

Sub-categories	Brand name	Generic name	First Approval Year	Note
Fabry disease				
	Fabrazyme	Agalsidase beta	2001	
	Replagal	Agalsidase alfa	2001	
Others				
	Cerezyme	Imiglucerase	1994	
	Sucraid	Sacrosidase	1998	
	Elitek	Rasburicase	2001	Fasturtec [TR in EU]
	Aldurazyme	Laronidase	2003	

2.4.3.5 Biopharmaceuticals approved for treatment of infectious disease

Twelve products are indicated for treatment of infectious diseases, and this accounts for 8% of all the biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004 (Table 2.13).

The only licensed antisense oligonucleotide, Vitravene (Formivirsen) is indicated for the treatment of cytomegalovirus retinitis in patients with AIDS.

Eight products are indicated for the treatment of hepatitis. Nabi-HB (Hepatitis B, Hbs, immune globulin) is the only immune globulin approved over the 10 years from 1995 to 2004 for the treatment of hepatitis, whose detailed indication is for the treatment of acute exposure to blood containing Hbs-antigen (HbsAg), perinatal exposure of infants born to HbsAg-positive mothers, sexual exposure to HbsAg-positive persons and household exposure to persons with acute HBV infection. All the other seven products are sub-types of interferons; Alfatronol is indicated for Hepatitis B, C and various cancers; Infergen, Peginterferon, PEG-Intron and Pegasys are indicated for hepatitis C; Wellferon and Vitron are indicated for hepatitis B and C.

Two products, Synagis (Palivizumab) and Respigam (RSV immunoglobulin) are indicated for the prevention of lower respiratory tract disease caused by respiratory syncytial virus (RSV).

Xigris is for treatment of sepsis.

Table 2.13: Biopharmaceuticals approved for treatment of infectious disease

Sub-categories	Brand name	Generic name	First Approval Year	Note
Hepatitis				
	Alfatronol	IFN-a-2b	1983	A new trade name for IntronA. Treatment of Hepatitis and various cancers.
	Infergen	Interferon alfacon-1	1997	
	Nabi-HB	Hepatitis B Immune Globulin	1999	
	Wellferon	Interferon alfa-N1	1999	
	PEG-Intron	Peginterferon alfa-2b	2000	Rebetol[TR];PegIntron[TR in Europe];ViraferonPeg [TR in Europe]
	Vitron	IFN-a-2b	2000	Another trade name for Viraferon.
	Pegasys	Peginterferon alfa-2a	2002	
	Peginterferon	Peginterferon alfa-2a copackaged with Ribavirin	2004	
Infection, Lower Respiratory Tract				
	Respigam	RSV immunoglobulin	1996	
	Synagis	Palivizumab	1998	
Infection, Cytomegalovirus retinitis Antisense oligonucleotide				
	Vitravene	Formivirsen	1998	
Sepsis				
	Xigris	Drotrecogin alfa(activated)	2001	

2.4.3.6 Biopharmaceuticals approved for treatment of diabetes

Table 2.14 shows that ten biopharmaceutical products, which were approved between 1995 and 2004 are indicated for the treatment of diabetes.

Insuman and Actrapid are human insulin produced by recombinant DNA technology (EMEA scientific discussion, available from: www.emea.eu.int).

Humalog and Liprolog are known as insulin lispro, which is a human insulin analog. The difference between these products and human insulin is that the amino acids at position 28 and 29 on the B chain are reversed. Hence, Humalog and Liprolog are Lysine (B28) and Proline (B29) insulin (FDA Label). The structure modification leads to the rapid onset of action and shorter duration of activity.

Novorapid and NovoMix30 are known as insulin aspart. The difference between human insulin and insulin aspart is that the amino acid proline (Pro) is replaced by aspartic acid (Asp) at position 28 of the B-chain (FDA label). The result of structure difference is a faster onset and longer duration of action. (FDA label)

Lantus and Optisulin are known as insulin glargine. The difference between insulin glargine and human insulin is that the amino acid asparagine at position 21 of the A chain is replaced by glycine and two arginines are added to the C-terminus of the B-chain (FDA label). The duration of action can be prolonged to up to 24 hours compared to human insulin. (FDA label)

Apidra is called insulin glulisine. The difference between this compound and human insulin is the amino acid asparagine at position 3 of the B chain is replaced by lysine and the lysine at position 29 of the B chain is replaced by glutamic acid. The action of onset is quicker for Apidra compared with human insulin (FDA label).

Levemir is called insulin detemir. The difference between this compound and human insulin is threonine at position 30 of the B chain has been deleted and a C14 fatty acid chain has been attached to the amino acid of the 29 position of the B chain (FDA label). The duration of action can last for up to 24 hours for this product.

Table 2. 14: Biopharmaceuticals approved for treatment of diabetes

Brand name	**Generic name**	**First Approval Year**	**Note**
Humalog	Insulin lispro	1996	
Insuman	Human insulin	1997	
Novorapid	Insulin aspart	1999	NovoLog [TR in US]
Lantus	Insulin glargine	2000	
NovoMix 30	Insulin aspart	2000	
Optisulin	Insulin glargine	2000	
Liprolog	Insulin lispro	2001	
Actrapid/ Velosulin/ Monotard/Insulatard/ Protaphane/ mixtard/ actraphane/ ultratard	Insulin human rDNA	2002	
Apidra	Insulin Glulisine	2004	
Levemir	Insulin detemir	2004	

2.4.3.7 Biopharmaceuticals approved for treatment of growth failure

Six biopharmaceutical products were approved between 1995 and 2004 which are indicated for the treatment of growth failure (Table 2.15). They are all forms of somatropin, a kind of human growth hormone, which have been manufactured by DNA technology. All of them are identical in amino acid sequence to human growth hormone (FDA label).

The first somatropin product is Humatrope (Eli Lilly & Co.), which was approved by the FDA in 1987 as an orphan drug.

Humatrope's patent expired in 2003 (Coan, 2001), and Omnitrop was the first biogeneric to be filed for European approval. It was recommended for approval in the European Union in June 2003; however, the European Commission ultimately rejected it in April 2004.

Table 2.15: Biopharmaceuticals approved for treatment of growth failure

Brand name	**Generic name**	**First Approval Year**	**Note**
Nutropin	Somatropin	1994	
Bio-Tropin	Somatropin, rDNA	1995	Growject [TR in Japan],Zomacton [TR in Europe];Source:biopharma website
Norditropin	Somatropin, rDNA	1995	Norditropine [TR in France] Norditropin S-chu [TR in Japan] Nordipen [TR for injector]
Genotropin	Somatropin, rDNA	1995	Crescormon [TR foreign]; source: biopharma website
Saizen [TR for hGH deficiency]	Somatropin, rDNA	1996	Serostim [for AIDS-related cachexia];
Omnitrop	Somatropin	2003	

2.4.3.8 Biopharmaceuticals approved for treatment of hypoglycemia

Table 2.16 shows two biopharmaceutical products were approved between 1995 and 2004 for the treatment of hypoglycemia.

GlucaGen was licensed by Novo Nordisk and Glucagon was licensed by Lilly in 1998. Both of them are the same polypeptide hormone and are identical to naturally occurring human glucagon (FDA label).

For Glucagon, the indication approved by the FDA in 1998 is for the treatment of hypoglycemia and for use as a diagnostic aid. GlucaGen was initially approved for the treatment of hypoglycemia and then the indication was expanded to be used as a diagnostic aid in 2004 (used during radiologic examinations to temporarily inhibit the movement of the gastrointestinal tract) (FDA information).

Table 2.16: Biopharmaceuticals approved for treatment of hypoglycemia

Brand name	Generic name	First Approval Year
GlucaGen	Glucagon for injection, rDNA origin	1998
Glucagon	Glucagon for Injection, recombinant	1998

2.4.3.9 Biopharmaceuticals approved for treatment of infertility

Table 2.17 shows four biopharmaceutical products developed for treatment of infertility between 1995 and 2004.

Gonal-F (Follitropin alfa) and Puregon (Follitropin beta) were developed for the treatment of infertility of both men and women. Luveris (Lutropin alfa) and Ovitrelle (Choriogonadotropin alfa) are approved for the treatment of infertility suffered by the women (FDA label).

Table 2.17: Biopharmaceuticals approved for treatment of infertility

Brand name	Generic name	First Approval Year	Note
Gonal F	Follitropin alfa	1995	
Puregon	Follitropin beta	1996	Follistim [TR in US]
Luveris	Lutropin alfa	2000	
Ovitrelle	Choriogonadotropin alfa	2000	

2.4.3.10 Biopharmaceuticals approved for treatment of multiple sclerosis

Table 2.18 shows four biopharmaceutical products are indicated for the treatment of multiple sclerosis (MS) between 1995 and 2004.

Three of these products (Betaferon, Avonex and Rebif) for treatment of MS are interferons. One product (Tysabri) that was approved for multiple sclerosis in 2004 is a recombinant humanized monoclonal antibody. All of the four biopharmaceutical products are indicated for the treatment of relapsing forms of multiple sclerosis (FDA labels).

Table 2.18: Biopharmaceuticals approved for treatment of multiple sclerosis

Brand name	Generic name	First Approval Year	Note
Betaferon	Interferon beta-1b	1993	Betaseron [TR in US]
Avonex	Interferon beta-1a	1996	
Rebif	Interferon beta-1a	1998	
Tysabri	Natalizumab	2004	

2.4.3.11 Biopharmaceuticals approved for treatment of myocardial infarction

Table 2.19 shows four biopharmaceutical products approved between 1995 and 2004 are indicated for treatment of myocardial infarction.

Streptase (Streptokinase) is indicated for the treatment of acute evolving transmural myocardial infarction, pulmonary embolism, deep vein thrombosis, arterial thrombosis or embolism, occlusion of arteriovenous cannulae (available from: www.rxlist.com). All the other three products, Ecokinase (Reteplase), Rapilysin (Reteplase) and Metalyse (Tenecteplase) are indicated for the treatment of myocardial infarction only (FDA labels).

Table 2.19: Biopharmaceuticals approved for treatment of myocardial infarction

Brand name	Generic name	First Approval Year	Note
Ecokinase	Reteplase	1996	Retavase [TR in US]
Rapilysin	Reteplase	1996	
Streptase	Streptokinase	1997	
Metalyse	Tenecteplase	2000	

2.4.3.12 Biopharmaceuticals approved for treatment of organ rejection

Table 2.20 shows three biopharmaceutical products were approved for treatment of organ rejection between 1995 and 2004. All of them are immunosuppressive products indicated for the prophylaxis and treatment of organ rejection in patients receiving renal transplants. However, two products, Zenapax (Daclizumab) and Simulect (Basiliximab) are monoclonal antibodies. Thymoglobulin (Thymoglobulin) is an immuno-globulin (FDA label).

Table 2.20: Biopharmaceuticals approved for treatment of organ rejection

Brand name	Generic name	First Approval Year
Zenapax	Daclizumab	1997
Simulect	Basiliximab	1998
Thymoglobulin	Thymoglobulin	1998

2.4.3.13 Biopharmaceuticals approved for treatment of psoriasis

Two biopharmaceutical products were approved between 1995 and 2004 for treatment of plaque psoriasis (Table 2.21).

Table 2.21: Biopharmaceuticals approved for treatment of psoriasis

Brand name	Generic name	First Approval Year
Amevive	Alefacept	2003
Raptiva	Efalizumab	2003

2.4.3.14 Biopharmaceuticals approved for treatment of rheumatoid arthritis

Table 2.22 shows that five biopharmaceutical products were approved for treatment of rheumatoid arthritis between 1995 and 2004.

Enbrel (Etanercept), Remicade (Infliximab), Humira (Adalimumab) and Trudexa (Adalimumab) are targeted at tumor necrosis factor (TNF). Enbrel (Etanercept) is a TNF receptor mimic; it binds to TNF and inhibits its interaction with cell surface TNF receptors. Remicade (Infliximab), Humira (Adalimumab) and Trudexa (Adalimumab) are monoclonal antibodies against TNF.

Kineret (Anakinra) is a human interleukin-1 receptor antagonist (FDA label).

The indication of Enbrel has undergone significant extension in its use spectrum since it was licensed by Immunex in 1998. The initial indication was for the treatment of active rheumatoid arthritis. In 2000, the indication was expanded to active rheumatoid arthritis and active polyarticular-course juvenile rheumatoid arthritis. The indication in 2002 was further expanded to active rheumatoid arthritis, active polyarticular-course juvenile rheumatoid arthritis and psoriatic arthritis. The indication in 2005 has been finally expanded to active rheumatoid arthritis, active polyarticular-course juvenile rheumatoid arthritis and psoriatic arthritis, ankylosing spondylitis and plaque psoriasis (FDA product approval information).

The indication for Remicade (Infliximab) has been extended since it was licensed by Centocor in 1998. The indication approved in 1998 was for the treatment of Crohn's disease. In 1999, the indication was extended to the treatment of rheumatoid arthritis and Crohn's disease. In 2005, the indication was extended to the treatment of rheumatoid arthritis, Crohn's disease, psoriatic arthritis and ulcerative colitis (FDA product approval information).

The indication for Humira (Adalimumab) is currently for the treatment of rheumatoid arthritis and psoriatic arthritis in 2005 although the initial approved indication in 2002 was rheumatoid arthritis.

Table 2.22: Biopharmaceuticals approved for treatment of rheumatoid arthritis

Brand name	**Generic name**	**First Approval Year**
Enbrel	Etanercept	1998
Remicade	Infliximab	1998
Kineret	Anakinra	2001
Humira	Adalimumab	2002
Trudexa	Adalimumab	2003

2.4.3.15 Biopharmaceuticals developed as diagnostic reagents

Fourteen biopharmaceutical products were approved for diagnostic use between 1995 and 2004 (Table 2.23). Seven of them (CEA Scan, Indimacis 125, ProstaSchint, Tecnemab KI, Verluma, Humaspect and Thyrogen) are indicated for the diagnosis of cancer, which accounts for 50% of all the products. Two products (Calypte HIV-1 Urine EIA and Genetic Systems HIV-1/HIV-2 Plus O EIA) are indicated for the diagnosis of HIV.

Table 2.23: Biopharmaceuticals developed as diagnostic reagents

Brand name	Generic name	First Approval Year
Calypte HIV-1 Urine EIA	HIV-Type 1 (Recombinant)	1996
CEA Scan	Arcitumomab	1996
Indimacis 125	Igovomab	1996
Myoscint	Imciromab Pentetate	1996
ProstaSchint	Capromab Pendetide	1996
Tecnemab KI	Murine Mab fragments directed against HMW-MAA	1996
Verluma	Nofetumomab	1996
Leukoscan	Sulesomab	1997
Humaspect	Votumumab	1998
Thyrogen	Thyrotrophin alfa	1998
ID Micro Typing Systems	Anti-A (Murine Monoclonal)	2000
ID Micro Typing Systems	Anti-B (Murine Monoclonal)	2000
ID Micro Typing Systems	Anti-A and B (Murine Monoclonal); Anti-A,B (Murine Monoclonal)	2000
ID Micro Typing Systems	Anti-D (Human Monoclonal) (IgM)	2000
Indiclor	Indium In-111 Chloride Sterile Solution	2002
Genetic Systems HIV-1/HIV-2 Plus O EIA	Human Immunodeficiency Virus Types 1 and 2 (HIV-1 and HIV-2/Enzyme Immunoassay (EIA)/Recombinant and Synthetic)	2003
NeutroSpec	Technetium 99m Tc Fanolesomab	2004

2.4.3.16 Other biopharmaceuticals

Table 2.24 describes 14 biopharmaceuticals with unique indication that were retrieved into the database and Table 2.25 details the vaccines approved during the ten years between 1995 and 2004.

Table 2.24: Other biopharmaceuticals

Brand name	Generic name	Indication	Approval Year
Regranex	Becaplermin	Treatment of lower extremity diabetic neuropathic ulcers	1997
Revasc Iprivask [TR in US]	Desirudin	For the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.	1997
Forcaltonin	Recomb salmon calcitonin	Paget's disease and hypercalcaemia in malignancy.	1999
Beromun	Tasonermin	As an adjunct to surgery for subsequent removal of the tumour so as to prevent or delay amputation, or in the palliative situation, for irresectable soft tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion (ILP).	1999
CroFab	Crotalidae Polyvalent Immune Fab (Ovine)	Management of patients with minimal or moderate North American rattlesnake envenomation.	2000
Myobloc	Botulinum Toxin Type B	Treatment of cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.	2000
Ceprotin	Protein C	Purpura fulminans and coumarin induced skin necrosis in patients with severe congenital protein C deficiency. Short term prophylaxis in patients with severe congenital protein C deficiency	2001
Natrecor	Nesiritide, rDNA	Intravenous treatment of acute decompensated congestive heart failure with dyspnea at rest or with minimal activity.	2001
Vibragen Omega	rFeline IFN-w	Veterinary; reduction in mortality/ symptoms of canine parvovirus	2001
Wydase	Hyaluronidase, bovine	Aid absorption of medications (e.g., anesthetics) or water preparations (hypodermoclysis) given by s.c., i.p. or i.m. injection.	2001
Somavert	Pegvisomant	Acromegaly in patients with an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate. Normalize serum IGF-I levels.	2002
Xolair	Omalizumab	Moderate to severe persistent asthma with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.	2003
Amphadase	Hyaluronidase	Adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents	2004
Vitrase	Ovine Hyaluronidase	Adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents	2004

2.4.3.17 Biopharmaceuticals developed as vaccines

Table 2.25: Biopharmaceuticals developed as vaccines

Brand name	Generic name	Approval Year
Havrix	Hepatitis A Virus Vaccine, Inactivated	1995
Varivax	Varicella Virus Vaccine	1995
Comvax	Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine	1996
Porcilis porcoli	Combination vaccine containing r E.coli adhensions	1996
Tritanrix-HepB	Comb vaccine DTPW-Hep B	1996
Twinrix adult	Comb Hep A and B vaccine	1996
Vaqta	Hepatitis A vaccine, inactivated	1996
Fevaxyl pentofel	Combination vaccine containing r Feline leukaemia viral antigen	1997
Infanrix	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine	1997
RabAvert	Rabies Vaccine	1997
Twinrix paediatric	Comb Hep A and B vaccine	1997
Certiva	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed	1998
Lymerix	Recombinant OSP-A (lyme disease vaccine)	1998
Primavax	Combination vaccine, containing rHBsAg	1998
RotaShield	Rotovarus Vaccine, Live, Oral, Tetravalent	1998
Procomvax	Haemophilus b conjugated and hepatitis B vaccine	1999
Triacelluvax	Combination vaccine, containing r(modified) pertussin toxin	1999
Hepacare	r S, pre-S and pre-S2 hepatitis B surface antigen	2000
Hexavac	Comb vaccine	2000
Infanrix hexa	Hep B-IPV HIB vaccine	2000
Infanrix penta	Hep B-IPV vaccine	2000
Porcillis AR-T DF	Combination vaccine containing a modified toxin	2000
Prevenar	Pneumococcal conjugate vaccine	2000
Porcillis pesti	Vaccine containing r classical swine fever virus antigen	2000
Bayovac CSF E2	Vaccine containing classical swine fever virus antigen	2001
Hbvaxpro	Recombinant Hepatitis B virus small surface antigen (HbsAg)	2001
Twinrix	Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine	2001
Ambirix	Inactivated hepatitis A virus hepatitis B surface antigen, rDNA	2002
Daptacel	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed (DTaP)	2002
Pediarix	Diphtheria & Tetanus Toxoids & Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) & Inactivated Poliovirus Vaccine Combined	2002
FluMist	Influenza Virus Vaccine, Live, Intranasal	2003
Dukoral	Vibrio cholerae and recombinant cholera toxin B-subunit	2004

2.4.4 Identification of blockbuster biopharmaceuticals on the market

Based on the sales data derived from company reports of 2003, ten of the biopharmaceuticals approved between 1995 and 2004 can be classified as blockbuster biopharmaceuticals (sales more than US$ 1 billion per annum), Table 2.26.

These ten blockbusters are Aranesp (approved in 2001), Avonex (approved in 1996), Enbrel (approved in 1998), Eprex (approved in 1999), Humalog (approved in 1996), Neorecormon (approved in 1997), Neulasta (approved in 2002), PEG-Intron (approved in 2000), Remicade (approved in 1998) and Rituxan (approved in 1997).

The top selling biopharmaceutical in 2003 was Eprex/ Procrit (Epoetin alfa), which was approved in 1999 with global sales of $ 3,984 million.

The indications of these biopharmaceuticals are for the treatment of anaemia (3 products), rheumatoid arthritis (2 products), multiple sclerosis (1 product), diabetes (1 product), neutropenia (1 product), hepatitis (1 product) and lymphoma (1 product) respectively.

Four of the blockbuster biopharmaceutical products (Avonex, Enbrel, Remicade and Rituxan) are orphan drugs according to ORPHANET's drug list (Available from: http://www.orpha.net/consor/cgi-bin/pat_index.php?Lng=GB).

Table 2.26: Biopharmaceuticals approved between 1995 and 2004 with sales exceeding US$ 1 billion

Trade name	Generic name	Company	Approval year	Indication	Note	Sales of 2003 ($ million)
Aranesp	Darbepoetin alfa	Amgen	2001	Anemia	Nespo [TR Europe]	$1,500
Avonex	Interferon beta-1a	Biogen, Inc	1996	Relapsing forms of Multiple Sclerosis		$1,168
Enbrel	Etanercept	EU: Wyeth Europe Ltd; US: Immunex Corp	1998	Rheumatoid arthritis		Nearly $1.6 billion(worldwide sales)
Eprex	Epoetin alfa	Ortho Biologics LLC	1999	Anemia	Procrit [Other TR]	$3,984
Humalog	Insulin lispro	Eli Lilly	1996	Diabetes mellitus		$1,021
Neorecormon	Epoetin beta	Roche Registration Ltd	1997	Anemia		$1,527
Neulasta	Pegfilgrastim	Amgen, Inc	2002	Neutropenia	Neupopeg [TR in EU]	$1,300
PEG-Intron	Peginterferon alfa-2b	Schering-Plough	2000	Hepatitis C	Rebetol [TR]; PegIntron [TR in Europe]; ViraferonPeg [TR in Europe]	$1,851
Remicade	Infliximab	Centocor, Inc	1998	Crohn's disease and Rheumatoid arthritis		$1,729
Rituxan	Rituximab	EU:Roche Registration Ltd; US: Genentech, Inc	1997	Lymphoma.	MabThera [TR used by Roche outside of U.S. and Japan]	$2,243

Note: Data were retrieved from companies' annual report of 2003.

TR means trade name.

2.4.5 Biopharmaceuticals withdrawn from the market

As seen in Table 2.27, 18 biopharmaceuticals, which were approved between 1995 and 2004, have been withdrawn from the market; a 12% (18/147) failure rate. Of those 18 biopharmaceuticals, 5 are vaccines, 3 are monoclonal antibodies, 1 is an antisense oligonucleotide and 9 of them are other proteins. Most of them are being withdrawn on the holder's request for safety and commercial reasons. For some products, information was not available on the reason of withdrawal, for others a summary statement of the reasons for withdrawal is provided.

Omnitrop (somatropin) is the first and only biogeneric to be filed under the EMEA. It was recommended for approval in the European Union in June 2003 but was ultimately rejected by the European Commission in April 2004.

All of the three monoclonal antibodies withdrawn from the market were originally approved for diagnostic use.

The only oligonucleotide antisense biopharmaceutical (Vitravene, first approved in 1998) was withdrawn from the EU in 2002 for commercial reasons and not due to any safety-related concerns.

Table 2.27: Biopharmaceuticals withdrawn from the market

Trade name	Generic name	Company	Year	Indication	Reason of withdrawal
Protein					
Actrapid/ Velosulin/ Monotard/Insulatard/ Protaphane/ mixtard/ actraphane/ ultratard	Insulin human rDNA	Novo Nordisk	1999	Diabetes mellitus	Discontinued from the market by November of 2003, because available of new product.
Ecokinase	Reteplase	Galenus Mannheim [EU];Centocor, Inc [US]	1996	Acute myocardial infarction (AMI)	Retavase [TR in US]; Withdrawn from the market in 1999 in EU because of incompatibility with heparin and precipitation following reconstitution.
Forcaltonin	Recomb salmon calcitonin	Unigene UK Limited	1999	Treatment of Paget's disease and hypercalcaemia in malignancy.	CPMP adopted an opinion recommending the suspension of the marketing authorisation of Forcaltonin from Unigene UK Ltd, as the company couldn't identify an authorised manufacturer to ensure the quality of the product on Dec 2003.
Liprolog	Insulin lispro	Eli Lilly Nederland B.V.	1997	Diabetes mellitus	On 7 December 2000, the marketing authorisation holder notified the European Commission decision to withdraw marketing authorization.
Omnitrop	Somatropin	Sandoz GmbH		Treatment of growth hormon deficiency	Recommended for approval in Europe in June 2003. Omnitrop was ultimately rejected by the European Commission in April 2004.
Puregon	Follitropin beta	Organon	1996	Infertility	US trade name is Follistim, discontinued in US.
Respigam	RSV immunoglobulin	Medimmune (Massachusetts Public Health Biologic Labs)	1996	Prevention of serious lower respiratory tract infection caused by Respiratory Syncytial Virus in children less than 24 months of age	Polyclonal antibodies; Because RespiGam has been replaced in the marketplace by the Company's second generation product, Synagis, the manufacture of RespiGam was discontinued as of the end of 2003.

Wellferon	Interferon alfa-N1	GSK	1999	Hepatitis B&C	Withdrawal from the market in 1999,due to a decline in demand
Wydase	Hyaluronidase, bovine	Baxter healthcare	2001	Management of IV extravasation	Wyeth-Ayerst's hyaluronidase injection was not withdrawn for reasons of safety or effectiveness.
Monoclonal antibodies					
Humaspect	Votumumab	Organon Teknika	1998	Detection of carcinoma of the colon or rectum	The marketing authorisation was subsequently transferred to KS Biomedix Ltd. Humaspect is not marketed anywhere in the world. On 22 Sep 2003, KS Biomedix Ltd notified the EC of its decision not to renew the marketing authorisation for commercial reasons.
Indimacis 125	Igovomab	CIS Bio	1996	Diagnosis of ovarian adenocarcimona	Withdrawal from the market on holders request in September of 1999.
Tecnemab KI	Murine Mab fragments directed against HMW-MAA	Sorin	1996	Diagnosis of cutaneous melanoma lesions	Withdrawal on holders request
Vaccine					
Hepacare	r S, pre-S and pre-S2 hepatitis B surface antigen	Medeva Pharma	2000	Immunization against hepatitis B	Withdrawal from the market on Aug 2002 for commercial reasons
Lymerix	Recombinant OSP-A (lyme disease vaccine)	SmithKline Beecham Biologicals, S.A.	1998	Active immunization against Lyme disease	Manufacturer withdrew the vaccine from the market in spring 2002 because of lack of demand.
Primavax	Combination vaccine, containing rHBsAg	Pasteur Merieux MSD	1998	Immunization against diphtheria, tetanus and hepatitis B	Withdrawal from the market on May 2000 on holder's request

RotaShield	Rotovarus Vaccine, Live, Oral, Tetravalent	Wyeth Laboratories, Inc	1998	Primary immunization of infants at 2, 4, and 6 months of age	On July 16, 1999, Wyeth-Lederle Vaccines temporarily suspended further distribution and administration of RotaShield until more data on the potential association between vaccine administration and intussusception became available.reports to the Vaccine Adverse Events Reporting System (VAERS) of a possible association between the use of RotaShield and the development of intussusception.
Triacelluvax	Combination vaccine	Chiron SpA	1999	Immunization against diphtheria, tetanus and pertussis	Withdrawal from the market on Oct 2001 for commercial reasons
Antisense oligonucleotide					
Vitravene	Formivirsen	Ciba Vision Europe Ltd. (2001 name of the marketing authorisation holder changed to Novartis Ophthalmics Europe Ltd);ISIS Pharmaceuticals [US]	1998	Local treatment of cytomegalovirus (CMV) retinitis in patients with AIDS	2002: withdrawal from the EC based on commercial reasons and not due to any safety related concerns. Still authorised in Switzerland and the MAH will be able to supply Vitravene to European Member States.

2.5 Conclusion and discussion

Since the FDA approved the first recombinant protein in 1982, the biopharmaceutical industry has developed very fast. The biopharmaceutical industry is a very important component of the pharmaceutical industry now and it will face many challenges in the next few years as patents expire and orphan drug status is completed. This can be partly predicted following a close analysis of recent trends in the biopharmaceutical industry as undertaken here.

- **Compared with the conventional pharmaceutical industry, the biopharmaceutical industry is still small or medium-sized;**

There are 101 biopharmaceuticals which have been approved by the FDA and 97 approved by the EMEA between 1995 and 2004. In order to compare drug development trends with those of conventional medicines, the number of new molecular entities (NMEs) approved by the FDA and List B products approved by the EMEA (most of which are considered to be conventional pharmaceuticals; Council Regulation (EEC) 2309/93) were calculated. There are 187 NMEs (FDA: CDER new drug and biologic approval report, available from: http://www.fda.gov/cder/rdmt/default.htm) and 73 biopharmaceuticals which have been approved by the FDA during 1998 to 2004. At the EMEA, the number of List B drugs approved over this period is 172 and the number of biopharmaceuticals approved is 97 between 1995 and 2004. Biopharmaceuticals only account for 28% of all pharmaceutical agents approved in the United States and 36% of all pharmaceutical agents approved in the European Union.

The pharmaceutical company with the greatest income is Pfizer (Table 2.29) with pharmaceutical revenues of $ 39,631 million in 2003. In contrast, the top biopharmaceutical company (Table 2.28) is Amgen with biopharmaceutical revenues of $7,886 million (Major pharmaceutical companies' annual report of 2003; Top companies, available from: www.contractpharma.com). The detailed information is seen in Appendix 4. Compared with the conventional pharmaceutical industry, the biopharmaceutical industry is still small or medium sized.

Table 2.28 Top 10 biopharmaceutical companies (2003)

Company	Biopharmaceutical revenues (Million)	Total revenues (Million)
Amgen	$7,886	$8,356
Genentech	$2,621	$3,300
Serono	$1,858	$2,019
Biogen Idec	$1,722 *	$1,852
Genzyme	$ 1,563	$ 1,713
Chiron	$ 1,346	$1,766
MedImmune	$993	$ 1,054
Gilead	$836	$868
Millennium	$244	$434
Intermune	$154	$154

*Data from www.contractpharma.com

All the other data were confirmed by the companies' annual report of 2003.

Table 2.29 Top 20 Pharmaceutical companies (2003)

Company	Pharmaceutical revenues (Million)	Total revenues (Million)
Pfizer	$39,631	$ 45,188
GlaxoSmithKline	$29,736(£ 18,181)	$ 35,068 (£ 21,441)
Merck	$21,038*	$22,486
Jonhnso & Johnson	$19,517	$41,862
Aventis	$19,009 (€ 16,791)	$20,168 (€ 17,815)
AstraZeneca	$18,849	$19,049*
Novartis	$15,913	$ 24,864
Bristol-Mayers Squibb	$14,925	$20,894
Roche	$12,208*	$ 21,558 *
Wyeth	$12,623	$15,850
Lilly	$11,856 *	$12,853
Abbott	$11400	$19,680
Sanofi-Synthelabo	$9,111	$9,111 (€ 8,048)
Takeda	$7,578*	$9,387*
Schering-Plough	$6,672	$8,334
Boehringer-Ingelheim	$6,264(€ 5,533)	$ 8,357 (€ 7,382)
Bayer	$5,372 (€ 4,745)	$32,340 (€ 28,567)
Schering AG	$3,602*	$5,466 (€ 4,828)
Sankyo	$3,100*	$3,253 *
Merck KgA	$2,015*	$8,153 (€ 7,202)

*Data from www.contractpharma.com

All the other data were confirmed by the companies' annual report of 2003.

- **More and more biopharmaceuticals seem to be launched globally and the average additional time taken (the approval date of the FDA minus the approval date of the EMEA) for the EU biopharmaceutical products to break into the U.S. market or vice versa is similar;**

Regional analysis of biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004 shows that of the total 147 biopharmaceuticals, 39% (57 biopharmaceuticals) were approved by both the FDA and EMEA. More and more biopharmaceuticals seems to be launched globally as 60% (34 products) of the 57 biopharmaceuticals approved by both the FDA and EMEA between 1995 and 2004 at least have one approval date after year 2000.

Further analysis of these 57 biopharmaceuticals approved by both the FDA and EMEA revealed that 68% (39 products) were approved by the FDA first, 30% (17 products) were approved by the EMEA first except that the approval date for GlucaGen was not available. More biopharmaceuticals were licensed in the U.S. market first. Another trend is biopharmaceuticals developed by the European-based companies would license in the EU first and then break into the U.S. market. The average additional time (the approval date of the EMEA minus the approval date of the FDA) taken for the 39 biopharmaceuticals approved by the EMEA is similar to the average additional time (the approval date of the FDA minus the approval date of the EMEA) taken for the 17 biopharmaceuticals approved by the FDA, which is 572 days and 588 days respectively.

- **Trends in biopharmaceutical product approval over time reveal that the number of biopharmaceuticals approved by the FDA and EMEA between 2001 and 2004 has decreased compared with the former four years between 1997 and 2000;**

It seems that the number of biopharmaceuticals approved has been decreasing in recent years. The possible reasons are the increased clinical trial duration (Reichert, 2004) and the increased R&D cost (Schmid et al., 2005). However, two four-year periods' analysis in this thesis maybe too narrow to draw the conclusion. It remains to be seen whether this trend will be sustained.

- **Biopharmaceuticals approved thus far are mainly protein-based;**

There is no gene-therapy product approved by either the FDA or EMEA. Only one antisense oligonucleotide compound produced by direct chemical synthesis has been approved thus far. With this exception, all the other biopharmaceuticals approved by the FDA and EMEA in the recent 10 years are proteins.

However, the China State Food and Drug Administration (SFDA) licensed the first worldwide gene therapy product, which is called Gendicine on 16th Oct. 2003. It was developed by Shenzhen SiBiono Gene Tech Co., Ltd and is indicated for the treatment of nasopharyngeal cancer (SFDA news, available from: www.cde.org.cn). It presents one of the great breakthroughs in the world biopharmaceutical industry.

- **The biopharmaceutical industry is and will continue to target areas of un-met needs, e.g. cancer, infection, diabetes, autoimmune diseases, blood-related diseases and rare diseases;**

Recent discoveries in biomedical research present many new opportunities for biopharmaceuticals to be used in disease areas with critical, un-met medical needs. Analysis of the biopharmaceuticals approved over the 10 year period surveyed in this thesis shows that 13 biopharmaceuticals were approved for blood-related disease, 12 biopharmaceuticals were for treatment of infectious disease, 10 biopharmaceuticals were for treatment of diabetes and 10 biopharmaceuticals were for treatment of cancer.

Identification of the 10 blockbuster biopharmaceuticals (sales revenue more than US $1 billion per annum) on the market reveals that 3 biopharmaceuticals were developed for treatment of anemia, 2 biopharmaceuticals for treatment of rheumatoid arthritis, 1 biopharmaceutical for treatment of multiple sclerosis, 1 biopharmaceutical for treatment of diabetes, 1 biopharmaceutical for treatment of neutropenia, 1 biopharmaceutical for treatment of hepatitis and 1 product for treatment of lymphoma. Again, the biopharmaceutical industry is focusing on the treatment of life-threatening, chronic and rare diseases such as blood-related diseases, infection, diabetes, cancer and autoimmune diseases and the market value for these indications is huge.

As more therapeutic targets are validated by genomic research, the biopharmaceutical industry is likely to continue focusing on the treatment of life-threatening, chronic and rare diseases. Of the 324 biotechnology medicines either in clinical trials or under review by the FDA, 154 are for cancer treatment, 43 for infectious diseases, 26 for autoimmune diseases and 17 for AIDS/HIV and related conditions (Anon, 2004. Available from: www.phrma.org/newmedicines/surveys.cfm?newmedsrindex=76).

One interesting finding is that four blockbuster biopharmaceuticals for treatment of rare diseases according to ORPHANET's drug list (Available from: http://www.orpha.net/consor/cgi-bin/pat_index.php?Lng=GB), which accounts for 40% of all the blockbuster biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004. Worldwide orphan drug regulations have provided several inspiring incentives for the biopharmaceutical companies; between 1982 and 2000, 56% of biopharmaceuticals were approved under the orphan drug designation compared with only 14% of conventional drugs. Since 1998, 70% of orphan designations went to biotechnology firms (Anon, 2001)

- **The financial risks linked with biopharmaceutical drug development are significant although the reward is huge. Biopharmaceutical companies should address the issues of how quality, safety and efficacy can be achieved;**

Of the 147 biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004, 18 biopharmaceuticals were withdrawn from the market, which represents a 12% failure rate.

Some of the biopharmaceuticals withdrawn are because of safety or quality reasons. Following are some of the instantces: Ecokinase (Reteplase) was approved by the EMEA in 1996 for treatment of acute myocardial infarction. Nevertheless, the marketing authorisation holder notified the European Commission in 1999 that they had decided to withdraw the market authorisation (EMEA press release, available from: www.emea.eu.int). The reason was that this product is incompatible with heparin and precipitates following reconstitution. Another biopharmaceutical product withdrawal from the market for a quality reason was Forcaltonin (recombinant salmon calcitonin). In 2003, CPMP suspended the marketing

authorisation of this product because the sponsoring company could not identify an authorised manufacturer to ensure the quality of the product.

Other biopharmaceutical products withdrawn from the market because of commercial reasons were the oligonucleotide antisense (Vitravene), Wellferon, Hepacare and so on. However, it is not possible to draw any conclusion on whether there is a pattern to compound withdrawal because some of the withdrawal information is not available.

The key to increasing the number of clinically useful biopharmaceuticals is not simply advancing more compounds into clinical study, but improving the quality of the candidates selected for study. As the manufacturing process of biopharmaceuticals is complicated compared with conventional pharmaceuticals, biopharmaceuticals should address on the issues such as how quality, safety and efficacy can be achieved. Compliance with GMP, development of manufacturing methods, quality control and improved clinical validation to prevent unforeseen toxicity is very important in this case. Acturally, some changes have been happened in the clinical validation process. According to the Tufts Center for the study of drug development's research result (Reichert, 2004), the average clinical phase for new protein therapeutics has been increased, from 50.3 months between 1991 and 1994, to 64.0 months between 1996 and 1999 and 73.2 months between 2000 and 2003.

- **Lots of unmet challenges will emerge in the recent future, e.g. biogenerics;**

The failure to approve the first biogeneric "Omnitrop" (Somatropin) by the EMEA in June 2003 has lead a regulatory action. On 31 March 2004, the European Parliament Council enacted Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (available from: http://pharmacos.eudra.org/F2/review/doc/final_publ/ Dir_2004_27_20040430_EN.pdf). The directive defines a generic biological medicinal product and states that such a product cannot usually be regarded as a generic medicinal product as is commonly done with conventional medicinal products. "Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process characteristics, raw materials used, molecular characteristics and therapeutic modes of action. When a biological medicinal

product does not meet all the conditions to be considered as a generic medicinal product, the results of appropriate tests should be provided in order to fulfil the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both" (Directive 2004/27/EC).

Hence, standards for biogenerics have been firstly developed by the European Union. The statement implies that proof another biopharmaceutical is the generic version of the brand-name biopharmaceutical product will be definitely far more difficult than the conventional biogenerics.

The EMEA is perceived to be the most progressive agency for regulatory approval of biogenerics (or bioequivalents). The decision not to approve Omnitrop in 2004 implies that the Commission is still not confident that the bioequivalence has been established. The manufacture and quality control of biopharmaceuticals is more complicated that conventional medicines, therefore the task of establishing bioequivalence of biogenerics is even more problematic than for conventional drugs. With more and more patents for biopharmaceuticals expiring in the next few years, this issue will become even important for the regulatory agencies.

How to demonstrate bioequivalence will become even more important for the regulatory agencies or other stakeholders. As biopharmaceuticals are more difficult to characterize than conventional drugs, the brand-name biopharmaceutical's sponsor companies may try their best to establish tough criteria to avoid generic competition.

Chapter 3: Case study of biopharmaceutical development: Interferon beta products and The Orphan Drug Act

Previous work （Filippini et al., 2003; Rice et al., 2004) has compared the effectiveness and side effects of interferons with those of placebo in treating relapsing remitting multiple sclerosis. To examine how the orphan drug incentives influence the development of biopharmaceuticals and try to develop an appropriate tool for the evaluation of orphan products, interferon beta products were chosen as a case study to investigate the licensing process, pre-marketing clinical trials evaluation and post-marketing sales performance.

3.1 Introduction

3.1.1 Worldwide Orphan Drug Regulations

Bringing any new drug to the market is a time-consuming and costly process. Pharmaceutical companies therefore mainly focus on those medicines which are likely to be profitable. Rare diseases have therefore been neglected by the pharmaceutical industry.

Governments have recently launched initiatives to encourage the pharmaceutical industry to develop and market drugs for rare diseases. With increasing biomedical research, such as the human genome project, and improved understanding of molecular biology, more drug targets have been identified. Biotechnology companies have become a major driving force in drug research and many of the biopharmaceuticals currently on the market are indicated for the treatment of rare diseases.

The first pivotal step was taken in 1983 when the US Congress passed the Orphan Drug Act, which introduced financial incentives for manufacturers to introduce such drugs. Since then, several governments have passed similar orphan regulations. Orphan drug laws have had a significant impact on the biotechnology industry. Some data shows that between 1982 and 2000, 56% of biopharmaceuticals approved in the US was reviewed under orphan drug designation compared with only 14% for conventional medicines. Since 1998, 70% of orphan designations went to biotechnology firms (Anon, 2001).

The 1983 Orphan Drug Act defined a rare disease or condition as: "in the case of a drug, any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug." (The Orphan Drug Act, available from: http://www.fda.gov/orphan/oda.htm)

The incentives offered to manufacturers include: federal funding through grants and contracts for clinical trials of orphan products; tax credit of fifty percent of clinical testing costs and a seven-year period of exclusive marketing given to the first sponsor.

Japan followed a similar path in application of orphan drug legislation (Garcia 2004; Mirza, Treating rare disease: The orphan drug act). In Oct 1993, the Organization for Pharmaceutical Safety and Research (OPSR) amended the orphan drug legislation so that orphan drug status was given to drugs that were intended to treat severe diseases which are defined as:

- Affecting less than 50,000 patients in Japan;
- Having no alternative treatment available, or for which only poorly effective or toxic treatments are available; or
- Where further development is highly likely to lead to a useful drug (in the absence of equivalent alternative).

The incentives provided by Japan include: financial funds, tax reduction, guidance to facilitate development, accelerated assessment of drug approval application, and a ten-year period of exclusivity. (ORPHANET: Orphan drugs in Japan, available from: http://www.orpha.net)

Australia's orphan drug programme was set up in November 1997 (Mirza, Treating rare disease: The orphan drug act; ORPHANET: Orphan drugs in Australia, available from: http://www.orpha.net). It automatically recognizes orphan drug regulations of the US as part of its evaluation process when the prevalence of the disease in the Australian population is "not more than one person per 2,000". Therapeutic Goods Administration (TGA) will

provide an exclusive marketing period of 5 years and waiver of application evaluation and no annual registration fees.

On 16 December 1999, the European Parliament enacted the Council Regulation (EC) 141/2000 Orphan drug legislation (Regulation (EC) No 141/2000; EMEA: Report on the first 3-year mandate of the Committee for Orphan Medicinal Products). A drug can be designated as an orphan drug if: "

(a) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and

(b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition. "

When a drug receives an orphan drug designation, the company can seek protocol assistance, obtain fee reductions, use the centralized procedures for marketing authorisations and obtain a 10-year marketing exclusivity (the exclusivity period maybe reduced to 6 years if it is found that criteria are no longer met at the end of 5^{th} year).

3.1.2 The "same drug" and clinical superiority

Once an orphan drug has been approved, another application for the same drug and the same indication will not be accepted during the period of marketing exclusivity unless the other applicant can prove its product is clinically superior or the original holder gives consents; the original sponsor cannot supply sufficient amounts of the drug. Orphan drug regulations have the similar definitions for "same drug" across the world (21CFR Pt 316), that is: two drugs with similar physical/ chemical characteristics are the same, and the exclusivity granted to one drug will block approval of the other drug for the same indication, for

instance, if the product "contains the same principal molecular structural features (but not necessarily all of them the same structural features". Macromolecular drug products are considered to be the same product if they have only minor differences in amino acid sequence, different glycosylation patterns or different tertiary structures. For micro-molecular drugs, if the active moiety is identical, they are considered to be the same product as well. What's more, differences in formulation, dose or other product characteristics by themselves do not render a drug different. However, despite physical/ chemical similarities, the subsequent drug can get marketing approval if it can be shown to have "clinical superiority" (FDA review: Office of Orphan Products Development (OOPD) Analysis of Exclusivity Issues Raised in the Serono BLA for Rebif).

The orphan drug regulations have also defined the meaning of "clinical superiority": if the subsequent drug can demonstrate either greater effectiveness, greater safety or even some form of a major contribution to patient care, this new product can be considered clinically superior.

For demonstration of greater effectiveness there will usually need to be direct comparative clinical trials but for demonstration of greater safety only "in some cases" are direct comparative trials required.

The sponsors can choose either safety or efficacy for comparison, because the regulations indicate that only one aspect is necessary to demonstrate clinical superiority.

The approval of interferon beta products for the treatment of relapsing forms of multiple sclerosis is an example of how the Orphan Drug Act regulations were applied. The evidence for "clinical superiority" is evaluated in the following section along with how the products performed in the market place subsequent to licensing.

3.2 Therapeutic indication for the orphan drug, Interferon beta, in the treatment of Multiple Sclerosis (MS)

3.2.1 Introduction of multiple sclerosis and interferon products

3.2.1.1 Multiple Sclerosis (MS)

Multiple sclerosis (MS) is generally considered to be a disorder of the central nervous system (CNS), which is chacterized by inflammation and abnormalities of nerve tracts within the white matter of CNS. The cause of multiple sclerosis is still unknown. Caucasians have higher incidence than other races, even at the same latitudes. Women have a higher incidence of MS than men, which is approximately 2 to 3 times. (Granieri et al., 2001; Hader et al., 1988; Sweeney et al., 1986)

There are three forms of MS: relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS). About 85% of patients experience a relapsing-remitting course (RRMS) at first, characterized by intermittent and localized impairment followed by complete or near-complete recovery (Revel 2003; Weinshenker et al., 1995). Generally, exacerbations will happen again and disability will accumulate in the following years. About 50% of subjects with RRMS will develop SPMS within 20 years of onset (Ebers et al., 2000; Weinshenker et al., 1989) and show neurological decline over time. The secondary progressive phase is characterized by accumulation of neurological disability followed by incomplete recovery, or even leading to death in some patients. A small portion of patients suffer from the primary progressive multiple sclerosis (PPMS), which is characterized by steady accumulation of disease progression from the beginning (Compston et al., 2002).

Magnetic resonance imaging (MRI) is an important criterion in the diagnosis of MS. MRI readily visualizes the MS lesions scattered throughout the brain. Diagnosis generally requires confirming at least two lesions, where presenting lesions occur at different times and in different parts of the CNS (Compston et al., 2002).

There are mainly two categories of therapies (Revel 2003): those tried to reduce symptoms are more successful than those intended to control the disease process.

There are currently six drugs approved in the United States for treatment of MS (FDA data). Betaseron (Interferon beta-1b), Avonex (Interferon beta-1a), Rebif (Interferon beta-1a), Copaxone (glatiramer acetate – formerly known as copolymer-1) and Tysabri (Natalizumab) are licensed for the treatment of relapsing-remitting MS or relapsing forms of MS. Novantrone (Mitoxantrone), a cancer chemotherapeutic agent, was approved in 2000 for patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis.

3.2.1.2 Interferon products

Interferons are cytokines (a family of naturally occurring proteins and glycoproteins), which have anti-viral, anti-proliferative, and immunomodulatory functions. When foreign bodies infect cells, interferons are secreted naturally and play an essential role in the immune system by repairing damage and helping to destroy the infecting material (FDA review: Medical officer review of Betaseron). They were first discovered in 1957, and the name "interferons" was coined because they "interfere" with the replication of genetic material in foreign cells.

There are two types of interferons: Type I and Type II. Type I interferons are composed of the interferon-alfa (of which there are many), and interferon-beta. Type II interferon is interferon gamma.

Fig 3.1 shows the licensing history of different interferon products.

The first interferon alfa-2a (Roferon-A) and interferon alfa-2b (Intron A) were approved by the FDA in 1986, both of which were licensed by Hoffmann-La Roche Inc. The following interferon product was interferon alfa-N3 (Alferon N), which was approved by the FDA in 1989.

The first interferon gamma product (interferon gamma-1b, Actimmune) was approved by the FDA in 1990.

Three forms of recombinant interferon beta products have been approved for treating relapsing-forms multiple sclerosis patients. The first is Betaseron, which was approved by the FDA in 1993. The second, Avonex was licensed by Biogen in 1996, who provided evidence that it was not the "same drug" as Betaseron. Approval was on the basis of a reduction of a single adverse effect (injection site reaction). The third interferon beta product, Rebif was approved in 2002 based on a direct comparative clinical trial against Avonex to demonstrate greater effectiveness.

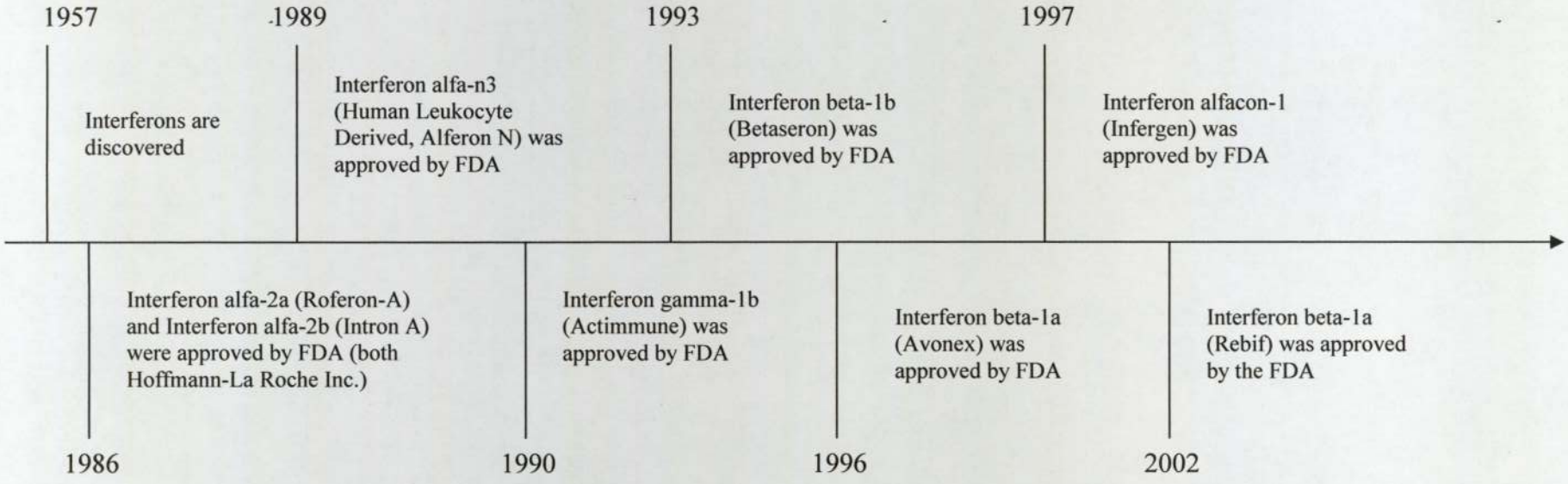


Fig 3.1 Licensing history of interferon products

Table 3.1 demonstrates the therapeutic indications of interferon products. All the information has been retrieved from the FDA approved labels (www.fda.gov) and a black dot means the indication has been approved by the FDA.

Interferon-alfa is indicated for the treatment of a variety of malignancies and viral diseases. Interferon-beta is indicated for the treatment of multiple sclerosis at present. Type II interferon, interferon-gamma (also known as immune interferon), is a cytokine produced primarily by natural killer cells and T-lymphocytes. Originally characterized based on its anti-viral activities, interferon-gamma also exerts anti-proliferative, immunoregulatory and pro-inflammatory activities and is thus important in host defense mechanisms.

Table 3.1 Therapeutic indications of interferon products

Brand Name (Manufacturer)	Generic name	Approval date	chronic hepatitis C	hairy cell leukemia	AIDS related Kaposi's sarcoma	Philadelphia chromosome (Ph) positive chronic myelogenous leukemia (CML)	Maligant melanoma	Follicular lymphoma	Condylomata acuminate	Chronic hepatitis B	relapsing forms of multiple sclerosis	chronic granulomatous disease	severe, malignant osteopetrosis
Roferon A (Hoffmann-La Roche)	Interferon alfa-2a	04/06/1986	●	●	●	●							
Intron A (Schering)	Interferon alfa-2b	04/06/1986	●	●	●		●	●	●	●			
Alferon N Injection (Interferon Science,Inc)	Interferon alfa-n3 (Human Leukocyte Derived)	10/10/1989							●				
Infergen (InterMune)	Interferon alfacon-1	06/10/1997	●										
Betaseron (Chiron Corp)	Interferon beta-1b	23/07/1993									●		
Avonex (Biogen, Inc)	Interferon beta-1a	27/05/1996									●		
Rebif (Serono, Inc)	Interferon beta-1a	07/03/2002									●		
Actimmune (InterMune)	Interferon gamma-1b	25/02/1999										●	●

Note: Data from FDA label; Black dot means the indication has been approved.

Table 3.2 shows the characteristics of different interferon products. All the information is obtained from the FDA approved labels (www.fda.gov).

Interferon beta products are sub-classified as interferon beta-1a (Avonex and Rebif) and interferon beta-1b (Betaseron). The differences between interferon beta-1a and interferon beta-1b products are the cell origin and number of amino acids. The cell origin of interferon beta-1a products is Chinese Hamster Ovary (CHO) cell and the cell origin of interferon beta-1b product is Escherichia Coli bacteria. Interferon beta-1a products contain 166 amino acids. They receive the designation "1a" because their amino acid sequence is identical to that of the naturally occurring interferon beta. Interferon beta-1b product consists of 165 amino acids compared with the 166 amino acids of interferon beta-1a products. The N-Methionine at position 17 is absent and Cysteine was replaced with Serine for interferon beta-1b product.

Interferon gamma-1b (Actimmune) is a single-chain polypeptide containing 140 amino acids.

Table 3.2 Characteristics of different interferon products

Brand Name	Roferon A	Intron A	Infergen	Alferon N	Avonex	Rebif	Betaseron	Actimmune
Generic Name	Interferon alfa-2a	Interferon alfa-2b	Interferon alfacon-1	Interferon alfa-n3	Interferon beta-1a	Interferon beta-1a	Interferon beta-1b	Interferon gamma-1b
Cell origin	Escherichia coli bacteria	Escherichia coli bacteria	Escherichia coli bacteria	human leukocyte derived	Chinese Hamster Ovary (CHO) cells	Chinese Hamster Ovary (CHO) cells	Escherichia coli bacteria	Escherichia coli bacteria
Number of amino acids	165	165	166	166	166	166	165	140
Administration Route	Subcutaneous or intramuscular	Intramuscular, subcutaneous, intralesional, or intravenous	Subcutaneous	Intra-lesional	Intramuscular	Subcutaneous	Subcutaneous	Subcutaneous
Additional information			Interferon alfacon-1 differs from interferon alfa-2b at 20/166 amino acid (88% homology) and comparison with interferon –beta shows homology at over 30% of amino acid position.			Receives the designation "1a" because its amino acid sequence is identical to that of the naturally occurring interferon beta.	Absent N-Methionine at position 17, Cysteines was replaced with Serine. Non-glycosylated.	Non-glycosylated

Note: Data from FDA label

Table 3.3 shows the approval information for interferon beta products. The information in this table was obtained from the FDA and EMEA's website (www.fda.gov and www.emea.eu.int).

The indication approved by the FDA for all the three interferon beta products is for "relapsing forms of multiple sclerosis". However, the indications approved by the EMEA are different. The indication for Betaferon [EU tradename] approved by the EMEA is: "Treatment of patients with relapsing remitting multiple sclerosis and two or more relapses within the last two years. Betaferon is also indicated for patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses". The indication for Avonex in the Europe Union is: "Treatment of patients with relapsing multiple sclerosis (MS); Treatment of patients who have experienced a single demyelinating event". And the indication for Rebif in the EU is: "Treatment of patients with multiple sclerosis and with 2 or more relapses within the last two years."

Table 3.3 Approval information for interferon beta products

Brand name	Generic name	Sponsor company	FDA approval date	EMEA approval date	FDA Indication	EMEA Indication
Betaseron [TR in US] Betaferon [TR in EU]	Interferon beta-1b	Chiron	23/07/1993	30/11/1995	Relapsing forms of multiple sclerosis	Treatment of patients with relapsing remitting multiple sclerosis and two or more relapses within the last two years. Betaferon is also indicated for patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.
Avonex	Interferon beta-1a	Biogen	17/05/1996	13/03/1997	Relapsing forms of multiple sclerosis	Treatment of patients with relapsing multiple sclerosis (MS); Treatment of patients who have experienced a single demyelinating event
Rebif	Interferon beta-1a	Serono	07/03/2002	04/05/1998	Relapsing forms of multiple sclerosis	Treatment of patients with multiple sclerosis and with 2 or more relapses within the last two years.

3.2.2 Licensing of interferon beta products by the FDA

3.2.2.1 Licensing of first interferon beta product by the FDA

The first interferon product, Betaseron was licensed by the FDA for commercial sale in the US in 1993. A clinical trial with Betaseron showed efficacy in reducing the rate of exacerbations by approximately one third (FDA review: Medical officer clinical review of Betaseron). It also had effects on the MRI lesion loads. As expected with an interferon, the side effects were considerable and are considered below.

Betaseron received orphan drug designation prior to approval. Its indication is for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations (Betaseron label).

3.2.2.2 Licensing of alternative interferon beta products (Avonex and Rebif) by the FDA

Subsequently, a second interferon beta product, Avonex (an interferon beta-1a) was shown to be effective for reducing the incidence of exacerbations and reducing the accumulation of physical disability. Avonex was deemed to be safe and effective by the FDA but Betaseron was still within the 7-year period of marketing exclusivity at the time that Avonex was under review. However, Biogen, the manufacturer of Avonex, provided evidence that Avonex was not the same drug by showing Avonex was clinically superior over Betaseron. Specifically, Biogen supplied evidence showing a significant difference between the safety profiles of the two products with regard to skin necrosis at injection sites, Table 3.4 (FDA review: Summary basis for approval of Avonex).

Table 3.4 Side effects comparison between Avonex and Betaseron

Adverse Reaction	Placebo (n=789)	Betaseron (n=1115)	Placebo (n=143)	Avonex (n=158)
Body as a Whole				
Injection site reaction	**29%**	**85%**	**1%**	**4%**
Asthenia	54%	61%	13%	21%
Flu-like symptom complex	41%	60%	40%	61%
Headache	48%	57%	57%	67%
Pain	42%	51%	20%	24%
Fever	22%	36%	13%	23%
Chills	11%	25%	7%	21%
Abdominal pain	13%	19%	6%	9%
Chest pain	7%	11%	4%	6%
Malaise	4%	8%	3%	4%
Injection site necrosis	**0%**	**5%**	**NA**	**NA**
Infection	NA	NA	6%	11%
Injection site inflammation	NA	NA	0%	3%
Hypersensitivity reaction	NA	NA	0%	3%
Ovarian cyst	NA	NA	0%	3%

Note: Data from FDA label; NA = not available

Table was compiled from Summary Basis for Approval of Avonex

All the data from Table 3.4 are extracted from the FDA approved label for Avonex and Betaseron. No injection site necrosis was reported in the 158 patients treated with Avonex in the phase III study (0%). In contrast, the incidence of injection site necrosis reported for Betaseron in the phase III study was 5%. Further supportive evidence for a difference in skin necrosis incidence was suggested by the 85% incidence of injection site reactions for Betaseron-treated patients compared with only 4% for Avonex-treated patients in the phase III trial (Avonex and Betaseron label).

Avonex was not deemed to be the same drug as Betaseron, therefore Biogen received marketing approval for Avonex in May 1996. Biogen also had orphan drug designation for Avonex for treatment of RRMS and was granted a 7-year period of marketing exclusivity, which expired in May 2003.

Avonex's indication is for "Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations." (FDA: Avonex label).

Serono, a third manufacturer of an interferon beta product, Rebif (an interferon beta-1a) also conducted clinical studies in relapsing-remitting MS. Serono completed their studies and submitted a Biologics License Application (BLA) for Rebif for use in MS in February 1998. The major safety and efficacy data came from a three-group, controlled, randomized, double blind study of doses of 22μg or 44μg vs. placebo. Based on a review of the information supplied in the license application, FDA concluded that Rebif was safe and effective for use in the treatment of RRMS (FDA review: Medical Officer's clinical review of Rebif. BLA 98-0621). However, Rebif was regarded as a "same drug" as both Betaseron and Avonex. As a consequence, because Serono couldn't demonstrate Rebif was different from Avonex and Betaseron, Rebif was not granted marketing approval until marketing exclusivity was ended for both Betaseron and Avonex.

Serono recognized that the Betaseron period of exclusivity would expire in July 2000. Thus, in the late 1999 Serono commenced an open-label, randomized controlled clinical study to show superior clinical efficacy of Rebif compared to Avonex（FDA review: Medical Officer's review of Rebif）. The objective of this study was to provide sufficient evidence in order to enable marketing of Rebif prior to the expiration of Avonex's exclusivity period. The primary endpoint is the proportion of patients who were exacerbation-free. After 24 weeks of treatment, 254 of 339 subjects (74.9%) in the Rebif treatment group were exacerbation free, compared with 214 of 338 subjects (63.3%) in the Avonex® treatment group ($p<0.001$). Following 48 weeks of treatment, 209 of 339 subjects (61.7%) in the Rebif treatment group were exacerbation free, compared with 177 of 338 subjects (52.4%) in the Avonex treatment group($p=0.009$) (FDA review: Medical Officer's review of Rebif).

Based on the complete results of the initial 24 weeks of this comparative study, as well as summary data from 48 weeks, CBER concluded that Rebif demonstrated a superior clinical benefit over Avonex, allowing Serono to break Biogen's orphan drug exclusivity and thus, to market Rebif in the U.S. for the treatment of relapsing-remitting MS in March of 2002 (FDA review: Medical Officer's review of Rebif). Rebif is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability (FDA: Rebif label).

Since Rebif obtained marketing approval, Multiple Sclerosis (MS) was no longer considered to be an orphan disease; MS now affects more than 200,000 people in the US (Biogen annual report 1999). However, because interferon beta products have already been granted orphan drug status for MS indication, the market exclusivity still applies to Rebif (FDA review: Medical Officer's review of Rebif).

The marketing exclusivity periods for these three interferon beta products are shown below (Fig 3.2).

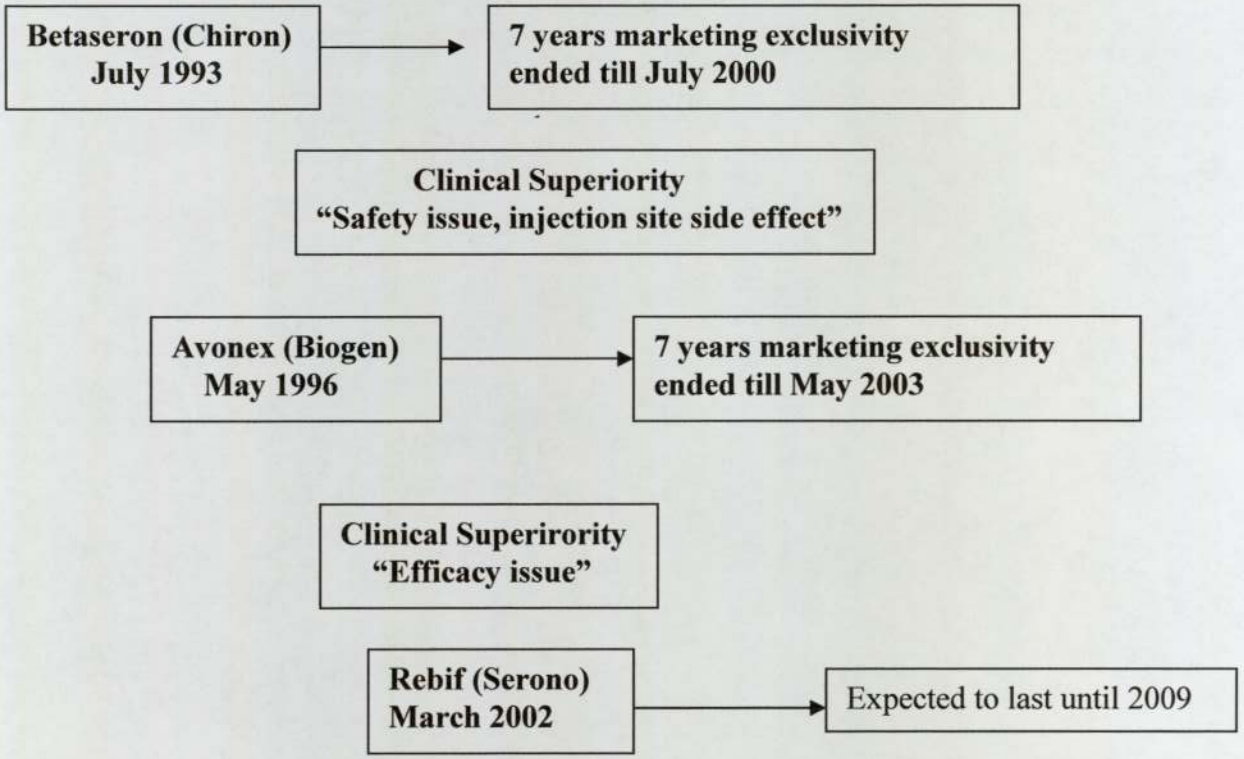


Fig 3.2 Market exclusivity of interferon beta products

Note: The sponsoring company name is in the parenthesis.

3.2.3 Evidence-base of efficacy demonstrated by pre-marketing clinical trials of interferon beta products

There are three different interferon beta products on the market at present. All of them have received orphan drug designation.

Betaseron was the first interferon beta product to be approved by the FDA in 1993. The seven-year period of marketing exclusivity expired in 2000. The second interferon beta product, Avonex was approved by the FDA in 1996 by demonstrating only a simple "injection site reaction" offering superiority to Betaseron. It is not yet clear whether Avonex is more effective than Betaseron or not. Avonex's seven-year marketing exclusivity expired in year 2003. Rebif was the most recent interferon beta product to be launched on the market and was approved in 2002 by showing the result of a comparative clinical trial which compared the effectiveness between Rebif and Avonex （FDA review: Medical Officer's review of Rebif）. The comparative effectiveness of the three interferon beta products remains unknown.

Objectives: To undertake a systematic analysis to compare the effectiveness between three different interferon beta products based on pre-marketing clinical trials submitted to the FDA. To study the performance of the three interferon beta products on the market by analysing post-marketing sales of interferon beta products.

3.2.3.1 Method

3.2.3.1.1 Selection criteria

The clinical trials selected were pre-marketing double blind, placebo-controlled, randomized clinical trials of interferon beta product submitted to the FDA review undertaken in patients with multiple sclerosis given by the subcutaneous or the intramuscular route. There were no language restrictions.

3.2.3.1.2 Search Strategy

Pre-marketing clinical trials were searched from within FDA reviews, Endnote (Remote search MEDLINE by PubMed) and reference lists of other systematic reviews. The search result was finally updated in 1st March 2005. For evaluation of the post-marketing sales of interferon beta products, the sales data of interferon products and the total revenue of the sponsoring companies were obtained from company annual reports between 1997 and 2003. Some of the data are from publicly accessible websites.

3.2.3.1.2.1 FDA reviews

In order to assess clinical trials using evidence based medicine, it is essential to review the regulatory files. Relevant information from the FDA's review of these three marketed interferon beta products was retrieved from FDA website (www.fda.gov).

There are a total of 6 pre-marketing clinical trials, which have been submitted to FDA for approval.

Chiron has submitted 3 clinical trials for Betaseron. One clinical trial was intended for relapsing forms of multiple sclerosis. The other two clinical trials were for secondary progressive multiple sclerosis.

Biogen has submitted only one clinical trial for Avonex. The indication of this clinical trial was relapsing forms of multiple sclerosis.

Serono has submitted two clinical trials for Rebif. The indication of these two clinical trials was relapsing forms of multiple sclerosis.

Five of the trials were double-blind, placebo-controlled, randomized clinical trials. Only one of them (Rebif) was open-label, randomized, active comparator study (Rebif vs. Avonex).

3.2.3.1.2.2 Published pre-marketing clinical trials

The EMBASE database was not accessible from Aston University, so in my search strategy, I only used endnote software (remote search Medline by PubMED) combined with the reference lists of two systematic reviews describing interferons in relapsing-remitting multiple sclerosis. The systematic retrieval of papers is summarised in Figure 3.3.

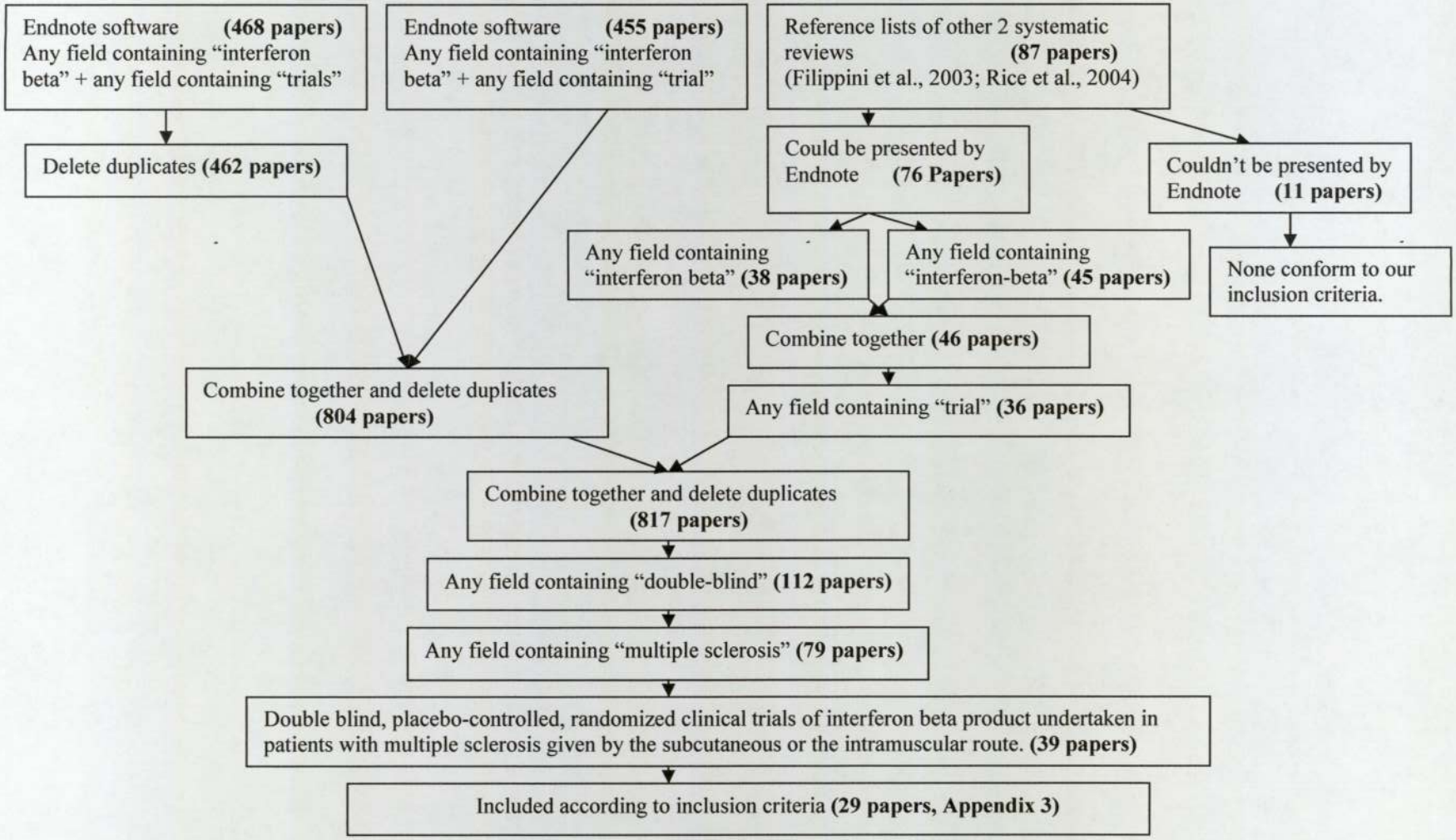


Fig 3.3 Search strategy for published works describing clinical "trials" for "interferon beta" products

When searching using endnote software, the key word "interferon beta" was found to completely cover the key word "interferon-beta", so "interferon beta" was chosen as one key word. But key word "trials" or "trial" did make a difference.

Therefore, the search strategy in endnote was made using the key word [any field containing "interferon beta" and any field containing "trials"], which yielded 468 papers (462 papers after deleting duplicates); using key word [any field contain "interferon beta" and any field contain "trial"], which yielded 455 papers. Combining these two results together, that is, [any field contain "interferon beta" and any field contain "trials"/ "trial"], identified 804 independent reports.

Within each reference, information was extracted describing clinical efficacy. The EDSS (Kurtzke Expanded Disability Status Scale) was searched for as a disability measure. EDSS scores range from 0 to 10 (Kurtzke 1983), 0: normal neurological examination; 1.0: no disability, minimal signs on one functional system to 10.0: death.

Each reference was evaluated for the primary outcome measures or the effectiveness of different interferon beta products determined as:

- The number of patients who were exacerbation free;
- The number of patients who were not suffering from disease progression;
- The time to confirmed EDSS progression.

In addition, clinical trials were separated into three design types:

- Double blind, multicentre randomized placebo controlled trials indicated for RRMS;
- Double blind, multicentre randomized placebo controlled trials indicated for SPMS;
- Evaluator blind, open label, randomized, active comparator study indicated for RRMS.

Odds ratios and 95% CI were used for the comparative assessment of clinical efficacy between treatments where 95% CI means Confidence Interval of outcome at 95% percent probability level. The odds ratio is a way of comparing whether the probability of a certain event is the same for two groups (Definition: Odds ratio, available from: http://www.cmh.edu/stats/definitions/or.htm). An odds ratio of 1 implies that the event is equally likely in both groups whereas an odds ratio greater than one implies that the event is

more likely in the first group. An odds ratio less than one implies that the event is less likely in the first group.

Shown below is the typical 2 by 2 contingency table for calculating ORs. a is the incidence of X^- for group Y^-; b is the incidence of X^+ for group Y^- ; c is the incidence of X^- for group Y^+ ; d is the incidence of X^+ for group Y^+.

	X^-	X^+	
Y^-	a	b	a+b
Y^+	c	d	c+d
	a+c	b+d	n=a+b+c+d

$$OR = \frac{a/b}{c/d}$$

Which can be simplified to $OR = \frac{ad}{cb}$

Online calculator was used for the calculation of Odds Ratios and 95% CIs (available from: http://www.hutchon.net/ConfidOR.htm).

3.2.3.2 Results

There were 87 references from the two systematic reviews (Filippini et al., 2003; Rice et al. 2004), 76 of which were imported to endnote. The other 11 papers could not be searched by endnote because most of them were from a Cochrane reviewer's handbook, book, EMEA report or meeting abstract. A few of these 11 papers were from other databases. After looking at the titles of these 11 papers, no papers were suitable according to the inclusion criteria. The remaining 76 papers were sorted by key word [any field contain "interferon beta" / "interferon-beta"], resulting in 46 papers and then searched by another key word [any field contain "trial"], resulting 36 papers. These 36 papers were compared with the 804 papers obtained from the endnote search method, leading to 817 papers after deleting duplicates.

"Double-blind" and "multiple sclerosis" are quite discriminating therefore were chosen as

key words. These "817 papers" were searched using key word [any field contain "double-blind"], resulting in 112 papers. These 112 papers were searched using key word [any field contain "multiple sclerosis"], which identified 79 papers.

The results of these 79 papers were exported and the titles and abstracts were assessed. Of these 79 papers, 39 papers were double blind, placebo-controlled, randomized clinical trials of interferon beta product undertaken in patients with multiple sclerosis given by the subcutaneous or the intramuscular route. From these 39 papers again, 29 papers describe the pre-marketing clinical trials.

The 29 papers can be categorized to 5 clinical trials, that is: IFNB Group (Betaseron, RRMS), PRISMS Study Group (Rebif, RRMS), MSCRG (Avonex, RRMS), European Study Group (Betaseron, SPMS) and The North American Study Group (Betaseron, SPMS). The detailed classification for these 29 papers can be seen in Appendix 3.

All of the five clinical trials are the same as the five placebo-controlled pre-marketing clinical trials submitted to FDA review.

3.2.3.2.1 Clinical endpoints described in pre-marketing clinical trials

All the information in this section is obtained from the FDA review and the 29 reference papers.

There are a total of six pre-marketing clinical trials which have been identified for interferon beta products. This thesis assessment is based on these six pre-marketing clinical trials (IFNB Group, European Study Group, The North American Study Group, MSCRG Group, PRISMS Group and Rèbif trial 2). The six trials included 3567 randomised patients (Fig 3.4).

All the clinical trials use EDSS (Kurtzke Expanded Disability Status Scale) as a disability measure. EDSS scores range from 0 to 10(Kurtzke 1983), 0: normal neurological examination; 1.0: no disability, minimal signs on one functional system to 10.0: death.

The basic characteristics of these pre-marketing clinical trials are shown in Table 3.5.

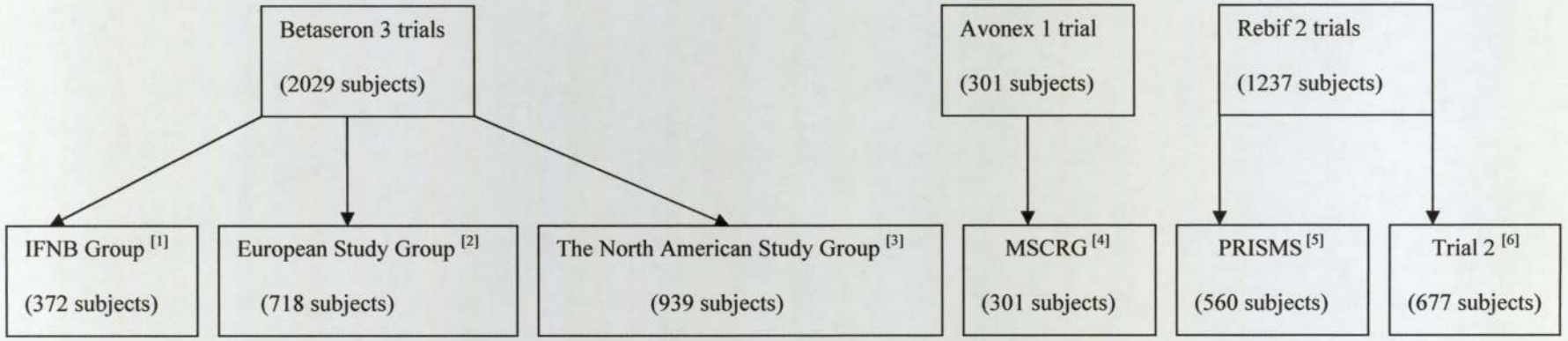


Fig 3.4 Trials and patients involved in pre-marketing trials of the marketed interferon beta products for multiple sclerosis

Note: [1] The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Neurology 1995.
[2] Freeman JA, et al., 2001
[3] Panitch H, et al., 2004
[4] Jacobs L, et al., 2000
[5] PRISMS Study Group. Lancet 1998.
[6] FDA Review: Medical Officer's review of Rebif.

Table 3.5 General description of pre-marketing clinical trials

Product	Clinical Trial (Disease type)	Study Design	No. of Patients Enrolled	Intervention (No.)	Length of trials (months)	Route of Administration	Inclusion Criteria
Betaseron	IFNB Group (RRMS)	Double blind, multicenter, randomized, parallel, placebo controlled trial	372	1.6 MIU (0.05mg) interferon beta-1b (125); 8.0 MIU (0.25mg) interferon beta-1b (124); Placebo (123)	24	Subcutaneous, every other day	Age: 18-50 years; Clinical or laboratory-supported definite RR-MS; EDSS≤5.5; Disease duration>1 year; At least two exacerbations in the 2 years before randomization; No exacerbations for at least 1 month before randomization
	European Study Group (SPMS)	Double blind, multicenter randomized, placebo controlled trial	718	8 MIU (0.25mg) interferon beta-1b (360); Placebo (358)	36	Subcutaneous, every other day	Age: 18-55 years; Clinically or laboratory supported definite MS; EDSS 3.0-6.5; A recorded history of either two relapses or 1.0 point increase in EDSS in the previous 2 years
	The North American Study Group (SPMS)	Double blind, multicenter randomized, placebo controlled trial	939	8 MIU (0.25mg) interferon beta-1b (317); 5MIU (0.16mg)/m2 body surface area interferon beta-1b (314); Placebo (308)	36	Subcutaneous, every other day	Age: 18-65 years; Clinically definite or laboratory-supported definite MS of at least 2 years; EDSS 3.0-6.5; A history of at least one relapse followed by progressive deterioration sustained for at least 6 months; An increase of EDSS of at least 1.0 in the 2 years prior to screening (at least a 0.5 point increase for subjects with a screening EDSS score of 6.5)
Avonex	MSCRG (RRMS)	Double blind, multicenter randomized, placebo controlled trial	301	6.0 MIU (30mcg) interferon beta-1a (158); Placebo (143)	24	Intramuscular, once weekly	Age: 18-55 years; Definite MS; EDSS 1-3.5; Disease duration ≥1 year; At least two documented exacerbations in the 3 years before randomization; No exacerbations at least 2 months before

							randomization
Rebif	PRISMS Group (RRMS)	Double blind, randomized, placebo controlled study	560	6.0 MIU (22mcg) interferon beta-1a (189); 12.0 (44mcg) MIU interferon beta-1a (184); Placebo (187)	24	Subcutaneous, three times a week	Age: NA; Clinical or laboratory-supported definite RRMS; EDSS 0-5.0; Disease duration≥1year; At least two relapses in the 2 years before randomization
	Trial 2 (RRMS)	Evaluator blinded, open-label, randomized, active comparator study	677	44mcg Rebif (339); 30mcg Avonex (338)	48 weeks	Rebif: Subcutaneous, three times per week; Avonex: Intramuscular injection once weekly.	Age: 18-55 years; Clinical or laboratory supported diagnosis of RR MS; EDSS 0-5.5; At least two relapses in the 2 years before randomization Clinical stability or improving neurological state during the four weeks prior to study day 1; Two or more lesions consistent with MS on a screening T2-weighted MRI performed within 28±4 days of study day1;

Note:

1. RRMS: Relapse-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis
2. MIU= million international units; mcg means microgram
3. EDSS: (Kurtzke 1983) Kurtzke Expanded Disability Status Scale, from 0: normal neurological examination; 1.0: no disability, minimal signs on one functional system to 10.0: death.
4. NA means not available.

3.2.3.2.2 Analysis of outcome measures between studies

If the six pre-marketing clinical trials were categorized by clinical presentation, two trials (European Study Group and The North American Study Group) were classified for SPMS; four trials (IFNB, MSCRG, PRISMS and directive study between Rebif and Avonex) were indicated for RRMS. If the trials were categorized by study design, one of them (Directive study between Rebif and Avonex) was evaluator blind, open label, randomized, active comparator study, all of the other five trials were double blind, multicentre randomized placebo controlled trials.

Therefore clinical trials were separated into three types:

- Double blind, multicentre randomized placebo controlled trials indicated for RRMS (IFNB, MSCRG, PRISMS), see Table 3.6;
- Double blind, multicentre randomized placebo controlled trials indicated for SPMS (European Study Group and the North American Study Group), see Table 3.9;
- Evaluator blind, open label, randomized, active comparator study indicated for RRMS (Directive study between Rebif and Avonex), see Table 3.10;

The primary outcome measures were used as comparators between studies and the effectiveness of different interferon beta products determined as:

- The number of patients who were exacerbation free;
- The number of patients who were not suffering from disease progression;
- The time to confirmed EDSS progression.

According to these studies, the definition of relapse or exacerbation is: appearance of new, or reappearance of, neurological abnormality present at least for 24 hours (IFNB Group, PRISMS, the European Study Group, directive study between Rebif and Avonex) or 48 hours (MSCRG, the North American Study Group) and not attributable to fever, infection or withdrawal of corticosteroid therapy. The definition of progression is: an increase in EDSS of at least one point (≥0.5 point if the baseline EDSS score is 6.0 to 6.5) recorded in a period when the patient has no exacerbation (3 months (IFBN, PRISMS, the European Study Group, directive study between Rebif and Avonex) or 6 months (MSCRG, the North American Study Group)).

3.2.3.2.3 Outcome measures of double blind RCT trials indicated for RRMS

As shown in Table 3.6, the data extracted from the FDA review and original articles for exacerbation free patients refers to efficacy after two years treatment. However, the data extracted for progression patients are different: the IFNB Group follow 46 months of treatment (IFNB Neurology 1995); the MSCRG Group (Jacobs et al., 2000) and the PRISMS Study follow two years of treatment (FDA review).

As the data for progression patients are not comparable, only analysis for exacerbation free patients was undertaken (Table 3.7 and Table 3.8). An odds ratio of 1 implies that the event is equally likely in both groups whereas an odds ratio greater than one implies that the event is more likely in the first group. An odds ratio less than one implies that the event is less likely in the first group.

In order to evaluate whether any bias existed in defining the end points between the different studies under comparison, odds ratios between the three different placebo groups were first calculated (Table 3.7). The results show that odds ratios for change in disease activity for the three clinical trials are about 1, which suggests that the clinicals trials were comparable and were reporting similar levels of disease activity.

As shown in Table 3.8, using the OR calculation described in the methods section, the odds ratio of Betaseron vs. Avonex is 1.3; Avonex vs. Rebif is 0.5 and Rebif vs. Betaseron is 1.4. The probability of a patient remaining exacerbation free is Rebif > Betaseron > Avonex.

Table 3.6 Outcome measures of double blind RCT trials indicated for RRMS

Product	Trial (Type)	Interferon Group (No.)		Placebo Group (No.)		Interferon Group (No.)		Placebo Group (No.)		Reference
		Exacerbation free	Total	Exacerbation free	Total	Confirmed disease	Total	Confirmed disease	Total	
Betaseron	IFNB (RR-MS)	31*	124	20*	123	43**	124	56**	123	FDA label; IFNB Group: Neurology 1995
Avonex	MSCRG (RR-MS)	32*	158	23*	143	18*	158	29*	143	FDA label; Jacobs et al., 2000
Rebif	PRISMS (RR-MS)	59*	184	30*	187	27*	184	38*	187	FDA review; PRISMS Group: Lancet 1998

Note:

1. The definition of relapse or exacerbation was taken from the original articles. Appearance of new, or reappearance of, neurological abnormality present at least for 24 hours (IFNB Group, PRISMS) or 48 hours (MSCRG) and not attributable to fever, infection or withdrawal of corticosteroid therapy;
2. The definition of progression was taken from the original articles. Most investigators used the expanded disability status scale (EDSS) and defined progression as a sustained at least (3 (IFBN, PRISMS) or 6 (MSCRG) months) increase in EDSS of at least one point (≥0.5 point if the baseline EDSS score is 6.0 to 6.5) recorded in a period when the patient had no exacerbation.
3. The higher dose of interferon beta was selected for analysis as it was the most frequently used in clinical practice.

*: Two year study results (FDA label; FDA review; PRISMS Group, Lancet 1998, Jacobs et al., 2000)

**: 46 months result (IFNB Group, Neurology 1995)

Table 3.7 Odds ratios and 95% confidence intervals for exacerbation free status in MS patients following placebo treatment for 2 years in the double blind RCT trials indicated for RRMS

Product (Study)	No. of exacerbation-free	No. of at least one exacerbation	Total No.	OR (95% CI)
Placebo (IFNB)	20	101	123	1.01 (0.53-1.95)
Placebo (MSCRG)	23	120	143	

Product (Study)	No. of exacerbation-free	No. of at least one exacerbation	Total No.	OR (95% CI)
Placebo (MSCRG)	23	120	143	1.00 (0.55-1.81)
Placebo (PRISMS)	30	157	187	

Product (Study)	No. of exacerbation-free	No. of at least one exacerbation	Total No.	OR (95% CI)
Placebo (PRISMS)	30	157	187	0.98 (0.53-1.83)
Placebo (IFNB)	20	101	123	

Table 3.8 Odds ratios and 95% confidence intervals for exacerbation free status in MS patients following interferon treatment for 2 years in the double blind RCT trials indicated for RRMS

Product (Study)	No. of exacerbation-free	No. of at least one exacerbation	Total No.	OR (95% CI)
Betaseron (IFNB)	31	93	124	1.31 (0.75-2.30)
Avonex (MSCRG)	32	126	158	

Product (Study)	No. of exacerbation-free	No. of at least one exacerbation	Total No.	OR (95% CI)
Avonex (MSCRG)	32	126	158	0.54 (0.33-0.88)
Rebif (PRISMS)	59	125	184	

Product (Study)	No. of exacerbation-free	No. of at least one exacerbation	Total No.	OR (95% CI)
Rebif (PRISMS)	59	125	184	1.42 (0.85-2.36)
Betaseron (IFNB)	31	93	124	

3.2.3.2.4 Outcome measures of double blind RCT trials indicated for SPMS

Betaseron was the first interferon beta product to be approved by the FDA in 1993. The sponsoring company (Chiron) conducted two clinical trials to seek approval to expand the indication to include SPMS (The European Study Group and The North American Study Group). The primary outcome measure of these two clinical trials is the time to confirm EDSS progression as measured by a 1.0 point increase on the EDSS (Table 3.9).

The time to confirmed EDSS progression between the interferon group (901 days) and the placebo group (549 days) was shown to be significantly different in the European Study ($p=0.0007$), in favor of the interferon group (FDA review: Medical Officer Clinical Review of Betaseron. sBLA 98-0737). But the time to confirmed EDSS progression between two groups has no difference in the North American Study ($p=0.61$) (Panitch et al., 2004).

However, as Table 3.9 shows, for the other outcome measures, such as annual relapse rate, absolute change in T2-weighted MRI lesion area and number of exacerbation free patients, the results are in favour of interferon beta group.

Based on the different primary outcome measure of these two trials, that is, the time to confirmed EDSS progression, the evidence was not adequate to expand the indication to SPMS.

Table 3.9 Outcome measures of double blind RCT trials indicated for SPMS

Trial (Type)	Time to confirmed EDSS progression *	Annual relapse rate	Absolute change in T2-weighted MRI lesion area	Interferon Group (No.)		Placebo Group (No.)		OR (95% CI)	Interferon Group (No.)		Placebo Group (No.)		OR (95%CI)	Reference
				Exacerbation free	Total	Exacerbation free	Total		Confirmed disease progression	Total	Confirmed disease progression	Total		
European Study Group (SP-MS)	Interferon: 901 days; Placebo: 549 days; (p=0.0007)	Interferon: 0.44; Placebo:0.64 (p=0.002),	Interferon: -5%; Placebo; 8%; (p<0.0001)	166	360	134**	358	1.43 (1.06-1.93)	140	360	178	358	0.64 (0.48-0.87)	FDA clinical review; European study group Lancet 1998
The North American Study Group (SP-MS)	No difference in the pooled interferon vs placebo recipients (logrank test: p=0.71) or for the individual comparisons of 250mcg vs placebo (p=0.61)	Interferon: 0.16; Placebo: 0.28	Interferon: 0.4% Placebo: 10.9%; (p<0.0001)	225	317	191**	308	1.50 (1.07-2.09)	124	317	106	308	1.22(0.88-1.70)	FDA clinical review: FDA label; Panitch et al., 2004

1. The definition of relapse or exacerbation was taken from the original articles. Appearance of new, or reappearance of, neurological abnormality present at least for 24 hours (The European Study Group) or 48 hours (The North American Study Group) and not attributable to fever, infection or withdrawal of corticosteroid therapy;
2. The definition of progression was taken from the original articles. Most investigators used the expanded disability status scale (EDSS) and defined progression as a sustained at least (3 (The European Study Group)or 6 (The North American Study Group) months') increase in EDSS of at least one point (≥0.5 point if the baseline EDSS score is 6.0 to 6.5) recorded in a period when the patient had no exacerbation.
3. The higher dose of interferon beta was chosen for analysis as it was the most frequently used in clinical practice.

*: Time to confirmed progression in disability: as measured by a 1.0 point increase on the EDSS, sustained for at least 3 months (European Study Group), 6 months (The North American Study Group) or a 0.5 point increase if the baseline EDSS was 6.0 or 6.5.

**: 3 year study result (European Study Group, Lancet 1998; Panitch et al., 2004)

3.2.3.2.5 Outcome measures of evaluator blind, open label, randomized active comparative study indicated for RRMS

In order to prove Rebif was clinically superior to Avonex, the sponsoring company conducted a direct comparative clinical trial with Avonex. The primary outcome measure was the number of exacerbation free patients at 24 weeks. For the measurement of exacerbation free, a higher odds ratio indicates a favorable outcome. However, for the measurement of disease progression, a lower odds ratio indicates a favorable outcome.

Table 3.10 and Table 3.11 show that the odds ratio (Rebif vs. Avonex) of a patient remaining exacerbation free is 1.7 at 24 weeks and 1.5 at 48 weeks which is in favour of Rebif; the odds ratio of disease progression is 0.9 at 3 month and 0.7 at 6 month which is also in favour of Rebif.

Based on the further analysis of the results from these trials, Rebif is deemed to be more effective than Avonex.

Table 3.10 Outcome measures of comparative study indicated for RRMS

Product	Type	Rebif Group (No.)		Avonex Group (No.)		Rebif Group (No.)		Avonex Group (No.)		Reference
		Exacerbation free	Total	Exacerbation free	Total	Confirmed disease progression	Total	Confirmed disease progression	Total	
Rebif	RR-MS	24 weeks: 254 48 weeks: 209	339	24 weeks: 214 48 weeks: 177	338	3 months: 43 6 months: 20	339	3 months: 49 6 months: 28	338	FDA Review

1. The definition of relapse or exacerbation was taken from the original articles. Appearance of new, or reappearance of, neurological abnormality present at least for 24 hours and not attributable to fever, infection or withdrawal of corticosteroid therapy;
2. Progression of disability, defined as a 1.0 point increase in the EDSS (FDA review, Medical Officer's clinical review)

Table 3.11 Odds ratios and 95% confidence intervals for exacerbation free and progression free in the comparative trial indicated for RRMS

Time	Rebif Group (No.)		Avonex Group (No.)		OR (95% CI)
	Exacerbation free	At least one exacerbation	Exacerbation free	At least one exacerbation	
24 weeks	254	85	214	124	1.73 (1.24-2.41)
48 weeks	209	130	177	161	1.46 (1.08-1.99)

Time	Rebif Group (No.)		Avonex Group (No.)		OR (95% CI)
	Confirmed progression	Non progression	Confirmed progression	Non progression	
3 months	43	296	49	289	0.86 (0.55-1.33)
6 months	20	319	28	310	0.69 (0.38-1.26)

3.2.4 Post-marketing sales of interferon beta products

Recombinant interferon beta is one of the most cited examples of the so-called "orphan blockbusters" (sales revenues more than $1 billion). Table 3.12, Fig 3.5 and Fig 3.6 show that although there are three recombinant interferon beta products available on the market at the same time, the sales revenues for all of the three products increased significantly and steadily once they obtained market approval. Sales revenues of Avonex which was approved in 1996 have exceeded $1 billion since 2001 (5 years after market approval) despite the fact that the other interferon beta products were already available on the market. Betaseron and Rebif's sales revenues were more than $800 million in 2003. Fig 3.6 shows how the proportion of interferon beta product sales revenues compared to the sponsor company's total revenues varies for the three companies studied. The percentage of interferon beta sales revenues versus company's total sales revenues for Avonex has been about 90% over the three years from 1999 to 2001 inclusive. This shows that Avonex is the most important drug produced by Biogen. The percentage interferon beta sales versus total sales for Serono of Rebif has increased from 5% in 1998 (only approved in the EU) to 41% in 2003. However, Betaseron accounts for about 15% of total revenue for the manufacturing company. This suggests that Schering has steady product pipeline as the company's total revenues have increased steadily in line with the increase in Betaseron sales.

Table 3.12 Interferon beta products' sales data from 1997 to 2003

Year	Betaseron (Betaferon) sales(€m)	Betaseron (Betaferon) sales($m)	Schering total revenues (€m)	Schering total revenues ($m)	Betaseron/ company revenues (%)	Avonex sales ($m)	Biogen total revenues ($m)	Avonex /company revenues (%)	Rebif sales ($m)	Serono total revenues ($m)	Rebif / company revenues (%)
1997		297*	3193			239	412	58	19*	883	2
1998		321*	3285			395	558	71	44*	950	5
1999	453	430	3674	3490	12	621	794	78	143	1133	13
2000	593	646	4493	4897	13	761	926	82	254	1240	20
2001	681	606	4842	4309	14	972	1042	93	380	1376	28
2002	783	744	5023	4772	16	1034	1148	90	549	1547	35
2003	770	878	4828	5504	16	1168	1344**	87	819	2019	41

Note: 1. Biogen total revenues = product revenues + royalty revenues; Serono total revenues = product revenues + royalty revenues (2001 annual report p62)

2. All the figures are from company annual report (Chiron, Serono, Schering AG, Biogen) except that:

*: Figures are from the website of www.i-s-b.org (Accessed: 15 March 2004)

**: Product revenue1228+royalty116

3. Annual average rate (basis 1€)

1€ = 1.14 US dollar in year 2003

1€ = 0.95 US dollar in year 2002

1€ = 0.89 US dollar in year 2001

1€ = 1.09 US dollar in year 2000

1€ = 0.95 US dollar in year 1999

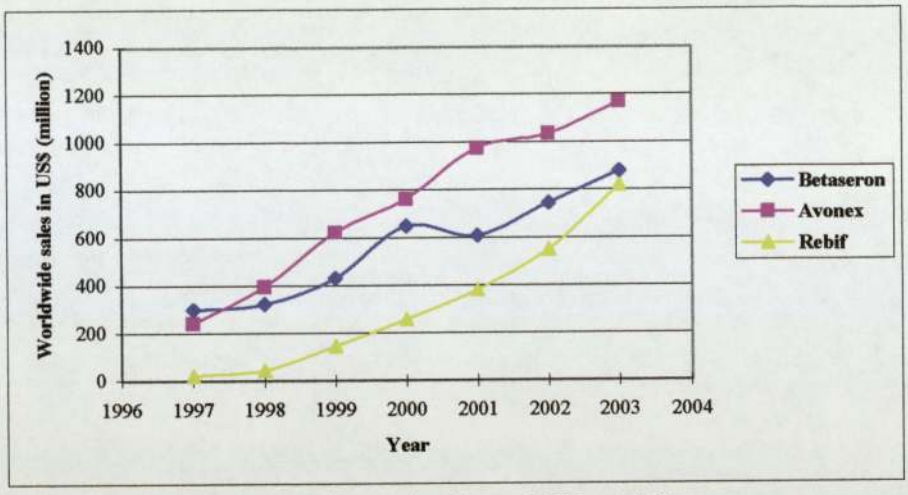


Fig 3.5 Interferon beta products sales from 1997 to 2003

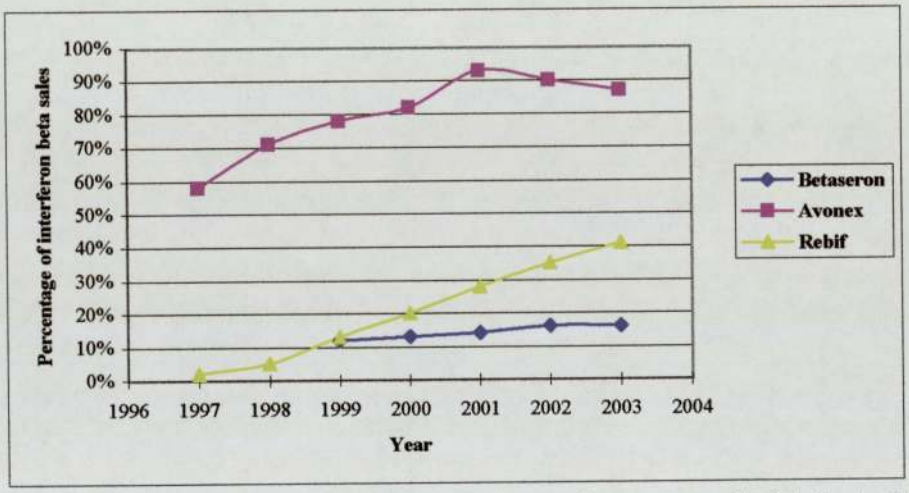


Fig 3.6 Percentage of interferon beta products sales compared with the total sponsor companies' sales from 1997 to 2000

3.2.5 Discussion

Two systematic reviews (Filippini et al., 2003; Rice et al., 2004) were identified which described interferon usage in relapsing remitting multiple sclerosis. However, both of the systematic reviews compared the effectiveness and side effects of interferons with those of placebo. There was no assessment between interferon beta products. In this chapter, determination of odds ratios was undertaken to allow analysis of the relative effectiveness of the three different interferon beta products. Furthermore, this analysis was undertaken with a view to developing a methodological and strategic approach to develop tools appropriate for evaluating orphan drugs.

The search strategy of this analysis was based on searching pre-marketing clinical trials of interferon beta products submitted to the FDA from FDA website, other systematic reviews and by endnote software. This analysis was based on six pre-marketing clinical trials submitted to the FDA. These six trials were sub-divided according to different study design and clinical severity.

The Orphan Drug Act states that showing "clinical superiority" needn't provide the overall risk-benefit superiority over the other drug. This is demonstrated by the three large-scale double blind RCT trials indicated for RRMS. In this chapter outcome measures for the number of exacerbation free patients were studied because the data of disease progression were not comparable. The likelihood of a patient remaining exacerbation free was found to be Rebif > Betaseron > Avonex. Therefore, although Avonex obtained market approval based on superior safety to Betaseron, it seems that from the effectiveness point of view, Betaseron is more effective than Avonex in prevention of exacerbation.

The Orphan Drug Act states that showing "greater effectiveness" will in most cases need a direct comparative clinical trial. Since Orphan Drug Act was enacted in the US,

Rebif was the first product licensed by the FDA by showing clinical superiority through a direct comparative clinical trial. The outcome of the clinical trial (Rebif vs. Avonex) is based on a 24-week and 48-week result. The result of both exacerbation free patients and non-progression patients was in favour of Rebif which consistent with the results of RCT trials.

The indication for interferon beta products approved by the FDA is only for relapsing forms of MS. However, interferon beta-1b (Betaseron) is now also licensed in the European Union for SPMS based on the results of European study. Two clinical trials have been submitted to the FDA for SPMS, however, the FDA informed the sponsoring company that the evidence for approval was not enough because the result of primary outcome measure (time to confirmed EDSS progression) was contradictory. The time to confirmed EDSS progression between the interferon group (901 days) and the placebo group (549 days) was shown to be significantly different in the European Study ($p=0.0007$) but the time to confirmed EDSS progression between two groups has no difference in the North American Study ($p=0.61$). However, for the other outcome measures of the treatment of SPMS, like annual relapse rate, change in MRI area and number of exacerbation free patients, Betaseron does have significant beneficial effect. (FDA review: Medical Officer Clinical Review of Betaseron. sBLA 98-0737; Panitch et al., 2004).

The question raised in this assessment is how to choose the most appropriate endpoint to be evaluated. For the two clinical trials indicated for SPMS (The European Study Group and The North American Study Group), the time to confirmed progression was chosen as the clinical endpoint in the study design. But for the other four clinical trials indicated for RRMS, the assessed parameters were exacerbation free patients and disease progression free patients. Using the number of exacerbation free patients as the primary outcome measure, Rebif was shown as an effective treatment in SPMS patients. However, more data are needed to evaluate the overall benefit of other interferon beta products treating SPMS.

This analysis is based on the total number of patients enrolled in each clinical trial. The results have some bias because of the high dropout rates in both arms (Filippini et al., 2003), the variable reasons for dropout and the variability in endpoints chosen.

Biogen and Serono are biopharmaceutical companies whereas Schering is a major pharmaceutical company. Serono ranked 3rd and Biogen ranked 4th of the top 10 biopharmaceutical companies in 2003 (Top companies, 2003). Biogen is mainly financially dependent on Avonex as a profitable interferon beta "orphan drug" and Rebif is also an important drug for Serono as well. Avonex's US patent was expired in year 2003, which can represent a very attractive market for biogeneric players. It can be anticipated that if Serono and Biogen continue mainly relying on the sales of interferon beta products, they will face severe threat if interferon beta products lose their profitability.

The result of the post-marketing performance of interferon beta products illustrates that orphan drug status does support the development of novel drugs. Even for the treatment of rare disease, the market can be huge. The probable reasons are that some rare diseases need chronic treatment or the patient population expand rapidly either through increased diagnosis or incidence. The other leading cause of profitable orphan drug is the market exclusivity (Garcia 2004), which bars any other actual or potential competition for the designation orphan drug, enabling the sponsor control the monopoly prices for the drug.

The interferon beta product is only one specific case. A large proportion of sponsors developing orphan products can be classified as small and medium size companies (EMEA: Report on the first 3-year mandate of the orphan medicinal products). Also, some of biopharmaceuticals intended for the treatment of rare diseases have been withdrawn from market because of commercial reasons. For instance, Lymerix (recombinant OSP-A) was licensed by SmithKline Beecham Biologicals in 1998 for

the active immunization against Lyme disease. However, its manufacturer withdrew the vaccine from the market in 2002 because of lack of demand (Chapter 2). The other case example is Triacelluvax which is a combination vaccine licensed by Chiron SpA in 1999 for the treatment of immunization against diphtheria, tetanus and pertussis, all of which are deemd to be rare diseases according to ORPHANET's rare diseases' list (available from: www.orpha.net). It was withdrawn from the market in 2001 for commercial reasons as well.

Some of the other successful marketing stories of orphan biopharmaceuticals are: Neulasta whose worldwide sales in 2003 was $1300 million is indicated for the treatment of neutropenia (Amgen 2003 annual report); Eprix's world wide sales in 2003 was $3894 million, which is indicated for the treatment of anemia (Ortho Biologics 2003 annual report) and Rituxan, whose 2003 annual report was $2243 million is indicated for the treatment of nonHodgkin's B-cell lymphoma (IDEC Pharmaceuticals 2003 annual report) etc. Some (Garcia 2004) have argued that the Orphan Drug Regulations should be reformed to prevent sponsoring companies taking advantage of the monopoly position to earn such enormous benefits a year by charging patients. Japan has made some efforts to this end, that is: companies making profits on sales of orphan drugs must return a proportion of the subsidy granted as a contribution to the financial funding (eg. Funding, tax reduction, reimbursement of development cost) (Orphan Drugs in Japan, available from: www.orpha.net).

3.3 Conclusion

It is said there are thousands of rare diseases world wide (EMEA: Report on the first 3- year mandate of the Committee for Orphan Medicinal Products), however, few drugs for rare diseases were launched before the orphan drug regulations were enacted because it was thought unlikely that companies which invested in this area would likely to make sufficient financial returns on their investment. Therefore government incentives are necessary to encourage the development of such drugs. Since the first

Orphan Drug Act was enacted in the US in 1983, Japan, Australia, Singapore and EU have subsequently launched Orphan Drug Regulations.

The aim of this chapter has been to take interferon beta products as a case example to illustrate how the Orphan Drug Act balances the licensing process of orphan products in the US and how the orphan products have performed on the market.

Although there are already two published systematic reviews which evaluate interferons in RRMS (Filippini et al., 2003; Rice et al., 2004), they only conduct comparison between interferons and placebo. Hence, comparison the effectiveness between the three interferon beta products was performed in this chapter. The systematic assessment was based on the pre-marketing clinical trials submitted to the FDA. Odds ratios and 95% CI were chosen as an appropriate tool for the evaluation of effectiveness, and are commonly used in meta-analysis (Siadaty et al., 2004; Wiedermann, 2005). In order to eliminate bias between different clinical studies, odds ratios and 95% CIs were first calculated among placebo groups. The odds ratios among the three placebo groups are almost equal to 1, which indicates that the patient populations in the three clinical trials were comparable and that the application of criteria for evaluating disease were being used consistently. Such a demonstration is essential before any further comparison of the active study arms can be undertaken.

The Orphan Drug Act states that demonstration of only one aspect (either safety or efficacy) of superiority is enough for proof that the second product is not the same as the first one and hence gains marketing approval. This point is well-illustrated by the analysis made in this chapter. The probability of a patient remaining exacerbation free on treatment with different interferon drugs is Rebif > Betaseron > Avonex. Although Avonex was previously demonstrated to have "clinical superiority" over Betaseron in reducing injection site side effects, from the effectiveness point of view, this study has shown that Betaseron is more effective than Avonex in keeping patients exacerbation

free. The limitation of this analysis is that the conclusion is only based on the randomized clinical trials and it maybe that some negative data has not be covered.

It is important to consider how the orphan products performed on the market. Although there are three interferon beta products available on the market at the same time, Avonex has still become an "Orphan Blockbuster" (sales more than 1 US$ billion) since 2002. What's more, the sales revenues for the other two interferon beta products' (Betaseron and Rebif) sales revenues are approaching to "Orphan Blockbuster" status, which is US $ 878 million and US $ 819 in 2003 respectively.

Several points worthy of answering have been raised during the analysis of the licensing and marketing performance of interferon beta products.

Firstly, from the marketing performance point of view, there are two types of condition can be defined as rare disease by the 1983 Orphan Drug Act of the US. The first is a disease or condition affects less than 200,000 persons in the US. The second is if the disease or condition affects more than 200,000 persons in the US, but the cost of development could not be recovered from the sales. Hence, the Orphan Drug Act provides lots of incentives to manufacturers of orphan drugs such as federal funding, tax reduction and 7-year marketing exclusivity. Of course, the majority of orphan products were developed to treat diseases which affect less than 200,000 persons and for which the cost of development couldn't be recovered from the sales. But, an orphan drug doesn't necessarily equal an un-profitable drug. Several products have become "orphan blockbusters", which means the sales revenues are in excess of 1 billion US dollors, such as Avonex (2003 sales $1168 million), Neulasta (2003 sales $1300 million); Eprix (2003 sales $3894 million) and Rituxan (2003 sales $2243 million) and so on. One of the leading reasons for the profitability of orphan drugs is the 7-year marketing exclusivity which bars a second drug being approved. Should the Orphan Drug Act set some limitations to prevent sponsoring companies taking advantage of the incentives once the drug becomes profitable? Japan has stated in its

Orphan Drug Regulation that companies making profits on sales of orphan drugs must return a proportion of the subsidy granted as a contribution to the financial funding.

Secondly, this analysis attempts to develop a tool for the evaluation of orphan products since other systematic reviews only compare one orphan drug towards the placebo. Odds ratios of disease activity/event and 95% CI are an effective tool for the evaluation. In order to compare the effectiveness between active treatment groups, odds ratio was first compared between placebo groups. An odds ratio equal to 1 means the event is equally in both groups. Hence, if the odds ratio for placebo group is equal to 1, it means that the clinical trials are homogenous and may be compared. Nevertheless, the question faced in the pre-marketing clinical trial analysis of interferon beta products is the requirement for defining the endpoint: choosing one endpoint may support the new drug, but choosing another endpoint for evaluation may give completely different results. The outcome measure of double blind RCT trials (The European Study Group and the North American Study Group) indicated for SPMS is this case. This raises the question of whether industry or the regulatory authorities should define the standard criteria for the evaluation of treatments for rare diseases because it will influence the clinical assessment and the new drug licensing evaluation criteria.

Thirdly, the Orphan Drug Act requires the demonstration of effectiveness; superiority over the other drug will normally need a direct comparative clinical trial between the two drugs which is really challenging and economically costly. Rebif was the first product to obtain marketing approval by a direct comparative clinical trial versus Avonex. However, the sales data of the other two interferon beta products' (Betaseron and Avonex) in 1999 when Serono decided to start the comparative clinical trial may shed some light on why Serono took such a big risk; the sales revenue for Betaseron was US $ 430 million in 1999 and was US $ 621 million for Avonex. In addition, the sales for Avonex almost doubled comparing 1998 with 1999, from US $ 395 million

to US $ 621 respectively. Without the marketing share temptation, it is unlikely that a sponsoring company would take the risk.

Chapter 4: General conclusion and future work

This thesis aims to provide a summary overview of the biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004 and try to highlight the trends in the development of biopharmaceutical industry in these 10 years (Chapter two). Licensing process, pre-marketing clinical trials submitted to the FDA and post-marketing sales of interferon beta products have been searched in order to illustrate how the Orphan Drug Act balances the licensing process of orphan drug in the U.S. and how the orphan products have performed on the market (Chapter three). The aims of this thesis have been generally met.

All the 147 biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004 were found to be protein-based. However, the first gene therapy product named Gendicine has been approved by the China State Food and Drug Administration (SFDA) in 2003 for the treatment of nasopharynageal cancer. With greater understanding of many diseases, many more drug targets will be discovered. According to PhRMA's report, 324 biotechnology medicines are undergoing trials or being reviewed by the FDA against various diseases. The 324 products include 90 vaccines, 76 monoclonal antibodies, 23 gene therapies, 14 antisense (Anon, 2004).

The risks exist in biopharmaceutical industry is still high although the reward is huge. On the one hand, the withdrawal rate of biopharmaceuticals approved by the FDA and EMEA between 1995 and 2004 after marketing authorisation is 12% according to the analysis in this thesis. On the other hand, with more and more drug patents expiring in the next few years, biogenerics will probably become a potential threat to some brand-name biopharmaceutical companies. These companies could either develop health product R&D pipelines or set up tough criteria for their brand-name biopharmaceuticals to avoid this kind of competition. For instance, although Biogen was ranked fourth most profitable of the biopharmaceutical companies in 2003, it was mainly relying on the sales of one interferon beta product (Avonex), which accounts for about 90% of the companies' total revenues over

the past years. However, there is a real question mark over Biogen's revenue stream if some biogeneric versions of Avonex are approved by the regulatory authorities as Avonex's patent expired in 2003.

Ten biopharmaceutical products were identified as "blockbuster drugs", which means the sales revenues exceed US $ 1 billion per year. Four biopharmaceuticals (Avonex, Enbrel, Remicade and Rituxan) among these ten products are orphan drugs, which accounts for 40% of sales of all the blockbuster drugs. It implies that for some rare diseases, the market share for new drugs can be large.

Hence, the licensing process, pre-marketing clinical trials and post-marketing evaluation of interferon beta products have been performed. Several questions have been raised during the analysis.

The intention of orphan drug regulations is to provide some incentives to the biopharmaceutical industry to develop medicines to treat rare diseases because the cost of development usually cannot be recovered from sales revenues. Nevertheless, the post-marketing evaluation of interferon beta products illustrates that the current definition of orphan drug does not result in a non-profitable drug.

The other question faced in the evaluation of pre-marketing clinical trials is that using one endpoint, the apparent benefit from a drug is negative while using another endpoint, the result is positive. Should the industry or the regulatory authorities define the standard criteria for the evaluation of treatments for rare diseases because it will influence the clinical assessment and the new drug evaluation criteria?

The aim of pharmaceutical industry is to provide more and more safe and effective pharmaceutical products. By doing so the industry hopes to improve public health and ensure its prosperous future. To speed up the licensing process and ensure uniformity of

product licensing process, biopharmaceutical regulations have changed significantly in recent years. For example, timeline approval goals and centralized procedure were established by the EMEA in 1995. The US Congress has passed several regulation to speed up the clinical trial and approval procedures as well, like the Prescription Drug User Fee Act (PDUFA) in 1992, the Food and Drug Administration Modernization Act (FDAMA) in 1997, the Medical Device User Fee and Modernization Act (MDUFMA) in 2002 and the transfer of certain products from CBER to CDER to accelerate.

Some experts suggest that the industry should work with organizations such as the ICH to build up "global drug approval procedures" (Garcia, 2004). Since different countries have different clinical trial requirements, harmonisation will save R&D costs.

During the past 20 years, the biopharmaceutical industry has met the highest public health expectations through offering novel approaches to management of life-threatening diseases. However, the biopharmaceutical industry is still small or medium sized compared with the conventional medicinal industry and faces many challenges as the industry is globalised.

Future work to be considered includes::

- Biopharmaceuticals searched in this thesis include: gene therapy products, monoclonal antibodies, antisense oligonucleotides, recombinant vaccines and other proteins intended for therapeutic use. However, the industry still does not provide a clear definition for biopharmaceutical; the definition of biopharmaceutical needs to be clarified in the future.

- The database set up in this project describing biopharmaceuticals approved by the FDA and EMEA was updated to the Feb. of 2005. Further trends need to be followed up.

- Given the rapid licensing of orphan drugs, there is not the opportunity to undertake rigorous evaluation of clinical effectiveness. To develop a possible approach to undertake direct comparison between RCTs which evaluate different drugs against placebo, odds ratio and 95% CIs were chosen as evaluation tools. The suitability of this evaluation tool needs to be further proven through direct comparison in clinical trials.

Abbreviations

BLA:	Biologics License Application
CBER:	Center for Biologics Evaluation and Research
CDER:	Center for Drug Evaluation and Research
CNS:	Central Nervous System
CPMP:	Committee for Proprietary Medicinal Product
EC:	European Commission
EDSS:	Kurtzke Expanded Disability Status Scale
EMEA:	European Medicines Agency
EU:	European Union
FDA:	Food and Drug Administration
GMP:	Good Manufacturing Practice
MRI:	Magnetic Resonance Imaging
MS:	Multiple Sclerosis
NMEs:	New Molecular Entities
OPSR:	The Organization for Pharmaceutical Safety and Research
OR:	Odds Ratio
PPMS:	Primary progressive multiple sclerosis
RRMS:	Relapsing remitting multiple sclerosis
SFDA:	China State Food and Drug Administration
SPMS:	Secondary progressive multiple sclerosis
TGA:	Therapeutic Goods Administration

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Appendix 1: Definition of List A and List B products in the EMEA

(Council Regulation (EEC) No 2309/93; Regulation(EC) No726/2004)

List A

1. Medicinal products developed by means of the following biotechnological processes:

- Recombinant DNA technology,
- Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells, and
- Hybridoma and monoclonal antibody methods

2.Veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.

3. Medicinal products for human use containing a new active substance which, on the date of entry into force of this regulation, was not authorised in the Community, for which the therapeutic indication is the treatment of any of the following diseases:

- Acquired immune deficiency syndrome,
- Cancer,
- Neurodegenerative disorder,
- Diabetes

And with effect from 20 May 2008

- Auto-immune diseases and other immune dysfunctions,
- Viral diseases

After 20 May 2008, the Commission, having consulted the Agency, may present any appropriate proposal modifying this point and the Council shall take a decision on that proposal by qualified majority.

4. Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

List B Medicinal products developed by other biotechnological processes which, in the opinion of the agency, constitute a significant innovation.

1. Medicinal products administered by means of new delivery systems which, in the opinion of the Agency, constitute a significant innovation.
2. Medicinal products presented for an entirely new indication which, in the opinion of the Agency, is of significant therapeutic interest.
3. Medicinal products based on radio-isotopes which, in the opinion of theAgency, are of significant therapeutic interest.
4. New medicinal products derived from human blood or human plasma.
5. Medicinal products the manufacture of which employs processes which, in the opinion of the agency, demonstrate a significant technical advance such as two-dimensional electrophoresis under micro-gravity.
6. Medicinal products intended for administration to human beings, containing a new active substance which, on the date of entry into force of this regulation, was not authorized by any Member State for use in a medicinal product intended for human use.
7. Veterinary medicinal products containing a new active substance which, on the date of entry into force of this Regulation, was not authorised by any Member State for use in animals.

Appendix 2: Biopharmaceuticals approved by the FDA and EMEA from 1995 to 2004 (In alphabetical order)

Trade Name	Generic Name	EU Sponsor	EU Approval	US Sponsor	US Approval	Indication	Note
Actrapid/ Velosulin/ Monotard/Insulatard/ Protaphane/ mixtard/ actraphane/ ultratard	Insulin human rDNA	Novo Nordisk	07/10/2002	Novo Nordisk	Velosulin 19/07/1999	EMEA: Treatment of diabetes mellitus	FDA news:Discontinued from the market by November 2003
Advate	Antihemophilic Factor (Recombinant)		04/03/2004	Baxter Healthcare Corp	25/07/2003	FDA: Prevention and control of bleeding episodes of hemophilia A (classical hemophilia).Perioperative management of patients with hemophiia A.	
Aldurazyme	Laronidase	Genzyme B.V.	10/06/2003	Biomarin Pharmaceutical Inc	30/04/2003	FDA: Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and Scheie form with moderate to severe symptoms. EMEA: Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPS I; a-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease	

Alfatronol	Interferon alfa-2b	Schering Plough	09/03/2000	Schering	04/10/1983	FDA: Hairy Cell Leukemia; Malignant Melanoma; Condylomata Acuminata; AIDS-Related Kaposi's Sarcoma; Chronic Hepatitis C; Chronic Hepatitis B; EMEA: Chronic Hepatitis B; Chronic Hepatitis C; Hairy Cell Leukaemia; Chronic Myelogenous Leukaemia; Multiple Myeloma; Follicular Lymphoma; Carcinoid Tumour; Malignant Melanoma	A new trade name for IntronA. SP Europe committed to withdraw the nationally authorised IntronA, and to transfer this trade name to the centrally authorised product.
Amevive	Alefacept			Biogen, Inc	30/01/2003	Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.	
Amphadase	Hyaluronidase			Amphastar Pharm	26/10/2004	An adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents	
Apidra	Insulin Glulisine, rDNA	27/09/2004	Aventis Pharma Deutschland GmbH	Aventis Pharms	16/04/2004	Treatment of adult patients with diabetes mellitus for the control of hyperglycemia.	
Aranesp	Darbepoetin alfa	Amgen Europe B.V.	08/06/2001	Amgen, Inc	17/09/2001	FDA: Treatment of anemia associated with chronic renal failure. For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the	Nespo [TR Europe]

						effect of concomitantly administered chemotherapy. EMEA: Treatment of anaemia associated with chonic renal failure in adults and paediatric subjects ≥ 11 years of age.	
Avastin	Bevacizumab	12/01/2005	Roche Registration Limited	Genentech Inc	26/02/2004	First-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy.	
Avonex	Interferon beta-1a	Biogen France S.A.	13/03/1997	Biogen, Inc	17/05/1996	FDA: Treatment of relapsing forms of multiple sclerosis. EMEA: Treatment of ambulatory patients with relapsing multiple sclerosis. Treatment of patients who have experienced a single demyelinating event.	
Benefix	Nonacog alfa (coagulation fator IX)	Genetics Institute of Europe B.V.	27/08/1997	Genetics Institute,Inc.	11/02/1997	FDA: Control and prevention of hemorrhagic episodes in patients with hemophilia B(congenital factor IX deficiency or Christmas disease) EMEA: Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)	

Beromun	Tasonermin	Boehringer Ingellheim International GmbH	13/04/1999			EMEA: As an adjunct to surgery for subsequent removal of the tumour so as to prevent or delay amputation, or in the palliative situation, for irresectable soft tissue sarcoma of the limbs, used in combination with melphalan via mild hyperthermic isolated limb perfusion (ILP).	
Betaferon	Interferon beta-1b	Schering AG	30/11/1995	Chiron Corp	23/07/1993	FDA: Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. EMEA: Treatment of patients with relapsing remitting multiple sclerosis. For patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	Betaseron [TR US]
Bexxar	Tositumomab and Iodine I 131 Tositumomab			Corixa Corp	27/06/2003	Treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.	
Bio-Tropin	Somatropin, rDNA			Savient Pharmaceuticals, Inc	25/05/1995	Treatment of pituitary growth hormone deficiency in children.	Growject [TR in Japan],Zomacton [TR in Europe]; In 2002, Labeling provides for a name change from Bio-Tropin to Tev-Tropin.

Calypte HIV-1 Urine EIA	HIV-Type 1 (Recombinant)			Calypte Biomedical Corp	06/08/1996	In vitro diagnostic test kit used in the detection of antibodies to HIV-1 present in urine	
Campath	Alemtuzumab	ILEX Phramaceuticals L.P.	06/07/2001	ILEX Phramaceuticals L.P.	07/05/2001	Treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.	MabCampath [TR in EU]
CEA Scan	Arcitumomab	Immunomedics B. V.	04/10/1996	Immunomedics, Inc	28/06/1996	EMEA: For patients with histologically-demonstrated carcinoma of the colon or rectum for imaging of recurrence and/or metastases, as an adjunct to standard non-invasive imaging techniques, such as ultrasonography or CT scan	
Ceprotin	Protein C	Baxter AG	16/07/2001			EMEA: Purpura fulminans and coumarin induced skin necrosis in patients with severe congenital protein C deficiency. For short term prophylaxis in patients with severe congenital protein C deficiency	
Cerezyme	Imiglucerase	Genzyme B.V.	17/11/1997	Genzyme Corp	23/05/1994	FDA: Long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of Type I Gaucher disease EMEA:Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Type I Gaucher Disease and who exhibit clinically significant manifestations of the	

						disease.	
CroFab	Crotalidae Polyvalent Immune Fab (Ovine)			Protherics Inc	02/10/2000	FDA: Management of patients with minimal or moderate North American rattlesnake envenomation.	CroTAb [TR former/original]
Dynepo	Epoetin delta	Aventis	18/03/2002			EMEA: Treatment of anaemia in patients with chronic renal failure.	
Ecokinase	Reteplase	Galenus Mannheim	29/08/1996	Centocor, Inc	30/10/1996	In the management of acute myocardial infarction (AMI) in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI	Retavase [TR in US],withdrawn from the market in EU on 1999
Elitek	Rasburicase	Sanofi-Synthelabo	23/02/2001	Sanofi-Synthelabo, Inc	12/07/2002	FDA: Initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies EMEA: Treatment and prophylaxis of acute hyperuricaemia, in order to prevent acute renal failure	Fasturtec [TR in EU]
Enbrel	Etanercept	Wyeth Europe Ltd	03/02/2000	Immunex Corp	02/11/1998	FDA: Active rheumatoid arthritis; active polyarticular-course juvenile rheumatoid arthritis;active arthritis in patients with psoriatic arthritis;active ankylosing spondylitis;chronic moderate to severe plaque psoriasis EMEA: Treatment of active rheumatoid	

						arthritis in adults; Treatment of active polyarticular-course juvenile chronic arthritis in children aged 4 to 17 years who have an inadequate response to, or who have proved intolerant of methotrexate.	
Eprex	Epoetin alfa			Ortho Biologics LLC	25/02/1999	Treatment of anemia in patients undergoing chemotherapy, elective orthopedic surgery and autologous blood donation	Procrit [Other tradename]
Erbitux	Cetuximab	29/06/2004	Merck kGaA	ImClone Systems, Inc.	12/02/2004	Treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemothrapy in combination with irinotecan. Treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy as a single agent.	
Fabrazyme	Agalsidase beta	Genzyme B.V.	03/08/2001	Genzyme Corp	24/04/2003	FDA: Fabrazyme is indicated for use in patients with Fabry disease. EMEA: For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).	
Forcaltonin	Recomb salmon calcitonin	Unigene UK Limited	11/01/1999			EMEA: Treatment of Paget's disease and hypercalcaemia in malignancy.	CPMP adopted an opinion recommending the suspension of the marketing authorisation

Foresteo	Teriparatide, rDNA	Eli Lilly and Company Ltd	10/06/2003	Lilly, Eli & Co.	26/11/2002	FDA: Postmenopausal women with osteoporosis who are at high risk for fracture. Forteo is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. EMEA: Treatment of established osteoporosis in postmenopausal women.	Forteo [TR in US]
Genetic Systems HIV-1/HIV-2 Plus O EIA	Human Immunodeficiency Virus Types 1 and 2 (HIV-1 and HIV-2/Enzyme Immunoassay (EIA)/Recombinant and Synthetic)			Genetic Systems Corp	05/08/2003	FDA: For detection of antibodies to human immunodeficiency types 1 and/or 2 (HIV-1 and HIV-2) in Human Serum, Plasma, or Cadaveric Serum Specimens.	
Genotropin	Somatropin, rDNA			Pharmacia and Upjohn, Inc.	24/08/1995	FDA: Long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone and due to Prader-Willi syndrome (PWS).Long-term treatment of growth failure in children born small for gestational age (SGA) who fail to manifest catch-up growth by age 2. Long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult-onset etiology.	Crescormon [TR foreign];

GlucaGen	Glucagon for injection, rDNA origin	Novo Nordisk	NA	Novo Nordisk	22/06/1998	FDA: For the treatment of hypoglycemia; For use as a diagnostic aid: GlucaGen is indicated for use during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.	
Glucagon	Glucagon for Injection, recombinant			Lilly, Eli & Co.	11/09/1998	FDA: For the treatment of hypoglycemia; For use as a diagnostic aid: as a diagnostic aid in the radiologic examination of the stomach, duodenum, small bowel, and colon when dimished intestinal motility would be advantageous.	
Gonal F	Follitropin alfa	Serono Europe Limited	20/10/1995	Serono	29/09/1997	FDA: Women: Induction of ovulation and pregnancy in the anovulatory infertile patient;for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program. Men: For the induction of spermatogenesis in men primary and secondary hypogonadotropic hypogonadism EMEA:(i) Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate.(ii) Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in	

						vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).(iii) Gonal-F in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency.(iv) Stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotrophin (hCG) therapy.	
Herceptin	Trastuzumab	Roche Registration Ltd	28/08/2000	Genentech, Inc	25/09/1998	FDA: Treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease as a single agent. Treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease in combination with paclitaxel. EMEA: Treatment of patients with metastatic breast cancer whose tumours overexpress HER2: a) as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic	

						disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy,unless patients are unsuitable for these treatments.b) in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.	
Humalog	Insulin lispro	Eli Lilly Nederlands B.V.	30/04/1996	Eli Lilly	14/06/1996	FDA: Treatment of patients with diabetes mellitus for the control of hyperglycemia. EMEA: For the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Humalog is also indicated for the initial stabilisation of diabetes mellitus.	
Humaspect	Votumumab	Organon Teknika	25/09/1998			Detection of carcinoma of the colon or rectum	Humaspect is not marketed anywhere in the world. On 22 Sep 2003,discontinue for commercial reasons

Humira	Adalimumab	Abbott Laboratories	08/09/2003	Abbott Laboratories	31/12/2002	FDA: For moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. EMEA: For the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.	
ID Micro Typing Systems	Anti-A (Murine Monoclonal)			Micro Typing Systems, Inc.	21/09/2000	In vitro test/antigen detection; monoclonal antibody, derived from the BIRMA-1 cell line, in MTS Gel Cards under a shared manufacturing agreement with Serologicals LTD	
ID Micro Typing Systems	Anti-B (Murine Monoclonal)			Micro Typing Systems, Inc.	21/09/2000	In vitro test/antigen detection; monoclonal antibody, derived from the LB-2 cell line, in MTS Gel Cards under a shared manufacturing agreement with Serologicals LTD	
ID Micro Typing Systems	Anti-A and B (Murine Monoclonal); Anti-A,B (Murine Monoclonal)			Micro Typing Systems, Inc.	21/09/2000	In vitro test/antigen detection; monoclonal antibody, derived from the ES-15 & ES-4 cell lines, in MTS Gel Cards under a shared manufacturing agreement with Serologicals LTD	
ID Micro Typing Systems	Anti-D (Human Monoclonal) (IgM)			Micro Typing Systems, Inc.	21/09/2000	In vitro test/antigen detection; monoclonal antibody, derived from the MS-201 cell line, in MTS Gel Cards under a shared	

						manufacturing agreement with Serologicals LTD	
Indiclor	Indium In-111 Chloride Sterile Solution			Medi-Physics, Inc	19/02/2002	FDA: Radioloabelling of monoclonal antibodies in preparations used for in vivo diagnostic imaging procedures. Indiclor is also indicated for radiolabeling Zevalin in preparations used for radioimmunotherapy procedures.	
Indimacis 125	Igovomab	CIS Bio	04/10/1996			Diagnosis of ovarian adenocarcimona	Withdraw from the market on holders request
InductOs	Dibotermin alfa	Wyeth Europa Ltd	09/09/2002	Medtronic Sofamor Danek -- Europe mark.; USA mark.	02/07/2002	EMEA: Treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation.	Trade is US is INFUSE Bone Graft [TR reg. by Medtronic]
Infergen	Interferon alfacon-1	Yamanouchi Europe B.V.	01/02/1999	InterMune, Inc	06/10/1997	Treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA.In some patients with chronic HCV infection, Infergen normalizes serum ALT concentrations, reduces serum HCV RNA concentrations to undetectable quantities (<100 copies/ml), and improves liver histology.	
Insuman	Human insulin	Aventis	21/02/1997			EMEA: Diabetes mellitus, where treatment with insulin is required. Insuman Treatment of hyperglycaemic coma and ketoacidosis, as	

						well as for achieving pre-, intra- and post-operative stabilisation in patients with diabetes mellitus.	
Kineret	Anakinra	Amgen Europe	08/03/2002	Amgen, Inc	14/11/2001	FDA: For moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs). EMEA: Treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone.	
Kogenate Bayer	Octocog alfa	Bayer AG	04/08/2000	Bayer	25/02/1993	FDA: Treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor FVIII. EMEA: Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).	Helixate NexGen [Other tradename]
Lantus	Insulin glargine	Aventis Pharma Deutschland GmbH	09/06/2000	Aventis Pharms	20/04/2000	FDA: Once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.	

						EMEA: Diabetes mellitus, where treatment with insulin is required.	
Leukoscan	Sulesomab	Immunomedics B.V.	14/02/1997			EMEA: Diagnostic imaging for determining the location and extent of infection/ inflammation in bone in patients with suspected osteomyelitis, including patients with diabetic foot ulcers.	
Levemir	Insulin detemir	Novo Nordisk	01/06/2004			EMEA: Treatment of diabetes mellitus	
Liprolog	Insulin lispro	Eli Lilly Nederland B.V.	07/05/1997			EMEA: For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Liprolog is also indicated for the initial stabilisation of diabetes mellitus.	Withdraw from the market
Luveris	Lutropin alfa	Ares Serono (Europe) Ltd	29/11/2000	Serono	10/08/2004	FDA: Stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH<1.2 IU/L) concomitantly administered with Gonal-F. EMEA: Stimulation of follicular development in women with severe LH and FSH deficiency in association with a follicle stimulating hormone (FSH) preparation.	
Metalyse	Tenecteplase	Boehringer Ingelheim International GmbH	23/02/2001	Genentech	02/06/2000	FDA: Reduction of mortality associated with acute myocardial infarction (AMI). EMEA: Thrombolytic treatment of suspected	TNKase [TR in US]

						myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of AMI symptoms.	
Mylotarg	Gemtuzumab ozogamicin,CD33 immunotoxin, rDNA			Wyeth Pharmaceuticals	17/05/2000	FDA: Treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age of older and who are not considered candidates for cytotoxic chemotherapy.	
Myobloc	Botulinum Toxin Type B			Elan Pharmaceuticals	08/12/2000	FDA: Treatment of cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.	
Myoscint	Imciromab Pentetate			Centocor B.V.	03/07/1996	Indium in 111 Myoscint is a cardiac imaging agent for detecting the presence and location of myocardial injury in patients with suspected myocardial infarction.	
Nabi-HB	Hepatitis B Immune Globulin			Nabi Biopharmaceuticals -- R&D; Tech.; USA mark.;IDIS World Medicines -- Intl. mark.	24/03/1999	Treatment of acute exposure to blood containing HBsAg, perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg-positive persons and household exposure to persons with acute HBV infection	
Natrecor	Nesiritide, rDNA			GlaxoSmithKline plc (GSK) -- Europe mark.;Scios Inc.	10/08/2001	FDA: Intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.	

				-- Manuf.; R&D; Tech.; USA mark.			
Neorecormon	Epoetin beta	Roche Registration Ltd	16/07/1997			EMEA: Treatment of anaemia associated with chronic renal failure (renal anaemia) in patients on dialysis; treatment of symptomatic renal anaemia in patients not yet undergoing dialysis; prevention of anaemia of prematurity in infants with a birth weight of 750 to 1500 g and a gestational age of less than 34 weeks; prevention and treatment of anaemia in adult patients with solid tumours and treated with platinum-based chemotherapy prone to induce anaemia (cisplatin: 75 mg/m2/cycle, carboplatin:350 mg/m2/cycle);increasing the yield of autologous blood from patients in a pre-donation programme.	
Neulasta	Pegfilgrastim	Amgen Europe	22/08/2002	Amgen, Inc	31/01/2002	FDA: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. EMEA: Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic	Neupopeg [TR in EU]

						chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).	
Neumega	Oprelvekin			Wyeth Pharms Inc	25/11/1997	FDA: Prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies	
NeutroSpec	Technetium 99m Tc Fanolesomab			Palatin Technologies	02/07/2004	FDA: For scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis who are five years of age or older.	
Nonafact	Human coagulation factor IX	Sanquin CLB	03/07/2001			EMEA: Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)	
Norditropin	Somatropin, rDNA			Novo Nordisk	08/05/1995	Pediatric Patients: Long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone. Adult Patients: For replacement of endogenous growth hormone in adults with growth hormone deficiency	Norditropine [TR in France] Norditropin S-chu [TR in Japan] Nordipen [TR for injector]
NovoMix 30	Insulin aspart	Novo Nordisk	01/08/2000			EMEA: Treatment of patients with diabetes mellitus	
Novorapid	Insulin aspart	Novo Nordisk	07/09/1999	Novo Nordisk	07/06/2000	FDA: Treatment of adult patients with diabetes mellitus, for the control of hyperglycemia.	NovoLog [TR in US]

						EMEA: Treatment of patients with diabetes mellitus	
NovoSeven	Eptacog alfa (activated) (coagulation factor VIIa)	Novo Nordisk	23/02/1996	Novo Nordisk	25/03/1999	EMEA: Bleeding episodes and surgery in patients with inherited or acquired haemophilia with inhibitors to coagulation factors (FVIII or FIX) > 10 BU or in patients with antibody titer < 10 BU who are expected to have a high anamnestic response to Factor VIII or Factor IX.	
Nutropin	Somatropin	Ipsen Ltd	16/02/2001	Genentech	09/03/1994	FDA: Pediatric patients: Long-term treatment of growth failure due to a lack of adequate endogenous GH secretion.Treatment of growth failure associated with chronic renal insufficiency up to the time of renal transplantation. Long-term treatment of short stature associated with Turner syndrome. Adult patients: Replacement of endogenous GH in patients with adult GH deficiency. EMEA: Long-term treatment of children with growth failure due to inadequate endogenous growth hormone secretion;Long-term treatment of growth failure associated with Turner syndrome;Treatment of prepubertal children with growth failure associated with chronic renal insufficiency up to the time of	Protropin [Other tradename]

						renal transplantation;Replacement of endogenous growth hormone in adults with growth hormone deficiency of either childhood or adult-onset etiology.	
Omnitrop	Somatropin	Sandoz GmbH				Treatment of growth hormon deficiency	Recommended for approval in Europe in June 2003. Omnitrop was ultimately rejected by the European Commission in April 2004.
Ontak	Denileukin diftitox			Seragen, Inc	05/02/1999	Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.	
Optisulin	Insulin glargine	Aventis Pharma Deutschland GmbH	27/06/2000			EMEA: Diabetes mellitus, where treatment with insulin is required	
Osigraft	Eptotermin alfa	Howmedica International S. de R.L.	17/05/2001			EMEA: Treatment of nonunion of tibia of at least 9 month duration, secondary to trauma, in skeletally mature patients, in cases where previous treatment with autograft has failed or use of autograft is unfeasible	
Osteogenic protein 1	rhOsteogenic Protein -1	Howmedica (EU)	14/12/2000			EMEA: Treatment of nonunion of tibia of at least 9 month duration, secondary to trauma, in skeletally mature patients, in cases where previous treatment with autograft has failed or	

						use of autograft is unfeasible	
Ovitrelle	Choriogonadotropin alfa	Ares Serono (Europe) Ltd	02/02/2001	Serono International S.A.	27/09/2000	FDA: Induction of final follicular maturation and early luteinization in infertile women, for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. EMEA: Ovitrelle is indicated in the treatment of (i) Women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF). (ii) Anovulatory or oligo-ovulatory women	Ovidrel [TR in US]
Pegasys	Peginterferon alfa-2a	Roche Registration Ltd	20/06/2002	Hoffman-La Roche Inc	16/10/2002	FDA: Pegasys, peginterferon alfa-2a, alone or in combination with COPEGUS, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alfa. EMEA: Treatment of histologically proven chronic hepatitis C in adult patients with elevated transaminases and who are positive for serum HCV-RNA, including patients with compensated cirrhosis.	
Peginterferon	Peginterferon alfa-2a copackaged with			Hoffmann-La Roche	04/06/2004	Combination therapy with Ribavirin, USP (Copegus), for the treatment of chronic	

	Ribavirin					hepatitis C virus infection	
PEG-Intron	Peginterferon alfa-2b	Schering Plough Europe	25/05/2000	Schering-Plough	19/01/2001	FDA: Treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alfa and are at least 18 years of age. EMEA: Treatment of adult patients with histologically proven chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.	Rebetol [TR]; PegIntron [TR in Europe]; ViraferonPeg [TR in Europe]
ProstaScint	Capromab Pendetide			Cytogen Corp	28/10/1996	A diagnostic imaging agent in newly-diagnosed patients with biopsy-proven prostate cancer, a diagnostic imaging agent in post-prostategtomy patients with a rising PSA and a negative or quivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease.	

Puregon	Follitropin beta	N.V. Organon	03/05/1996	Organon	29/09/1997	FDA: Women: Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. Men: Induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure. EMEA: Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate; Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programmes [e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra/fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)]	Follistim [TR in US], discontinued in US
Rapilysin	Reteplase	Roche Registration Ltd.	29/08/1996			EMEA: Thrombolytic therapy of acute myocardial infarction	

Raptiva	Efalizumab	Serono Europe Limited	20/09/2004	Genentech	27/10/2003	FDA: Moderate to severe plaque psoriasis whose psoriasis is appropriate for treatment with whole body (systemic therapy) or phototherapy. EMEA: Treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant of other systemic therapies including cyclosporin, methotrexate and PUVA.	
Rebif	Interferon beta-1a	Ares Serono (Europe) Ltd	04/05/1998	Serono, Inc	07/03/2002	FDA: Treatment of patients with relapsing forms of multiple sclerosis EMEA: Treatment of patients with multiple sclerosis and with 2 or more relapses within the last two years.	
Refacto	Moroctocog alfa	Genetics Institute of Europe B.V.	13/04/1999	Genetics Institute, Inc.	06/03/2000	FDA: Control and prevention of hemorrhagic episodes and for surgical prophylaxis in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia). For short-term routine prophylaxis to reduce the frequency of spontaneous bleeding episodes. EMEA: Hemophilia A (congenital factor VIII deficiency or classic hemophilia) for the control and treatment of bleeding and the	

						prevention of bleeding (prophylaxis).	
Refludan	Lepirudin	Schering AG	13/03/1997	Berlex	06/03/1998	EMEA: Anticoagulation in adult patients with heparin-associated thrombocytopenia (HAT) type II and thromboembolic disease mandating parenteral antithrombotic therapy.	
Regranex	Becaplermin	Janssen-Cilag International B.V.	29/03/1999	OMJ Pharmaceuticals, Inc	16/12/1997	FDA: Treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. EMEA: Promote granulation and thereby the healing of full-thickness, neuropathic, chronic, diabetic ulcers $\leq$ 5 cm2	
Remicade	Infliximab	Centocor B.V.	13/08/1999	Centocor, Inc	24/08/1998	FDA: Rheumatoid Arthritis; Crohn's disease EMEA: Rheumatoid arthritis; Crohn's disease	
Replagal	Agalsidase alfa	TKT Europe-5S AB	03/08/2001			EMEA: For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease (α-galactosidase A deficiency)	
Respigam	RSV immunoglobulin			Medimmune (Massachusetts Public Health Biologic Labs)	18/01/1996	Prevention of serious lower respiratory tract infection caused by Respiratory Syncytial Virus in children less than 24 months of age with bronchopulmonary dysplasia or a history of prematurity (less than or equal to 35 weeks gestation)	Polyclonal antibodies,discontinued at of the end of 2003.

Revasc	Desirudin	Aventis	09/07/1997	Canyon	04/04/2003	FDA: Prophylaxis of deep vein thrombosis. EMEA: Prevention of deep venous thrombosis in patients undergoing elective hip and knee replacement surgery	Iprivask [TR in US]
Rituxan	Rituximab	Roche Registration Ltd	02/06/1998	Genentech, Inc	26/11/1997	Rituxan is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-Hodgkin's lymphoma.	MabThera [TR used by Roche outside of U.S. and Japan]
Saizen [TR for hGH deficiency]	Somatropin, rDNA			Serono International S.A.	08/10/1996	Pediatric Patients: Long-term treatment of children with growth failure due to inadequate secretion of endogenous growth hormone. Adult patients: Replacement of endogenous growth hormone in adults with growth hormone deficiency	Serostim [for AIDS-related cachexia];cool.click [TR for injector];
Simulect	Basiliximab	Novartis Europharm Ltd	09/10/1998	Novatis Pharmacueticals Corp	12/05/1998	FDA: Prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporing, USP (modified) and corticosteroids. EMEA: Prophylaxis of acute organ rejection in de novo allogeneic renal transplantation and is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immuno-suppression in patients with panel reactive antibodies less than 80%.	
Somavert	Pegvisomant	Pfizer Limited	13/11/2002	Pharmacia and	25/03/2003	FDA: Treatment of acromegaly in patients to	

				Upjohn		normalize serum IGF-I levels. EMEA: Treatment of patients with acromegaly	
Streptase	Streptokinase			Aventis Behring GmbH	15/10/1997	Acute evolving transmural myocardial infarction, pulmonary embolism, deep vein thrombosis, arterial thrombosis or embolism, occlusion of arteriovenous cannulae.	
Sucraid	Sacrosidase			Orphan Medical, Inc	09/04/1998	Replacement for patients who do not have the enzymes needed to properly break down and absorb sucrose (table sugar) and isomaltose (a type of starch) in the intestines.	
Synagis	Palivizumab	Abbott Laboratories	13/08/1999	MedImmune, Inc	19/06/1998	FDA: Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. EMEA: For the prevention of serious lower respiratory tract disease requiring hospitalisation as caused by respiratory syncytial virus (RSV) in children who are born at 35 weeks of gestation or less and were less than 6 months of age at the onset of the RSV season, or in children who are less than 2 years of age and had required treatment for bronchopulmonary dysplasia within the last 6 months.	

Tecnemab KI	Murine Mab fragments directed against HMW-MAA	Sorin	23/09/1996			Diagnosis of cutaneous melanoma lesions	Withdraw on holders request
Thymoglobulin	Thymoglobulin			Sangstat (Pasteur Merieux Serums)	30/12/1998	Treatment of acute rejection in renal transplant patients	Polyclonal antibodies,rabbit
Thyrogen	Thyrotrophin alfa	Genzyme B.V.	09/03/1999	Genzyme	30/11/1998	FDA: An adjunctive diagnostic tool for serum thyroglobulin(Tg) testing with or without radioiodine imaging in the follow-up of patients with well-differentiated thyoid cancer. EMEA: Use with radioiodine imaging together with serum thyroglobulin (Tg) testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy (THST)	
Trudexa	Adalimumab	Abbott Laboratories	01/09/2003			Treatment of moderate to severe, active rheumatoid arthritis in adult patients	
Tysabri	Natalizumab			Biogen Idec Inc	23/11/2004	Treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.	
Verluma	Nofetumomab			Boehringer Ingelheim Pharma KG	20/08/1996	Detection of extensive stage disease in patients with biopsy-confirmed, previously untreated, small cell lung cancer.	
Vibragen	rFeline IFN-w	Virbac	2001			Veterinary; reduction in mortality/ symptoms	Veterinary

Omega						of canine parvovirus	
Vitrase	Ovine Hyaluronidase			Ista Pharms	05/05/2004	An adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents	
Vitron	IFN-a-2b	Schering Plough	09/03/2000			EMEA: Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated ALT and histologically proven active liver inflammation and/or fibrosis; Chronic Hepatitis C: Treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication.The efficacy of interferon alfa-2b in the treatment of hepatitis C is enhanced when combined with ribavirin	Another trade name for Viraferon. SP Europe committed to withdraw the nationally authorised Viraferon, and to transfer this trade name to the centrally authorised product.
Wellferon	Interferon alfa-N1			GSK	25/03/1999	Hepatitis B&C	Discontineued in 1999
Wydase	Hyaluronidase, bovine			Baxter healthcare	17/10/2001	Management of IV extravasation	Withdraw for safety reasons
Xigris	Drotrecogin alfa (activated)	Eli Lilly Nederland B.V.	22/08/2002	Eli Lilly & Co	21/11/2001	FDA: Reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II).	

						EMEA: Treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care.	
Xolair	Omalizumab			Genentech, Inc	20/06/2003	For adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.	
Zenapax	Daclizumab	Roche Registration Ltd	26/02/1999	Hoffman-La Roche Inc	10/12/1997	FDA: Prophylaxis of acute organ rejection in patients receiving renal transplants.It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. EMEA: Prophylaxis of acute organ rejection in de novo allogeneic renal transplantation and is to be used concomitantly with an immunosuppressive regimen, including cyclosporine and corticosteroids in patients who are not highly immunised.	
Zevalin	Ibritumomab tiuxetan	Schering AG	16/01/2004	IDEC Phrmaceuticals Corp	19/02/2002	FDA: Treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma. EMEA: Treatment of adult patients with	

						rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).	
Vaccines							
Ambirix	Inactivated hepatitis A virus hepatitis B surface antigen, rDNA	Glaxo Smith Kline Biologicals	30/08/2002			EMEA: For non-immune children and adolescents from 6 years up to and including 15 years for protection against hepatitis A and hepatitis B infection.	
Bayovac CSF E2	Vaccine containing r classical swine fever virus antigen	Bayer	2001			Veterinary; immunization of pigs against classical swine fever	Veterinary
Certiva	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed			North American Vaccine, Inc	29/07/1998	FDA: Active immunization against diphtheria, tetanus, and pertussis (whooping cough) in infants and children 6 weeks to 7 years of age(prior to seventh birthday).	
Comvax	Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine			Merck & Co., Inc.	02/10/1996	FDA: Vaccination against invasive disease caused by Haemophilus influenzae type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born of HBsAg negative mothers. Infants born of HBsAg positive mothers should be vaccinated with a passive-active regimen that includes the administration of Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth given according to a particular schedule; Vaccination should	

						ideally begin at approximately 2 months of age or as soon thereafter as possible.	
Daptacel	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed (DTaP)			Aventis Pasteur Limited	14/05/2002	FDA: Active immunization against diphtheria, tetanus and pertussis in infants and children 6 weeks through 6 years of age (prior to seventh birthday).Children who have had well-documented pertussis (culture positive for B. pertussis or epidemiologic linkage to a culture positive case) should complete the vaccination series with DT; some experts recommend including acellular pertussis vaccine as well.	
Dukoral	Vibrio cholerae and recombinant cholera toxin B-submit	SBL Vaccin AB	28/04/2004			EMEA: Active immunisation against disease caused by Vibrio cholerae serogroup O1 in adults and children from 2 years of age who will be visiting endemic/epidemic areas.	
Fevaxyl pentofel	Combination vaccine containing r Feline leukaemia viral antigen	Fort Dodge Laboratories	1997			Veterinary; immunization of cats against feline pathogens	Veterinary
FluMist	Influenza Virus Vaccine, Live, Intranasal			MedImmune Vaccines, Inc	17/06/2003	FDA: Active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5-17 years of age, and healthy adults, 18-49 years of age.	
Havrix	Hepatitis A Virus Vaccine, Inactivated			GlaxoSmithKline plc (GSK)	22/02/1995	Active immunization of persons 2 years of age or older against disease caused by hepatitis A	

						virus (HAV).	
HBVAXPRO	Recombinant Hepatitis B virus small surface antigen (HbsAg)	Aventis Pharma S.A.	27/04/2001			EMEA: Active immunisation against hepatitis B virus infection caused by all known subtypes in all age categories considered at risk of exposure to hepatitis B virus	
HEPACARE	r S, pre-S and pre-S2 hepatitis B surface antigen	Medeva Pharma	04/08/2000			Immunization against hepatitis B	Withdraw from the market in 2002
HEXAVAC	Comb vaccine	Aventis Pasteur MSD	23/10/2000			EMEA: Active immunisation against diphtheria, tetanus, pertussis, hepatitis B caused by all known subtypes of viruses, poliomyelitis and invasive infections caused by Haemophilus influenzae type b; for primary vaccination in infants (from 2 to 12 months of age);for booster vaccination in toddlers (from 12 to 18 months of age) provided the toddler has received a full primary vaccination course of each of the antigens contained in Hexavac	
Infanrix	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine	GlaxoSmithKline Biologicals S.A.	30/07/1997	SmithKline Beecham Biologicals, S.A.	29/01/1997	FDA: Active immunization against diphtheria, tetanus, and pertuss is (whooping cough) as a 5-dose series in infants and children 6 weeks to 7 years of age (prior to seventh birthday)	
Infanrix hexa	Hep B-IPV HIB vaccine	GlaxoSmithKline Biologicals S.A.	23/10/2000			EMEA: For primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by Haemophilus influenzae	

						type b.	
Infanrix penta	Hep B-IPV vaccine	GlaxoSmithKline Biologicals S.A.	23/10/2000			Primary and booster immunization of infants against diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis	
Lymerix	Recombinant OSP-A (lyme disease vaccine)			SmithKline Beecham Biologicals, S.A.	21/12/1998	FDA: Active immunization against Lyme disease in individuals aged 15-70 years.	Withdrawn in spring 2002.
Pediarix	Diphtheria & Tetanus Toxoids & Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) & Inactivated Poliovirus Vaccine Combined			SmithKline Beecham Biologicals	13/12/2002	FDA: Active immunization against diphtheria, tetanus, pertussis (whooping cough), all known subtypes of hepatitis B virus, and poliomyelitis caused by poliovirus Types 1, 2, and 3 as a three-dose primary series in infants born of HBsAg-negative mothers, beginning as early as 6 weeks of age. Infants born of HBsAg-positive mothers should receive Hepatitis B Immune Globulin (Human) (HBIG) and monovalent Hepatitis B Vaccine (Recombinant) within 12 hours of birth and should complete the hepatitis B vaccination series according to a particular schedule. Infants born of mothers of unknown HBsAg status should receive monovalent Hepatitis B Vaccine (Recombinant) within 12 hours of birth and should complete the hepatitis B vaccination series according to a particular schedule. Hepatitis D will also be prevented by vaccination with Pediarix.	

Porcillis AR-T DF	Combination vaccine containing a modified toxin	Intervet	2000			Veterinary; active immunization of sows	Veterinary
Prevenar	Pneumococcal conjugate vaccine	Wyeth-Lederle Vaccines S.A.	02/02/2001	Lederle Laboratories Division American Cyanamid Company	17/02/2000	FDA: Active immunization of infants and toddlers against invasive disease caused by S. pneumoniae due to capsular serotypes included in the vaccine (4, 6B,9V, 14, 18C, 19F, and 23F).For active immunization of infants and toddlers against otitis media caused by serotypes included in the vaccine. EMEA: Active immunisation of infants and young children from 2 months of age through 2 years of age against invasive disease (including bacteraemia, sepsis, meningitis, bacteraemic pneumonia) caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.	
Primavax	Combination vaccine, containing rHBsAg	Aventis Pasteur MSD	05/02/1998			Immunization against diphtheria, tetanus and hepatitis B	Withdraw from the market
Porcilis porcoli	Combination vaccine containing r E.coli adhensions	Intervet	1996			Veterinary; active vaccination of sows	Veterinary
Porcillis pesti	Vaccine containing r classical swine fever virus antigen	Intervet	2000			Veterinary; immunization of pigs against classical swine fever	Veterinary

Procomvax	Haemophilus b conjugated and hepatitis B vaccine	Aventis Pasteru Merieux MSD	07/05/1999			EMEA: Vaccination against invasive disease caused by Haemophilus influenzae type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age.	
RabAvert	Rabies Vaccine			Chiron Behring GmbH	20/10/1997	Rabies vaccine for immunization of children and adults	
RotaShield	Rotovarus Vaccine, Live, Oral, Tetravalent	Wyeth-Lederle Vaccines S.A.	14/05/1999	Wyeth Laboratories, Inc	31/08/1998	Primary immunization of infants at 2, 4, and 6 months of age	Withdraw from the market
Triacelluvax	Combination vaccine, containing r (modified) pertussin toxin	Chiron SpA	11/01/1999			Immunization against diphtheria, tetanus and pertussis	Withdraw from the market
Tritanrix-Hep B	Comb vaccine DTPW-Hep B	GlaxoSmithKline Biologicals S.A.	19/07/1996			EMEA: Active immunisation against diphtheria, tetanus, pertussis and hepatitis B (HB) in infants from 6 weeks onwards.	
Twinrix	Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine			SmithKline Beecham Biologicals	11/05/2001	FDA: Active immunization of persons 18 years of age or older against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus. As hepatitis D (caused by the delta virus) does not occur in the absence of HBV infection, it can be expected that hepatitis D will also be prevented by vaccination with Twinrix.	
Twinrix adult	Comb Hep A and B vaccine	GlaxoSmithKline Biologicals	20/09/1996			EMEA: For use in non immune adults and adolescents of 16 years of age and above who	

		S.A.				are at risk of both hepatitis A and hepatitis B infection.	
Twinrix paediatric	Comb Hep A and B vaccine	GlaxoSmithKline Biologicals. S.A.	10/02/1997			EMEA: For use in non-immune infants, children and adolescents from 1 year up to and including 15 years who are at risk of both hepatitis A and hepatitis B infection.	
Vaqta	Hapatitis A vaccine, inactivated			Merck & Co., Inc.	29/03/1996	FDA: Active pre-exposure prophylaxis against disease caused by hepatitis A virus in person 2 years of age and older. Primary immunization should be given at least 2 weeks prior to expected exposure to HAV.	
Varivax	Varicella Virus Vaccine			Merck & Co., Inc.	17/03/1995	Vaccination against varicella in individuals 12 months of age and older.	
Antisense oligonucleotide							
Vitravene	Formivirsen	Ciba Vision Europe Ltd. (2001 name of the marketing authorisation holder changed to Novartis Ophthalmics Europe Ltd)	29/07/1999	ISIS Pharmaceuticals	26/08/1998	Local treatment of cytomegalovirus (CMV) retinitis in patients with AIDS	CDER Antisense oligonucleotides; 2002 withdraw from the EC.

Appendix 3: Reference list of interferon beta published pre-marketing clinical trials

IFNB Group:

1. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology 1993; 43(4):655-61.
2. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology 1995; 45(7):1277-85.
3. Interferon beta-lb is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. 1993 [classical article]. Neurology 2001; 57(12 Suppl 5):S3-9.
4. Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. Neurology 1993; 43(4):662-7.
5. Paty DW, Li DK. Interferon beta-lb is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. 1993 [classical article]. Neurology 2001; 57(12 Suppl 5):S10-5.
6. Zhao GJ, Koopmans RA, Li DK, Bedell L, Paty DW. Effect of interferon beta-1b in MS: assessment of annual accumulation of PD/T2 activity on MRI. UBC MS/MRI Analysis Group and the MS Study Group. Neurology 2000; 54(1):200-6.

PRISMS Study Group

1. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998; 352(9139):1498-504.

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MSCRG

1. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, et al. A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Multiple Sclerosis Collaborative Research Group (MSCRG). Mult Scler 1995; 1(2):118-35.
2. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, Alam JJ, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Munschauer FE, 3rd, Priore RL, Pullicino PM, Scherokman BJ, Whitham RH, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996; 39(3):285-94.
3. Jacobs L, Rudick R, Simon J. Extended observations on MS patients treated with IM interferon-beta1a (Avonex): implications for modern MS trials and therapeutics. J Neuroimmunol 2000; 107(2):167-73.

4. Rudick RA, Goodkin DE, Jacobs LD, Cookfair DL, Herndon RM, Richert JR, Salazar AM, Fischer JS, Granger CV, Simon JH, Alam JJ, Simonian NA, Campion MK, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Munschauer FE, Priore RL, Whitham RH, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Neurology 1997; 49(2):358-63.
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sclerosis. The Multiple Sclerosis Collaborative Research Group. Ann Neurol 1998; 43(1):79-87.

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European Study Group

1. Interferon beta-1b and secondary progressive multiple sclerosis: licence extension. Useful, but further assessment required. Prescrire Int 2000; 9(48):110-1.
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Appendix 4: Top 10 Biopharmaceutical Companies of 2003

Company	Biopharmaceutical revenues	Total revenues
Amgen	$7,886	$8,356
Genentech	$2,621	$3,300
Serono	$1,858	$2,019
Biogen Idec	$1,722 *	$1,852
Genzyme	$ 1,563	$ 1,713
Chiron	$ 1,346	$1,766
MedImmune	$993	$ 1,054
Gilead	$836	$868
Millennium	$244	$434
Intermune	$154	$154

* Data from www.contractpharma.com

1. Amgen

Biopharmaceutical Revenues $7,868 (million)

Total Revenues $8,356 (million)

Top Selling Drugs

Drug	Indication	$ (million)
Epogen	Anemia	$ 2,435 (US sales)
Aranesp	Chemotherapy-induced	$ 1,544 (US +international sales) US sales: $ 979.9 International sales: $563.9
Neupogen	Chemotherapy	$ 1,267 (US +international sales) US sales: $ 880.5 International sales: $ 386.2
Neulasta	Chemotherapy-induced neutropenia	$ 1,255 (US +international sales) US sales: $ 1175.7 International sales: $ 79.3
Enbrel	Rheumatoid arthritis, psoriatic arthritis	$ 1,300 (US +international sales) US sales: $ 1253.7 International sales: $ 46.3

2. Genentech

Biopharmaceutical Revenues $2,621 (million)

Total Revenues $3,300 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Rituxan	Non-Hodgkin's lymphoma	$ 1,489
Herceptin	Breast Cancer	$ 425
Nutropin Depot + Neutropin AQ+ Nutropin + Protropin	Growth hormone	$ 322
Activase + TNKase + Cathflo activase	Thrombolytic	$ 185
Pulmozyme	Cystic fibrosis	$ 167

3. Serono

Biopharmaceutical Revenues $1,858 (million)

Total Revenues $2,019 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Gonal-F	Infertility	$ 526
Rebif	Multiple sclerosis	$ 819
Saizen	Growth retardation	$ 152
Serostim	Wasting	$ 89
Novantrone	Neurology and other	$ 77.1
Pergonal	Reproductive health	$ 45.8
Cetrotide	Reproductive health	$ 24.8
Metrodin HP	Reproductive health	$ 24.8
Crinone	Reproductive health	$ 20.8
Profast	Reproductive health	$ 15.4

4. Biogen IDEC

Biopharmaceutical Revenues $1,722 (data from www.contractpharma.com)

Total Revenues $1,852 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Avonex	Multiple sclerosis	$ 1,168
Rituxan	Lymphoma	$ 493

5. Genzyme

Biopharmaceutical Revenues	$ 1,563 (million)
Total Revenues	$ 1,713 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Cerezyme	Type 1 Gaucher disease	$ 733
Renagel (including sales of bulk sevelamer)	Renal	$ 281
Synvisc	Biosurgery	$ 108
Fabrazyme	Fabry disease	$ 80
Thyrogen	adjunctive diagnostic tool for serum thyroglobulin (Tg) testing	$ 43
Thymoglobulin / Lymphoglobulin	Transplant	$ 30

6. Chiron

Biopharmaceutical Revenues	$ 1,346 (million)
Total Revenues	$ 1,766 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Influenza vaccines	Vaccines	$ 332
Pediatric and other vaccines	Vaccines	$ 192.5
Tobi	Antibiotics	$ 172
Betaseron	Multiple sclerosis	$ 125
Proleukin	Metastatic melanoma	$ 115
Travel vaccines	Vaccines	$ 87.8
Menjugate	Meningococcal C disease	$ 65.5

7. MedImmune

Biopharmaceutical Revenues	$ 993 (million)
Total Revenues	$ 1,054 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Synagis	Prevention of serious lower respiratory tract disease	$ 849
Ethyol	Reduce the cumulative renal toxicity; Reduce the incidence of moderate to severe xerostomia	$ 100.2

8. Gilead

Biopharmaceutical Revenues $ 836 (million)

Total Revenues $ 868 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Tenofovir (Viread)	HIV	$566.5
Adefovir (Hepsera)	Hepatitis B	$ 50.5
Emtricitabine (Emtriva)	HIV	$10
Cidofovir (Vistide)	Cytomegalovirus	$7.6
Oseltamivir (Tamiflu)	Flu (Royalty from Roche)	$11.4

9. Millennium Pharmaceuticals

Biopharmaceutical Revenues	$244 (million)
Total Revenues	$434 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Integrilin	Cardiovascular disease	$ 184
Velcade	Multiple myeloma	$ 60

10. InterMune

Biopharmaceutical Revenues	$154 (million)
Total Revenues	$154 (million)

Top Selling Drugs

Drug	Indication	$ (m)
Interferon gamma 1b (Actimmune)	Chronic granulomatous disease, malignant osteopetrosis (Licensed from Genentech)	$ 141.4