SCRIP Reports

Biosimilars, Biogenerics and Follow-on Biologics

By Biophoenix

BS1342

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EXECUTIVE SUMMARY

The first generation of biopharmaceuticals manufactured using recombinant technologies was launched in the 1980s, and patents protecting them are now nearing expiration. As with small molecule drugs, the expiration of patents creates an opportunity for generic biologicals to enter the market. Due to the complexity of biological drugs, such products are usually referred to as 'biosimilars' or 'follow-on biologics', although the term 'biogenerics' may be applied to simple peptides.

Despite delays by the US FDA, and opposition from originator companies, biosimilars now represent one of the most rapidly evolving areas of product development in the pharmaceutical industry. The EU already has legislation in place for the approval of biosimilars, and the US is set to follow suit following the passing of landmark legislation by the US Senate Health Committee in June 2007. In the same month another significant milestone in the development of biosimilars was reached when the EMEA recommended three biosimilar versions of recombinant erythropoietin (EPO), a complex glycoprotein, for approval.

As discussed in this Report, companies active in the biosimilars sector are currently targeting products which are now off-patent in Europe: in particular human growth hormone (hGH), EPO and granulocyte colony-stimulating factor (G-CSF). However, there are many more potential targets for development in areas, which have so far attracted fewer developers in the Western markets.

This Report focuses on 59 protein and 14 peptide therapeutics, which achieved high-volume global sales in 2006. Half of the protein products generated sales in excess of $500 million. We analyse these potential targets in the context of other commercial products based on the same active ingredient which are on the market or in development worldwide. This information, derived from the Pharmaprojects database, will provide the reader with a snapshot of the commercial landscape relevant to each target product, and highlight related or improved products which may themselves become targets for biosimilar development.

We next examine the scientific issues involved in assessing the equivalence of biosimilar products and review the more important analytical procedures available for this purpose, including techniques with an established role in protein analysis, as well as emerging techniques like nuclear magnetic resonance spectroscopy and mass spectrometry. Regulatory requirements are likely to be more demanding for products bearing post-translational modifications, since relatively minor structural changes can alter therapeutically-relevant characteristics. Case studies focus on specific biosimilar products, which have recently undergone analytical and immunological evaluation.

The EU has been the initial target of most companies developing biosimilars for the regulated markets. Most development work in the biosimilars field is being conducted by large generic or speciality pharmaceutical companies. These firms have been busy setting up subsidiaries or spin-offs focused on biosimilars and linking up with smaller companies, which have enabling technologies for the production of biosimilars. We profile 15 selected companies based in India, Europe, the US, Canada and Israel, which are poised for competition in the (regulated) biosimilars market.

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We forecast in detail the top five protein therapeutics categories open to biosimilar competition, worth over 50% of the total protein market in 2006. We estimate that total sales of follow-on proteins and biosimilars will rise from $30 million in 2006 to $3.2 billion in 2011, which represents a market penetration of 2.7% across the board. We appreciate that this figure, which is low by the standards of conventional generics, may disappoint some. It is partly due to the fact that certain important product groups, most notably the epoetins, cannot be sold in the important US market during the forecast period owing to patent restrictions. Also, widespread physician dispensing in Japan creates a bias against generics in that country. Thus, Europe will lead the way in biosimilar sales, with 45% of the world market. Apart from a few niche proteins and peptides, there is currently no available full-year sales history for any approved biosimilar.

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CHAPTER 1
INTRODUCTION

1.1 The advent of biosimilars

The first generation of biopharmaceuticals manufactured using recombinant technologies was launched in the 1980s, and patents protecting them are now nearing expiration. Recombinant proteins currently command premium pricing due, in part, to the high manufacturing costs associated with their production, superior safety and efficacy profiles, and limited or absent competition. It has been estimated that by the end of the current decade, over $10 billion worth of biopharmaceuticals will have lost patent protection.

As with small molecule drugs, the expiration of patents creates an opportunity for generic biologicals to enter the market. Since biological products are complex and often heterogeneous, and cannot be replicated in a precise manner (as chemical compounds can), the term 'generic' is not entirely appropriate. Instead, a variety of other terms is currently used; in Europe, the EMEA refers to 'biosimilars', whereas in the US, the FDA favours the term 'follow-on biologics'. Since the EMEA is ahead of the FDA in the application of a consistent and continued regulatory pathway for biosimilars, this Report will follow its lead in the use of relevant terminology.

In April 2006, the first two biosimilar proteins were approved by the EMEA. These were both growth hormones; Valtropin from Biopartners and Omnitrope from Sandoz; the latter product was also approved by the FDA. Human growth hormone is a relatively simple, non-glycosylated protein, but the majority (70%) of approved recombinant proteins are glycoproteins, which require technically complex mammalian cell culture for their production.

Approved in 1989, Amgen's Epogen (epoetin alfa; recombinant human erythropoietin [EPO]) was one of the first recombinant human glycoprotein therapeutics. The EPO drugs, such as Epogen, have become best-sellers due to their ability to relieve anaemia-related fatigue and they allow kidney patients to forestall regular blood transfusions. In June 2007, a significant milestone was reached in the development of biosimilars when the EMEA recommended three biosimilar versions of epoetin alfa for approval – Sandoz's Binocrit, Hexal Biotech's Epoetin alfa Hexal, and Medice Arzneimittel's Abseamed.

Every successful biopharmaceutical is likely to face biosimilar competition when it comes off-patent and sooner or later every successful originator company will be involved or competing with biosimilars. The global development of biosimilars therefore represents a critical part of the future of biotechnology. This Report will examine significant recent developments in the biosimilars market and will arm the reader with strategic information needed to face new opportunities as well as the challenges of the biosimilars revolution.

1.2 The role of patents in the drug industry

The pharmaceutical industry has always relied on patents to safeguard the vast amount of investment, which is required to bring a drug to market. Patents underpin the modern biopharmaceutical industry and are for many biotechnology companies the key to survival.

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Genes and proteins can be patented as composition-of-matter, processes or combinations of both. Processes can involve uses of nucleic acids, proteins or other composition-of-matter in industrial processes, or to predict, detect or treat diseases. The gene for erythropoietin (EPO) was one of the first genes patented (it was isolated by working backwards from the protein product). The first patent was issued for isolated EPO protein having *in vivo* biological activity. There are now more than a dozen patents on EPO for new, novel uses of EPO, including a patent on a variant form of EPO.

The exclusive rights to exploit a patented invention are granted for only a limited period and, once this term has expired, the general public is free to use the invention. The European Patent Convention, which came into force in 1978, set a term of 20 years from the filing date for European patents. The Patents Act 1977, which came into force on the same day, set the same term for UK national patents. This has become the international standard and is now observed by most countries. In the US, the US Patent Term Guarantee Act, which came into force on March 29th, 2000 ensures that the term of a patent is extended to at least 17 years if the prosecution of the patent lasts longer than three years. Under the Domestic Publication of Foreign Filed Patent Applications Act, which took effect on May 29th, 2001 US patent applications are now being published 18 months after filing.

A particular problem in the pharmaceutical industry is that the time required for obtaining FDA approval typically reduces the period of exclusivity provided by the patent protection. The 1984 Patent Term Restoration Act provides up to five additional years of patent protection beyond the basic term (ie. 20 years from filing the application) to alleviate the unintended effects of the FDA approval process. Thus, the term of a patent protecting a drug may be extended for a period calculated based on the time needed for regulatory approval. However, this extended period may not extend the term of the patent to more than 14 years after the approval date. Only one patent may have its term thus extended. It is also possible to obtain extensions of the standard patent term in Europe and Japan.

Patents on improved drugs provide the best legal method for continuing market exclusivity for a branded drug. When the original patent term of a drug expires, a generics firm can practise the invention of the original patent, but may not practice the improvement invention until the improvement patent expires. If the improvement is sufficiently desirable, it is possible that the market will switch to the improved product and that there will be no market for the original drug.

1.3 Protein-based biopharmaceuticals

Biopharmaceuticals represent one of the fastest-growing segments of the pharmaceutical industry. There are currently more than 200 biopharmaceuticals on the market. Most are protein-based, although two nucleic acid-based products are now on the US/European market. Over 300 biopharmaceuticals are being investigated in clinical trials.

Most of the protein-based biopharmaceuticals currently on the market owe their existence to the efforts of biotech companies, as opposed to big pharma, which has traditionally focused on small molecule drug candidates. Many protein-based drugs provide effective and safe treatments for chronic conditions and they now include therapeutic monoclonal antibodies as well as the more traditional recombinant proteins and peptides.

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Drug delivery presents particular challenges because the products are generally hydrophilic in nature and of high molecular weight. Currently, most marketed therapeutic proteins and peptides are formulated as injectables for immediate release.

1.3.1 Background

In some diseases, proteins do not work properly or they may be absent, and the introduction of a biological drug (non-recombinant or recombinant) can improve symptoms or pathology. In the case of monoclonal antibodies (which are of the IgG format) and some fusion proteins, the therapeutic effect is obtained either by blocking a target, or by activating immune effector functions.

Proteins play crucial roles in almost every biological process. They are responsible in one form or another for a variety of physiological functions including: binding, transport and storage; enzymatic catalysis; structural support; immune protection; generation and transmission of nerve impulses; molecular switching, which controls cellular processes; control of growth and differentiation; and coordinated motion.

Genes can encode multiple proteins and a single protein can have multiple functions. The key to appreciating how individual proteins function lies in an understanding of three-dimensional protein structure. Secondary and tertiary structure represents the most thermodynamically stable conformation for the protein molecule in solution, and results from non-covalent interactions between the various amino acid side-chains within the molecule and with the water molecules surrounding it. Different regions of the protein, often with distinct functions, may form structurally-distinct domains. Structurally-related domains are found in different proteins which perform similar functions. The exposed surface of the protein may also be involved in interactions with other molecules, including proteins. Protein-protein interactions, for example between sub-units of enzyme complexes or polymeric structural proteins, result in the highest level of organisation, or quaternary structure.

Post-translational modification of a protein can have a profound effect on its structure, and consequently affect its activity or function. Natural proteins can display a broad range of post-translational modifications (PTMs), but only a subset of these PTMs are associated with currently marketed therapeutic proteins. Glycosylation represents one of the most common but complex PTM modifications. Other PTMs, including carboxylation, hydroxylation, sulfation and amidation, are characteristic of some therapeutic products. Some therapeutic proteins may also require proteolytic processing (for example, for the production of biologically active insulin) and disulfide bond formation.

Glycosylation is a complicated, enzyme-directed site-specific process; mammalian cells typically use hundreds of enzymes to glycosylate proteins. Two types of glycosylation exist: N-linked glycosylation to the amide nitrogen of asparagine side chains and O-linked glycosylation to the hydroxy oxygen of serine and threonine side chains. N-linked glycosylation is particularly influential in determining protein stability, ligand binding, immunogenicity and serum half-life.

Glycosylation is characterised by heterogeneity, in that several glycoforms are usually generated. Heterogeneity arises from the addition of several

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oligosaccharides at N- and O-glycosylation sites, together with heterogeneity of the oligosaccharide attached at any given site. Contributing to heterogeneity is variable-site glycosylation (in which some glycosylation sites remain unoccupied within a proportion of the glycoprotein molecules) and, more commonly, the occurrence of variable monosaccharide chain sequences. The glycoform profile may differ depending on the tissue in which a particular glycoprotein is expressed in the same organism.

1.3.2 Manufacturing processes

A recombinant therapeutic protein is produced by an organism after the relevant DNA is inserted into its genome. The bacterium *Escherichia coli* (*E.coli*) is one of the most widely used hosts for the production of heterologous proteins and its genetics are far better characterised than those of any other microorganism. However, many human proteins, including glycoproteins cannot be expressed at all in microbial cell culture. Cultivated mammalian cells have become the dominant system for the production of recombinant proteins for clinical applications because of their capacity for proper protein folding, assembly and post-translational modification. These cell lines thus far command an effective monopoly in terms of producing large therapeutic proteins that require post-translational modification, in particular glycosylation.

Mammalian cell culture is technically complex, slow and expensive. Commonly used mammalian cell lines include Chinese hamster ovary (CHO) or mouse NS0 myeloma cell lines. In recent years, a combination of improved expression constructs and increased understanding of animal cell metabolism and physiology has resulted in continuous improvements in product yield. Recombinant protein levels approaching 5g per litre are now possible. Also of note is the successful development of serum-free and animal component-free media for several cell lines.

Manufacturers are required to maintain strict control over the manufacturing, processing and purification of recombinant proteins and any changes must be documented and approved by regulators. Production processes must ensure consistency between batches, which is a difficult enough challenge for the innovator company, let alone the developer of a biosimilar product. Consistency in protein structure, activity, purity, stability and formulation are required in order to avoid, for example, immunogenic reactions and/or a lack of efficacy at the patient level.

The manufacture of therapeutic proteins with a reproducible and consistent glycoform profile remains a considerable challenge to the biopharmaceutical industry. Mammalian cell-derived glycoproteins are generally subject to heterogeneity of the glycans, which vary in exact detail of glycosylation, and glycocomponent profile can be influenced by changes to manufacturing cell culture conditions such as pH (acidity) and the availability of nutrients, cytokines or hormones. The nature of glycoforms produced may impact glycoprotein folding, stability, trafficking and immunogenicity as well as its primary functional activity. Glycosylation can alter protein serum half-life (the length of time it stays active in the body); for example, EPO is more readily cleared through the kidney when poorly glycosylated, thus reducing its serum half-life under this condition. Variability can be problematic if different product glycoforms have differential therapeutic properties, as is the case for EPO, tissue plasminogen activator, monoclonal antibodies, and some hormones and cytokines. Rendering this issue more complex is the fact that, in general, it is not possible to precisely predict the functional

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consequences of altering glycosylation profiles.

In addition, essential media nutrients may compromise product quality, by for example promoting the non-enzymatic addition of glucose or oxidation of methionine side chains. Some mammalian cell lines (CHO, NS0) produce carboxypeptidase-B which can cleave the C-terminal lysine residues from antibody heavy chains. Downstream processing could also potentially compromise product integrity by, for example, selectively purifying or enriching a particular PTM product variant. Current developments in mammalian cell culture attempt to address these problems, and include the manipulation of process parameters to minimise glycosylation heterogeneity, and exploring approaches based both on medium manipulation and genetic engineering to prevent or retard apoptosis and thus prolong protein production.

The production of therapeutic monoclonal antibodies is also tightly regulated; the product itself, the batch-to-batch process and the manufacturing plant are all highly scrutinised. Under non-optimal conditions CHO and NS0 cells can produce a number of abnormally glycosylated products that lack potency or are potentially immunogenic and unacceptable as therapeutics.

Non-mammalian production systems capable of carrying out glycosylation include yeast, insect and plant cells. Compared with mammalian cell lines, these cells typically grow to higher cell densities in shorter fermentation cycles and in less expensive and more chemically defined media, and they pose a lower risk of transmitting mammalian pathogens. Although yeast expression systems can produce large amounts of glycosylated protein at fairly low cost, they add sugar side chains of high mannose content. Glycoproteins produced naturally in insect cells display glycosylation patterns that differ significantly from characteristic mammalian patterns. Plants can synthesise human-like complex N-glycans but they cannot make galactose. Glycoproteins produced by plant cells lack sialic acid that characterises human glycoproteins; they also contain specific xylose and fucose residues that tend to be immunogenic in humans.

1.3.3 Protein characterisation

In the past, crude analytical methods based mainly on biological methods often rendered protein characterisation incomplete. *In vivo* studies were the gold standard for safety and efficacy. In recent years, characterisation has been transformed by the advent of a new generation of analytical technologies and bioinformatic tools.

The concept of well characterised biologicals originated from the FDA's Center for Biologics Evaluation and Research (CBER), which first employed the term in 1996. The regulations issued by the FDA in 1996 placed greater emphasis on the methodologies used to analyse protein therapeutics. The term well characterised biological meant that the natural molecular heterogeneity, impurity profile and potency could be defined with a high degree of confidence; this term has recently been replaced by the more precise term specified biological. The Biological License Application (BLA) now requires detailed analytical description of the molecular entity as the vehicle for systematisation of the reproducible manufacture of the biological pharmaceutical.

More detailed protein drug characterisation is now occurring earlier in the

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protein drug development process and it incorporates powerful techniques such as peptide mapping and mass spectrometry. Assays to characterise the final protein product tend to involve high performance liquid chromatography (HPLC), electrophoretic techniques, and biological assays for potency. Extensive protein characterisation studies may be performed for product comparability, release and stability assessment in support of preclinical studies.

Mass spectrometry (MS), coupled with HPLC is perhaps the ultimate analytical tool for a protein, now allowing molecular masses of proteins to be determined to within one Dalton (the atomic mass unit). Traditional electrophoretic methods are being converted from slab gels to capillary electrophoresis. The 2-D approach gives a much cleaner product than 1-D analysis and is useful for exploring PTMs, which is hard to do with other techniques.

Other useful techniques include light-scattering studies, UV/visible spectroscopy and circular dichroism to show correct folding of the protein and its alpha helix and beta sheet content, and microcalorimetry to study binding. Dynamic light scattering (DLS) can reveal the oligomeric state and homogeneity of a protein (monomer, dimer, oligomer, or a mixture of these), which can be important in terms of its clinical application.

Characterisation of the oligosaccharide profile of recombinant glycoproteins forms a crucial element of quality control procedures. Currently, the main analytical methods used include HPLC of released and derivatised oligosaccharides, MS and capillary electrophoresis. Specially developed software can analyse PTMs. For example, Applied Biosystems' MIDAS Workflow software on the 4000 Q TRAP mass spectrometer system performs selective detection and sequencing of PTMs in a single experiment.

With so many different technologies, the trend is towards building a multidimensional assessment of mass, sequence, structure, hydrophobicity and many other different properties.

An effective biological potency assay needs to be developed before a protein product enters clinical trials and this often requires cell-based assays. Often measurement of biological potency is a key measurement of the final active structure, which cannot always be measured by other physico-chemical characterisation methods. A change in the native protein structure can have direct effects on biological potency.

Immunogenicity testing is increasingly carried out at an early stage in product development, to detect antibody formation and neutralisation effects from preclinical studies and onward through clinical trials.

Good analytical data can be used to demonstrate pharmaceutical equivalence in order to support changes to the manufacturing process. It is also required to help show equivalence between products from different batches. In the context of biosimilars, it is likely to be required to show equivalence between a biosimilar and the branded original.

1.3.4 The global market

So far over 140 therapeutic proteins and peptides have been approved by the FDA. They include growth factors (including epoetins and colony

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stimulating factors); coagulation factors, anticoagulants and thrombolytics; insulins; interferons; interleukins; hormones; enzymes; and therapeutic vaccines. In addition, over 20 monoclonal antibody-based products have been approved by the FDA. Most of the mAb approvals have come in the past decade; only two products were approved before 1997.

Of the top 20 top-selling biopharmaceuticals in 2006, 14 were proteins (Table 1.1) and six were intact monoclonal antibodies (Table 1.2). The top-selling therapeutic protein, Amgen's Aranesp, is a hyperglycosylated variant of the company's first-generation recombinant EPO product (Epogen). The top-selling monoclonal antibody, Rituxan (developed by Genentech and Biogen Idec), is a humanised monoclonal antibody that selectively binds to CD20, a protein found on the surface of normal and malignant B cells.

The top 20 products include variants of EPO, insulin, interferons and TNF blockers. EPO is used to treat anaemia caused by renal disease or cancer chemotherapy. IFNs are used as antiviral or multiple sclerosis treatments. TNF blockers are used mainly in rheumatoid arthritis and other autoimmune diseases.

1.4 Biosimilars

In order to succeed, manufacturers of biosimilars will need to demonstrate a sufficient degree of resemblance between their product and the branded original. This is not straightforward, as in many cases neither the manufacturing process nor the end product can be replicated exactly. Products such as monoclonal antibodies and certain therapeutic proteins may be highly dependent on specific proprietary manufacturing systems.

1.4.1 Market drivers and inhibitors

The medical costs of biological therapeutics, which are used for the treatment of chronic illnesses and severe indications are extremely high, and represent a significant portion of the overall healthcare expenditures in Western countries. In the US, many cost more than $20,000 per patient per year, with some costing an order of magnitude more. The rising cost of healthcare expenditures in Europe and North America has initiated a push for lower priced biosimilars.

Many protein therapeutics nearing patent expiry are blockbuster drugs, and represent high revenue potential for new market entrants, even allowing for the fact that market entry-level prices are likely to be below those of the original product.

There is a possibility that non-clinical studies, combined with thorough process evaluation, testing and post-approval studies, will (at least in some cases) be sufficient to obviate concerns related to a shift in production process for a biosimilar product. The hope is that any differences in (or improper modifications of) a biosimilar which might compromise its safety will be detected by currently available *in vitro* analytical tests.

The key opposition to biosimilars comes from the biotech industry itself, which has traditionally enjoyed low levels of competition; indeed, the high success rate of recombinant proteins is attributed to this factor. Therefore, the advent of biosimilars is expected to have a negative impact on the current pricing scheme of biotherapeutics. In the US, the biotech industry is currently lobbying to retain requirements for a full approval process,

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including extensive clinical trials for safety and efficacy. Manufacturers of branded products may also fight back by creating improved, patented versions of their expired biotherapeutics, enabling them to maintain their premium pricing within a market open to biosimilars.

If extensive clinical trials prove to be necessary, this will create a barrier to entry for biosimilars, as development/marketing costs will be much higher than for small molecule generics (estimated at around $5-15 million *vs* $1-5 million). A high level of investment in manufacturing processes (in excess of $250 million) may also be needed in order to ensure the safety and efficacy of a biosimilar.

1.4.2 The INN nomenclature system

International Nonproprietary Names (INN) identify pharmaceutical substances or APIs. Each INN is a unique name that is globally recognised and is public property. A nonproprietary name is also known as a generic name. Under the current system, traditional generic versions of drugs based on chemical compounds are identical to the reference product and all generic versions of a branded drug are given the same INN.

The World Health Organization (WHO) is currently reviewing the INN nomenclature system with the aim of addressing the increasing complexity of biological medicines. In some areas, such as monoclonal antibodies, the science is advancing so quickly that the current naming system may not be able to keep up. The INN expert group is expected to come up with some recommendations in the latter part of 2007.

Biological products already in the INN nomenclature system include blood and transgenic products, recombinant proteins and glycoproteins, and monoclonal antibodies. Glycosylated proteins have a stem, such as epoetin, with a random prefix to indicate differences in amino acid sequence (eg. darbepoetin) and a Greek letter (alfa, beta, etc.) to show differences in glycosylation. The monoclonal antibody (mAb) naming system is very complex. There is a general stem (mab) as well as a sub-stem indicating the source (eg., -u- or -zu- for human products and -xi for chimeric products), plus another sub-stem for the disease or target (eg. -li(m)- for immunomodulators and -tu(m)- for miscellaneous tumours). Examples include sevirumab, erlizumab and trastuzumab.

In November 2006, the WHO held a meeting with industry groups, at which originator companies took the view that biosimilars should have a unique INN to distinguish them from the reference product, while generics companies took the opposite view. The Biotechnology Industry Organization (BIO), which represents more than 1,100 biotech companies worldwide, argued that because each biological product is unique, patients could respond to biosimilars differently than they do to the innovator product. Tracing any adverse events to the correct manufacturer would be greatly facilitated if all biological medicines had a distinct INN, the group said. In unison with BIO, five other trade associations – the European Biopharmaceutical Enterprises, EFPIA, EuropaBio, the International Federation of Pharmaceutical Manufacturers and PhRMA also lobbied the WHO on this issue.

The FDA, however, argues that changes to the current INN system are unnecessary and that the only way to establish pharmacologic interchangeability is through scientific data. In addition, the FDA does not

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consider the proposed change to the INN policy for the naming of biosimilars to be necessary to prevent inappropriate substitution in the US. The generics industry, represented by the European Generic Medicines Association (EGA) and the Generic Pharmaceutical Association (GPhA) in the US, strongly support the FDA's stance and have branded the biotech industry's complaints as commercially motivated and designed to hinder attempts to get biosimilar drugs on the market.

1.5 Biosimilars regulation

Regulation is a key area that will determine the rate of growth of the biosimilars market. Since the chemical differences between a branded product and a biosimilar are likely to result from the manufacturing processes involved, discussions centre around the issue of whether the manufacturing process really is the product. Although the regulatory framework for biosimilars is more defined in Europe, the US is also believed to be moving toward standardised pathways, although this is a slow and evolving process.

1.5.1 The EU position

Europe has the lead over the US in the development of biosimilars. In February 2006, after several early iterations that tried to define a path to approval for biosimilars, the EMEA and its Committee for Medicinal Products for Human Use (CHMP) released final guidelines providing a rigorous assessment of the quality, safety and efficacy requirements for biosimilar products.

The EMEA guidelines for novel production processes for biosimilars suggest that potential applicants should demonstrate consistency and robustness of the manufacturing process. Moreover, these guidelines indicate that, in addition to *in vitro* testing and pharmacokinetic studies, clinical trials will likely be required to compare the potential biosimilar to the reference product. Other published papers suggest that non-clinical studies are unsuitable for showing similarity and clinical studies comparing the biosimilar to the original biotherapeutic are necessary. However, the published EMEA guidelines also state that clinical studies are not required if *in vitro* characterisation of the protein can demonstrate similarity to the original reference drug.

For alterations to a manufacturing process, the EMEA approaches this issue on a case-by-case basis, and each company must track all changes within a pharmacovigilance database. Pharmacovigilance is the detection, assessment, understanding and prevention of adverse events post-market launch. EMEA guidelines state that a comprehensive pharmacovigilance plan should be submitted with the original data package and that the plan should be established upon product approval. Although voluntary by the manufacturer, pharmacovigilance should be of interest to guarantee quality, safety and efficacy of a biosimilar product.

The EU framework offers a 10-year period for innovator exclusivity, with the opportunity for an additional year for new indications. However, it is unlikely that biosimilar approvals will be easily obtained from the EMEA. The Swiss company Biopartners discovered this when the licensing authority rejected its interferon alpha for insufficient data regarding safety and effectiveness.

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1.5.2 US pathways

Innovative protein products can be brought to the US marketplace via either of two major regulatory pathways – the New Drug Application (NDA) pathway and the Biological License Application (BLA) pathway.

The NDA pathway was established in 1938 by the Food Drug and Cosmetic Act (FD&C Act). This pathway applies to products that are classified as drugs according to the FD&C Act definition. This definition of drug is quite broad and applicable to virtually any conceivable pharmaceutical product.

The Public Health Services Act (PHSA), later amended by the Food and Drug Administration Modernization Act of 1997, provides an alternative regulatory pathway for pharmaceuticals classified as biological products. Such products are licensed, but not approved. The PHSA defines biological product as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine, applicable to the prevention, treatment, or cure of a disease or condition of human beings". The FDA has classified some recombinant protein products as drugs and others as biological products.

The original mechanism for the approval of generic drugs followed from the NDA pathway. Under the FD&C Act, a number of routes to approval for generics were created that assumed that small molecule drugs could be more or less identical to reference compounds approved under the standard section 505(b)(1). These regulatory paths included the 505(b)(2), and the 505(j) or ANDA. Drugs approved under a 505(b)(2) application have a right of reference to clinical results from the original product, but require support from clinical trial data to show that the drug is efficacious, while drugs approved under an ANDA application only need to demonstrate that the drug is stable and is handled similarly by the body (bioequivalence).

The FDA defines a follow-on biologic (FOB) as "a protein product which is intended to be a similar version or duplicate of an already approved or licensed protein product". The road to FDA approval has been very challenging for FOB proteins, and much more hotly contested than in Europe. Although US patent protection for several biologicals currently going off-patent in Europe is in place until the beginning of the next decade, the FDA has been considering its guidance for FOB developers and manufacturers for some time.

When Sandoz filed an application for the follow-on human growth hormone product Omnitrope, it was thought that this product might represent a template for future approvals. After almost three years of debate, including legal action, the product received FDA-approved labelling in 2006. However, the FDA explicitly articulated that the product is not a generic biologic, is not therapeutically equivalent to the innovator product, and does not represent a pathway for future approvals. Nevertheless, its approval of Omnitrope demonstrated that the simplified approval process (505 (b)(2) pathway) may be available to biosimilars that demonstrate comparability with biologics regulated under NDAs. The key issue for the US market, therefore, relates to biologics regulated under BLAs rather than NDAs.

1.5.2.1 Government initiatives

Based on the assumption that biosimilars are 10-25% cheaper than branded biologics, savings under the Medicare Part B program that would result from

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the introduction of biosimilars have been valued at $14 billion over 10 years. And driven by the need for cheaper biologic drugs, the US government is seeking ways in which to expedite the approval of FOBs.

The first step towards this goal was taken in February 2007 with the introduction of Bill H.R.1038 entitled 'The Access to Life-Saving Medicine Act', which stated that any person may file a comparable biological product application provided that it includes data demonstrating comparability to the original biotherapeutic with respect to: molecular structure (allowing for minor differences); mechanism of action; dosing regimen; therapeutic strength; and biological manufacturing/processing standards.

The bill was strongly opposed by BIO, as well as some high-profile politicians from both parties. Public statements from BIO indicated that it would support a proposal that is similar to that implemented in the EU, which requires a significant R&D investment in order to demonstrate comparable and similar safety and efficacy data to that of the reference product. In particular, testing for immunogenicity was considered to be of utmost importance.

In June 2007, the US Senate Health Committee passed landmark legislation creating an approval pathway for biosimilars. The Biologics Price Competition and Innovation Act (S 1695) would give innovator companies 12 years of marketing protection for new biologicals and allow the FDA to approve biosimilars that are interchangeable with the reference product. The first interchangeable biosimilar that is approved for a given reference product would receive one year of market exclusivity.

Biosimilar applicants would have to provide one or more clinical studies to demonstrate that there are no clinically meaningful differences from the reference product, although the FDA could waive this requirement. The measure also outlines a multi-step process aimed at early identification and resolution of patent disputes.

Under the approval process laid out in the bill, biosimilarity to a reference product would have to be demonstrated through analytical data, animal testing and one or more clinical studies, including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics. However, the FDA could determine that these requirements are unnecessary.

For a determination on interchangeability, the applicant would have to demonstrate that the biosimilar will produce the same clinical results as the brand product in any given patient, with no additional risk in terms of safety or diminished efficacy if a patient is switched back and forth between products. Both BIO and the Massachusetts Biotechnology Council (MBC) objected to the interchangeability provisions. They said Congress should ensure that patients are not given biosimilars unless expressly prescribed by a physician.

A biosimilar could not be approved until 12 years after the date on which the reference product was first licensed. The bill's co-sponsors made a late revision to ensure that the 12 years of protection apply only to truly innovative products, or those that would be analogous to new chemical entities. Supplemental applications or new BLAs for a new indication, route of administration, dosage form or strength for a previously licensed reference product would not trigger an additional 12 years of protection.

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The generics trade group GPhA called the 12-year period arbitrary, excessive, unprecedented and unwarranted. In contrast, BIO reiterated its belief that 14 years is the appropriate duration for innovator exclusivity.

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Table 1.1: Leading protein products in 2006

Rank	Product	Type	Company	Therapy area	Sales ($ million)	%	CAGR (%)
1	Aranesp	EPO	Amgen	Haematology/ Oncology	4,733	7.1	14.6
2	Enbrel	TNF antagonist	Amgen/Wyeth/ Takeda	AIID	4,169	6.2	13.7
3	Procrit/Eprex	EPO	Johnson & Johnson	Oncology	2,933	4.4	-16
4	Epogen	EPO	Amgen	Haematology	2,627	3.9	2.3
5	Neulasta	G-CSF	Amgen	Oncology	2,573	3.8	10.4
6	Pegasys*	IFN-alpha-2a	Roche/Chugai	Infectious disease	1,995	3	11.1
7	Novolin	Insulin	Novo Nordisk	Diabetes & endocrinology	1,983	3	-10
8	NeoRecormon	EPO	Roche	Oncology/ other	1,852	2.8	-10
9	Lantus	Insulin	Sanofi-Aventis	Diabetes & endocrinology	1,639	2.4	5.4
10	Avonex	IFN-beta-1a	Biogen Idec	CNS	1,590	2.4	0.9
11	Intron	IFN-alpha-2b	Schering-Plough	Infectious disease	1,357	2	5.1
12	Rebif	IFN-beta-1a	Pfizer/Serono	CNS/other	1,344	2	1
13	Humalog	Insulin	Lilly	Diabetes & endocrinology	1,129	1.7	1.1
14	Beta(f|s)eron	IFN-beta-1b	Chiron/ Schering AG	CNS	1,115	1.7	-1
Subtotal					31,039	46.2	--
Other proteins and mAbs					36,090	53.8	--
Total					**67,129**	**100**	**9.8**

** Often used in combination with Copegus (ribavirin)*

Source: Biophoenix/Datamonitor

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Table 1.2: Leading monoclonal antibody products in 2006

Rank	Product	Type	Company	Therapy area	Sales ($ million)	%	CAGR (%)
1	Rituxan/ MabThera	Anti-CD20	Roche/Biogen Idec/Chugai	Oncology/AIID	4,723	7	8
2	Remicade	Anti-TNF	Johnson & Johnson/ Schering-Plough/Tanabe	AIID	4,020	6	6
3	Herceptin	Anti-HER2	Roche/Chugai	Oncology	2,209	3.3	7.6
4	Avastin	Anti-VEGF	Chugai/Roche	Oncology	1,758	2.6	23
5	Humira	Anti-TNF	Abbott	AIID	1,574	2.3	18
6	Synagis	Anti-RSV	Medimmune/ Abbott	Infectious disease	1,142	1.7	-16
Subtotal					**15,426**	**23**	**--**
Other proteins and mAbs					51,703	77	--
Totals					**67,129**	**100**	**9.8**

Source: Biophoenix/Datamonitor

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CHAPTER 2
PRODUCT OVERVIEW

2.1 Introduction

For a branded protein pharmaceutical product to have any value to a potential biosimilar manufacturer, it must present an adequate potential for economic return to justify the significant investment required. A number of high-selling branded products have already been targeted by biogeneric developers and several approvals of follow-on/biosimilar products have already taken place.

2.1.1 Approved follow-on proteins/biosimilars

The FDA has approved certain follow-on biologic (FOB) products in applications described in section 505(b)(2) of the FD&C Act. These products demonstrated comparability with biologics regulated under New Drug Applications (NDAs).

The first FOB was a hyaluronidase product approved for marketing in 1948. The hyaluronidases are enzymes that break down hyaluronic acid and chondroitin. Hyaluronidase injection is indicated for use to increase the absorption and dispersion of other injected drugs and for related uses. Most hyaluronidase products are natural source proteins, purified from mammalian testicles, whose amino acid sequences vary based on the species and the tissue from which it is obtained. There may also be variability within the same tissue source. The FDA initially approved follow-on versions of mammalian testicular hyaluronidase (ovine and bovine) and has more recently approved a human recombinant hyaluronidase follow-on product. No hyaluronidase product is rated by the FDA as therapeutically equivalent (substitutable) to any other approved hyaluronidase product.

Although Ferring Pharmaceuticals had basic patent protection on its peptide DDAVP (desmopressin) until 2008, a successful patent challenge was followed by the US launch of a follow-on product by Barr Pharmaceuticals in July 2005.

The FDA has approved a follow-on recombinant glucagon, Zymogenetics' GlucaGen; and a follow-on recombinant somatropin (human growth hormone), Sandoz's Omnitrope. In August 2005 the FDA approved Unigene's Fortical (recombinant salmon calcitonin) as a follow-on to Novartis's Miacalcin (which is synthetic salmon calcitonin), even though Miacalcin's patents will not expire until 2015.

In 2003 the FDA also approved a biologic (Biogen Idec's recombinant interferon-beta Avonex) on the basis of clinical data that were transferred between two manufacturers, which were not in competition with each other. The second manufacturer (Biogen) demonstrated that its product was indistinguishable from that of its partner Bioferon (a German company in which Biogen held 50% of the equity), which had manufactured the earlier batches of the product. The FDA allowed the clinical data generated with Bioferon's product to be transferred to Biogen's drug because process comparability had been demonstrated.

In February 2006, the EU approved Sandoz's Omnitrope, hailed by the company as the world's first biosimilar drug. In June 2007, three biosimilar

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recombinant human erythropoietin (epoetin-alfa) products received approval recommendations in the EU: Sandoz's Binocrit, Hexal Biotech's Epoetin alfa Hexal, and Medice Arzneimittel Putter's Abseamed.

2.2 Characteristics of high-selling peptides and proteins

Tables 2.1-2.5 list branded peptide and protein therapeutics launched on the US market which achieved global sales of at least $20 million in 2006. These high-selling products represent plausible target products for FOB/biosimilar development. Since it is generally acknowledged that targets for biosimilars should be well characterised, or at least well characterisable, products such as blood-derivatives, vaccines and toxoids, toxins and antitoxins, and digestive enzyme preparations were not included.

The high-selling products are presented in Tables 2.1-2.5 in ascending order of the number of amino acids in unique sequences in the product. This order roughly approximates ascending order of product complexity. They are also grouped according to the presence or absence of glycosylation, US filing mechanism (NDA or BLA), and expression system (in the case of recombinant products).

2.2.1 Products with expired patents

The basic patents covering the target products listed in Tables 2.1-2.5 are listed in Tables 2.6-2.10, together with information on priority country and priority dates. A number of protein and peptide targets are already available for FOB/biosimilar development, as the main patents protecting these patents have expired. Patents which have expired or are about to expire are shown in bold face in these tables.

It should be stressed that patent expirations are not clear-cut in the area of biologics. In order to market proprietary versions of currently marketed proteins, it is necessary to determine the expiration dates of existing patent claims that could cover a product candidate by analysing numerous, complex patent claims and, in some cases, judicial opinions.

The analysis of patents is subject to different interpretations. For example, Genentech's US patents relating to microbial production of proteins including human growth hormone (Nutropin) expired in 2003, but Genentech has numerous patents on its various somatropin formulations expiring at various times through to mid-2015. A similar situation exists with Genentech's Activase (tissue plasmigen activator). Genentech has several issued US patents that cover purified tPA protein, DNA-encoding tPA, and basic recombinant DNA processes for making tPA. Those patents expired from mid-2005 through to mid-2006. The company also has many US patents that cover particular technology that may be used in the manufacture or formulation of tPA, and those patents expire at various times through to late 2015.

2.2.2 Challenging originator's patents

In the US, the submission of an ANDA for a drug product claimed in a patent is an infringing act if the generic product is intended to be marketed before expiration of the patent. An incentive of 180 days of market exclusivity is provided to the first generic applicant that challenges a listed patent and thus runs the risk of having to defend a patent infringement suit.

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Challenging the patents covering certain brand products is a strategy employed by a number of generics companies. For example, in July 2005, the FDA approved first-time generic desmopressin acetate tablets made by Barr Pharmaceuticals, the generic equivalent of Ferring's DDAVP tablets (see later). Ferring manufactures DDAVP for Sanofi-Aventis, which markets the product in the US. Barr launched desmopressin acetate tablets following a district court ruling that applicable DDAVP patent was unenforceable and therefore not infringed. After Barr's 180-day exclusivity period ended, two additional competitors launched generic versions of DDVAP.

2.3 Target products for FOB/biosimilar development

High-selling branded products listed in Tables 2.1-2.5 will be discussed in this section in the context of other commercial products on the market and in development worldwide based on the same (or similar) active ingredient. This information, derived from *Pharmaprojects*, has been collated in order to provide the reader with a snapshot of the commercial landscape relevant to each target product (or group of related target products) and to highlight related or improved products which may themselves become targets for biosimilar development. Further information is provided in Tables 2.11-2.13.

Most biosimilars are likely to target comparatively well established categories with several existing branded products, where potential problem areas have already been identified. This approach minimises the risks involved with introducing new products, so it might be possible to run safety and efficacy trials using smaller numbers of patients.

Tables 2.14-2.60 provide information on each target product (or group of related products), including next-generation target products, competing branded products, products with engineered enhancements (such as increased plasma half-life) and products formulated for improved or non-injectable delivery. High sales volume products from Tables 2.1-2.5, ie. those with sales exceeding $20 million worldwide in 2006, are highlighted.

2.4 Peptides (NDA Pathway)

Peptides are generally less than 40 amino acid residues in length. Three major synthetic strategies for a peptide are: chemical (both solid-phase and solution-phase); biochemical (eg. fermentation); and recombinant DNA technology. Chemical synthesis is currently the most common approach to the production of peptides.

Table 2.1 lists natural, synthetic and recombinant peptides which have been approved through the NDA pathway. The first four products (sections 2.4.1-2.4.4 below) are the only products described in this chapter to have been listed in the FDA's 'Approved Drug Products with Therapeutic Equivalence Evaluations' (the Orange Book).

2.4.1 Octreotide

(Table 2.31)

Novartis's Sandostatin (octreotide) is an octopeptide that mimics natural somatostatin (growth hormone inhibiting hormone) pharmacologically, though it is a more potent inhibitor of growth hormone, glucagon and insulin than the natural hormone. Somatostatin has two active forms produced by alternative cleavage of a single preproprotein; one of 14 amino

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acids, the other of 28 amino acids. Sandostatin is indicated for the treatment of acromegaly, carcinoid syndrome and vasoactive intestinal peptide-secreting tumors. Although Sandostatin's basic patent protection has expired, Sandostatin LAR (long-acting) has patent protection to 2013 and beyond in the US. A number of companies are developing improved formulations of octreotide.

2.4.2 Desmopressin

(Table 2.32)

Ferring Pharmaceuticals' DDAVP (desmopressin) mimics the action of antidiuretic hormone and is indicated for use in the treatment of primary and nocturnal enuresis and diabetes insipidus. A number of formulations of desmopressin (sublingual and oral) are in development.

2.4.3 Cyclosporine

(Table 2.18)

Novartis's Neoral/Sandimmune (cyclosporine) is a peptide produced by the fungus *Tolypocladium inflatum*. Cyclosporine has been in use since 1983 and is one of the most widely used immunosuppressive drugs in organ transplantation, although it has a number of undesirable, often serious side-effects. Sandimmune is an immediate-release capsule, while Neoral is a microemulsion-forming formulation that minimises intraindividual absorption variability. Novartis is investigating an aerosolised cyclosporine formulation in lung transplantation. Several synthetic cyclosporine analogues are in development. Various formulations of cyclosporine are on the market or in development (including topical, oral, inhalable and implantable products).

2.4.4 Calcitonin

(Table 2.21)

Novartis's Miacalcin (salmon calcitonin) is a 32 amino acid polypeptide hormone that resembles human calcitonin, except that it is more active. Calcitonin is produced in humans primarily by the thyroid gland and is mainly known as a potent inhibitor of osteociastic bone resorption, which implicates bone attachment of osteoclasts and enzymatic degradation. Miacalcin is used primarily in the treatment of postmenopausal osteoporosis. Products on the market and in development include synthetic and recombinant calcitonin products for parenteral, nasal or oral delivery. Vasogenix has a calcitonin gene-related peptide in development.

The specific formulation of Novartis's synthetic Miacalcin product is covered by patents, which will expire in the US in 2015. Two companies have applied to the FDA for the right to sell a generic version of Miacalcin based on a different formulation. Unigene's Fortical (recombinant salmon calcitonin) nasal spray was approved in August 2005 as a follow-on product. In July 2006 the FDA turned down Nastech's generic version of Miacalcin. The regulator expressed concerns about the potential for immunogenicity that might result from a possible interaction between calcitonin, derived from salmon, and chlorobutanol, the preservative in Nastech's formulation which is also used in many nasal sprays already on the market. Theoretically, an interaction between calcitonin and chlorobutanol may lead to allergic reactions, although no allergic reactions have been observed in

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any of the clinical trials conducted by Nastech. The reason the company decided to use a different preservative from benzalkonium chloride (BKC) – which Novartis uses in the branded version of the drug – is because of the discomfort BKC can create and possible adverse effects on the nasal mucosa, a particularly strong concern in Europe.

2.4.5 Eptifibatide

(Table 2.52)

Integrilin (eptifibatide), jointly developed by Millennium Pharmaceuticals and Schering-Plough is a synthetic cyclic heptapeptide that blocks the platelet receptor GP IIb/IIIa. It is indicated for the treatment of acute myocardial infarction (MI), unstable angina and other diseases associated with arterial thrombosis.

2.4.6 LHRH

(Table 2.22)

Human luteinising hormone-releasing hormone (LHRH) acts primarily on the anterior pituitary, inducing a transient early rise in gonadotrophin release. With continued use, LHRH analogues cause pituitary desensitisation and/or down-regulation, leading to suppressed circulating levels of gonadotrophins and sex hormones. LHRH agonists are used to treat a wide range of sex hormone-related disorders including advanced prostatic cancer, endometriosis and precocious puberty.

The LHRH analogues leuprolide (Takeda's Lupron and QLT/Sanofi-Aventis's Eligard) and goserelin (AstraZeneca's Zoladex) are potent inhibitors of gonadotropin secretion. Lupron went off-patent in 2004, while Zoladex went off-patent in the US in 2005. Eligard, a six-month sustained release leuprolide formulation, was approved by the FDA for the palliative treatment of advanced prostate cancer in 2004. Several novel formulations of leuprolide are in development, including implantable, nasal and oral forms. Mediolanum's Avorelin is a novel LHRH analogue in development.

2.4.7 Bivalirudin

(Table 2.37)

Hirudin is a naturally occurring protein with a blood anticoagulant property that is found in the salivary glands of medicinal leeches (*Hirudo medicinalis*). It is difficult to extract large amounts of hirudin from natural sources. Direct thrombin inhibitors are derived chemically from hirudin. Angiomax (bivalirudin) is a synthetic eicosapeptide derived from hirudin, developed by The Medicines Company.

2.4.8 Enfuvirtide

(Table 2.39)

Trimeris/Roche's Fuzeon (enfuvirtide) is a 36 amino acid synthetic peptide HIV-1 inhibitor. Fuzeon has established a benchmark for the production of longer, more complex peptide drugs by chemical synthesis.

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2.4.9 Glucagon

(Table 2.40)

Glucagon is an important peptide hormone involved in carbohydrate metabolism. Produced by the pancreas, it is released when the glucose level of the blood is low (hypoglycaemia), causing the liver to convert stored glycogen into glucose and release it into the bloodstream. Glucagon is used to quickly increase blood sugar levels in diabetics with hypoglycaemia. Two leading recombinant glucagon products are Lilly's Glucagon and Zymogenetics' GlucaGen. GlucaGen is marketed by Novo Nordisk and was launched in the US in 1999, following its approval as a follow-on protein product.

2.4.10 Nesiritide

(Table 2.57)

Johnson & Johnson's Natrecor (nesiritide) is a recombinant brain natriuretic protein (BNP) product. BNP has a 32 amino acid ring structure. First discovered in the early 1990s, BNP was rapidly validated as a marker of haemodynamic stress. Rising BNP levels indicate left ventricular dysfunction, which precedes the onset of symptoms of cardiac dysfunction in congestive heart failure (CHF). BNP is found in increasingly higher levels as disease progression occurs. In 2001, Natrecor became the first new therapy for acute CHF to be approved since 1987.

2.4.11 Teriparatide

(Table 2.35)

Lilly's Forteo (teriparatide) is a recombinant active fragment (residues 1-34) of human parathyroid hormone (PTH). PTH is secreted by the parathyroid glands as a polypeptide containing 84 amino acids. It plays a significant role in bone formation and bone maintenance. Forteo is indicated for the treatment of osteoporosis in postmenopausal women who are at high risk of having a fracture. Several novel formulations of teriparatide are under development, including an oral formulation using Emisphere's oral drug delivery system, and two inhaled formulations (from Nektar Therapeutics and Alkermes).

2.5 Recombinant non-glycosylated proteins (NDA Pathway)

Table 2.2 lists non-glycosylated protein products, which have been approved through the NDA pathway. All but one (somatropin) of these products are produced in non-mammalian expression systems.

2.5.1 Insulin

(Table 2.15)

Insulin is a naturally-occurring small protein hormone secreted by the pancreas that regulates carbohydrate metabolism. Insulin is used to treat some forms of diabetes mellitus. Patients with type 1 diabetes mellitus depend on external insulin for their survival because of the absence of the hormone. Patients with type 2 diabetes mellitus have insulin resistance, relatively low insulin production, or both, and may require insulin when

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other medications become insufficient in controlling blood glucose levels.

Insulin is traditionally administered by subcutaneous injection. Regular insulin has an onset of action within 30 minutes of injection, it reaches a peak effect at 1-3 hours, and its effects last for 6-8 hours. However, unmodified insulins tend to complex with zinc in the blood, forming hexamers. Hexameric insulin is not readily available for the body when insulin is needed in large doses, such as after a meal.

Genetic modifications have been used to create two types of insulin, one that is faster acting and more bioavailable than natural insulin, to supply the level of insulin needed after a meal, and one that is less bioavailable, and released more slowly over a 24-hour period to supply the basal level of insulin for the day.

Non-hexameric insulins were developed to be faster acting and to replace the injection of normal unmodified insulin before a meal. Eli Lilly's Humalog was the first rapid-acting insulin analogue. It was engineered so that the penultimate lysine and proline residues on the C-terminal end of the B-chain were reversed in order to block the formation of insulin dimers and hexamers. Novo Nordisk's Novolog rapid-acting insulin analogue has a single amino acid substitution, while Sanofi-Aventis's Apidra has two amino acid substitutions.

A strategy to prolong insulin absorption involves the substitution and/or addition of basic amino acid residues to elevate the isoelectric point of the insulin. When an acidic solution enters the neutral pH subcutaneous tissue, insulin molecules crystallise, retarding absorption of the insulin into the circulation. These insulin analogues are used to replace the basal level of insulin, and are effective over a period of about 24 hours. Aventis's Lantus was created by modifying three amino acids.

Best-selling insulin products (Table 2.2) include two human recombinant unmodified insulins – Lilly's Humulin and Novo Nordisk's Novolin; both are now off-patent. Humulin is expressed in bacteria, while Novolin is expressed in yeast. Lilly recently discontinued intermediate-acting Humulin formulations (Humulin L and Humulin U) stating the reasons to be declining sales and the creation of better insulin therapies over the past few decades. Table 2.2 also includes the more costly insulin analogues that still enjoy patent protection – Lilly's Humalog and Novo Nordisk's Novolog (fast-acting analogues) and Sanofi-Aventis's Lantus (long-lasting analogue).

Other human insulin products on the market include unmodified recombinant products; engineered recombinant insulin analogues – Aventis's fast-acting Apidra, and Novo Nordisk's long-lasting Levemir; semi-synthetic insulins (from Sanofi-Aventis, Zymogenetics, Akzo Nobel, Novo Nordisk), an inhalable formulation (Pfizer and Nektar Therapeutics' Exubera) and a buccal formulation (Generex's Oralin).

The trend towards replacing unmodified insulin with engineered analogues is set to continue. In development there are fast-acting (for example, Biodel's VIAject) and long-acting (for example, Flamel Technologies' product condidate) analogues. Another trend set to continue is the development of new and improved methods for the delivery of insulin. Many formulations for pulmonary, nasal, oral, sublingual and transdermal insulin delivery are in various stages of development. It is anticipated that as new delivery technologies (in particular pulmonary delivery) replace traditional injection

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methods, they will require a greater supply of insulin due to the increased dosing requirement of inhaled products. Sembiosys Genetics is developing transgenic (plant-produced) insulin to supply this expanding market.

2.5.2 Somatropin

(Table 2.28)

Recombinant human growth hormone (hGH) is known as somatropin (somatotropin). Human growth hormone is a 191 amino acid, single-chain, non-glycosylated polypeptide hormone which is synthesised, stored and secreted by the pituitary gland. It stimulates growth and cell reproduction. Recombinant human growth hormone is indicated for the long-term treatment of paediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone, and for long-term replacement therapy in adults with growth hormone deficiency of either childhood or adult onset.

Table 2.2 lists five best-selling somatropin products available in the US (and their manufacturers): Nutropin (Genentech), Humatrope (Lilly), Genotropin (Pfizer), Norditropin (Novo Nordisk) and Saizen (Serono). The products are nearly identical in composition, efficacy and cost, varying primarily in the formulations and delivery devices. Patents on these products have either expired or face imminent expiry in the US (although Norditropin's patent runs until 2015).

Sanofi-Aventis's somatropin product is available on the French market. There are also a number of somatropin products on markets outside the US and the EU, such as those sold by Dong-A and LG Life Sciences. In 2005 Teva of Israel offered Tev-Tropin (licensed from Ferring) in the US at a lower price. Cangene and Daewoong have recombinant hGH products in pre-registration. Products in development include hGH variants, PEGylated hGH, and various formulations including long-acting conjugates, extended-release and sustained-release formats. Emisphere Technologies has an oral hGh preparation in development.

In February 2006, the EU approved Sandoz's Omnitrope and this was quickly followed by a second EU biosimilar approval, for Biopartners' Valtropin. Omnitrope is a similar of Pfizer's Genotropin, while Valtropin is a similar of Lilly's Humatrope.

In June 2006 Omnitrope was also approved as a follow-on product by the FDA. Sandoz performed four small clinical trials, relying on Omnitrope's similarity to Pfizer's Genotropin to get the product's approval. However, Sandoz had also carried out extensive animal testing, which allowed the FDA to conclude: "...despite their differences, Omnitrope and Genotropin are highly similar in their clinical effects". And because of this clear similarity, the FDA also relied on its previous "finding of safety and effectiveness for Genotropin to support approval of Omnitrope."

The FDA has stated that hGH has several characteristics that enable one rhGH product to be adequately compared to another for purposes of approval under section 505(b)(2) of the Act. For example: hGH is well characterised and non-glycosylated; the primary structure of hGH is known, and physicochemical tests exist for the determination of an hGH product's secondary and tertiary structures; clinically relevant bioassays and qualified biomarkers are available for hGH; hGH has a long and well documented

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history of clinical use as a replacement for endogenous growth hormone deficiency; hGH's mechanism of drug action is known, and its human toxicity profile is well understood.

2.5.3 Lepirudin

(Table 2.37)

Hirudin is a naturally occurring protein described in section 2.4.7. The problems associated with extracting large quantities from natural sources have led to the development and marketing of a number of hirudin-based anticoagulant pharmaceutical products such as Bayer's recombinant Refludan (lepirudin) (see Table 2.2). Another recombinant hirudin-derived product on the market is Novartis's Desirudin (desulfatohirudin).

2.6 Recombinant non-glycosylated proteins (BLA pathway)

Table 2.3 lists some non-glycosylated protein products, which have been licensed through the BLA pathway.

2.6.1 Interleukin-2

(Table 2.23)

Two recombinant interleukin-2 (IL-2) products appear in Table 2.3. Novartis's Proleukin (aldesleukin), is indicated for the treatment of melanoma and renal carcinoma. However, the side-effects of this product can often be severe, particularly when high doses of IL-2 are administered. Ligand Pharmaceuticals' Ontak (denileukin diftitox) is a recombinant fusion protein comprising diphtheria toxin fragments and an IL-2 fragment, approved for the treatment of cutaneous T-cell lymphomas. Ontak directs the cytocidal action of diphtheria toxin to cells, which express the IL-2 receptor.

Native IL-2 is a powerful immunostimulatory glycosylated cytokine produced by lectin- or antigen-activated T cells. It mediates its effects through ligand-induced hetero-trimerisation of three IL-2 receptor subunits. IL-2 stimulates the growth and activity of many immune cells, such as lymphocytes. It may induce T cell-mediated tumour regression in some tumour types.

Although non-glycosylated interleukin-2 produced in *E.coli* appears to have full biological activity, proper refolding of the recovered protein and the potential for altered pharmacokinetics have been areas of concern.

Another non-glycosylated recombinant IL-2 product was launched by Roche in the US for the treatment of renal cancer. Several recombinant IL-2 products are sold in Japan and some other countries outside the US and the EU. It is worth noting that in 2002, a US patent describing a method for the production of glycosylated recombinant IL-2 in mammalian cells was issued to Bayer.

IL-2-based products in clinical and preclinical development include many engineered recombinant proteins, for example Bayer's IL-2 engineered to have reduced natural killer cell activation activity, Bayer's IL-2-L19 fusion protein, and Merck KGaA's IL-2-mAb fusion protein. Aplagen's IL-2 mimetic peptide may avoid the toxic effects associated with currently available recombinant IL-2. Cel-Sci's natural IL-2 product and Flamel Technologies'

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nanoparticle IL-2 formulation are also in development.

2.6.2 Interferons

Many of the products listed in Table 2.3 are recombinant interferons. Natural interferons (IFNs) appear early after viral infection locally and systematically to limit the spread of viral infection. They also affect cell differentiation, growth, surface antigen expression and immunoregulation. There are three naturally occurring interferons: alpha, beta and gamma.

Interferon is classified into type I interferon, including interferon-alpha/-beta, and type II interferon, including interferon gamma. Interferon-alpha is derived from either B lymphocytes or macrophages, interferon-beta is derived from fibroblasts and interferon-gamma is derived from T lymphocytes.

IFN-alpha and IFN-beta signal through the common cell surface IFN-alphabetaR. IFN-alpha and IFN-beta interferons orchestrate the immune system's attack on viruses, slowing or blocking their growth or function. The side-effects associated with interferons are predominantly flu-like symptoms occurring in nearly 50% of patients. IFN-alpha is the type most widely used in cancer treatment, although IFN-beta and IFN-gamma are also under investigation.

Type I interferons up-regulate the expression of MHC I proteins, allowing for increased presentation of peptides derived from viral antigens. Type I interferons also induce the synthesis of several key antiviral mediators. IFN-alpha and IFN-beta also enhance macrophage antibody-dependent cytotoxicity and modulate cytokine production by macrophages. Type I interferons produced by macrophages enhance phagocytosis and the induction of iNOS, the enzyme that produces the antimicrobial compound nitric oxide. Type I interferons also have anti-proliferative activity for many cell types.

2.6.2.1 Interferon-alfa

(Table 2.14)

Human interferons-alpha exist as many subtypes (there are probably more than 26). Chemically they are quite closely related, but each one has a unique chemical composition and its own set of biological properties. Preparations of interferon-alpha derived from stimulated peripheral blood leukocytes or lymphoblastoid cell lines contain mixtures of these sub-types. The biological significance of the existence of multiple IFN-alpha subtypes is unknown but may represent a finely tuned mechanism whereby different subtypes are produced in response to different stimuli.

IFN-alpha subtypes have been shown to have two disulfide bonds in common. Human interferon-alpha does not contain an N-type glycosylation site, but wild type mature protein contains an O-type glycosylation site.

IFN-alpha has a number of therapeutic applications in the treatment of various human cancers and diseases of viral origin. Recombinant IFN-alphas from both natural and synthetic genes bind to a common cell surface receptor and induce anti-viral activity in a variety of cell lines. IFN-alpha, in particular the IFN-alpha-2 subtype (which exists in 3 forms: alpha-2a, alpha-2b and alpha-2c) remains the most frequently used IFN for clinical

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applications. It was first approved for combating malignancies. Anti-viral applications such as chronic hepatitis B and C now make up the bulk of sales.

Launched IFN-alpha products include four recombinant products listed in Table 2.3 which are already or nearly off-patent in the US. All four are non-glycosylated products expressed in bacteria. Schering's Intron A (interferon alfa-2b), approved by the FDA in 1991, was the first alpha interferon approved to treat hepatitis C. Schering's PEG-Intron was one of the first PEGylated therapeutic proteins. PEGASYS (interferon alfa-2a) was developed by Roche using Nektar's Advanced PEGylation to compete with Schering's PEG-Intron. Nektar's Advanced PEGylation is based on PEGs selected from a broader range of molecular weights, functional groups and improvements in attachment chemistry, and provides higher and more uniform blood levels. PEGASYS captured 60% of the market within two years of launch, virtually all at the expense of PEG-Intron. Amgen's consensus interferon Infergen (alfacon-1), approved in 1997, is a genetically engineered synthetic interferon created from the most common amino acid sequences from the naturally occurring alpha interferons.

There are a large number of launched proprietary products in this category. Most are recombinant products, but a few are natural IFN-alpha products. Natural IFN-alpha is produced largely in leukocytes such as monocyte/macrophage and B lymphocyte. Here, the proportion of subtypes of interferons produced depends on the cell type and production conditions. Hemispherx/Interferon Sciences' interferon alfa-n3, a new formulation derived from human leukocytes contains at least 14 alpha interferon molecules.

There are a number of engineered IFN-alpha products with improved characteristics in clinical and preclinical development. Engineered products include Nautilus Biotech's Belerofon (with improved t1/2 due to a single amino acid substitution), Human Genome Sciences/Novartis's Albuterol, an IFN-a-albumin fusion protein with improved antiviral activity, and Biogen Idec's inhalable IFN-alpha-Fc fusion protein. Other products in development include more potent IFN-alpha variants (Riotech's IFN-alpha8; Digna Biotech's IFN-alpha5), and Molecular Targeting Technology's transgenic IFN-alpha produced in plants.

There are also a number of novel IFN-alpha formulations in development. These include controlled and extended-release formulations, formulation nanoparticles, topical and oral formulations, and products produced using various PEGylation technologies, such as Bolder Biotechnology's cysteine-PEGylated IFN-alpha and Ambrx/Roche's GlycoPEGylated IFN-alpha.

Although most IFN-alpha products in development are non-glycosylated it has been suggested that the addition of carbohydrate side-chains may increase the molecule's *in vivo* stability.

2.6.2.2 Interferon-beta

(Table 2.20)

Human interferon-beta shows about 30% chemical homology with the interferons-alpha. The natural product is glycosylated, and there is only one molecular species. It is produced by most cell types (except leukocytes, which produce IFN-alpha). IFN-beta has 30% amino-acid homology with

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IFN-alpha, but only 1% homology with IFN-gamma. Although, like IFN-alpha, it binds to the type 1 IFN receptor, IFN-beta binds with a higher affinity.

One IFN-beta product listed in Table 2.3, Novartis's Betaferon (interferon beta-1b), and two products listed in Table 2.5, Biogen Idec's Avonex and Merck KGaA's Rebif (both interferon beta-1a), are approved for the treatment of relapsing-remitting multiple sclerosis (MS). The basic patents on these products have now expired.

Interferon beta-1a is produced in mammalian cells, and its amino acid sequence and glycosylation pattern are identical to those of endogenous human IFN-beta. By contrast, interferon beta-1b is produced in *E.coli* using an altered coding sequence that produces a protein in which serine is substituted for cysteine at position 17, the N-terminal methionine is missing, and the glycosylation of the natural product is lacking. However, there is evidence that the carbohydrate plays a vital role in stabilising the IFN-beta molecule, and its absence from interferon beta-1b may explain why this molecule, in a standard antiviral assay, has only approximately one-tenth of the biological activity of interferon beta-1a per milligram of protein.

Some MS patients do not respond to IFN-beta therapy, possibly due to the production of neutralising antibodies which can prevent the biological effect of IFN-beta. The interferon beta-1b molecule has been shown to be more immunogenic than the interferon beta-1a molecule. This may be due to the non-glycosylated, chemical structure of the former, which can produce aggregates and enhance antibody production.

Other IFN-beta products on the market have been approved for indications other than MS. The originating companies, with the indications being pursued in brackets, include Rentschler (brain inflammation), Mochida (HBV infection), Sclavo and Toray (cancer) and Yeda (keratoconjunctivitis). However, many recombinant IFN-beta products continue to be developed for multiple sclerosis. Developers include Rentschler, Bolder Biotechnology, Keryos, Sidus and Vakzine. Some are engineered products, such as Vakzine's Soluferon (a second-generation IFN-beta product with enhanced bioavailability) and Biogen's inhalable IFN-beta-Fc fusion protein. Merck KGaA and Nektar Therapeutics are collaborating on the development of an inhalable pegylated formulation of Rebif for CNS pain. Other novel formulations in development include Flamel Technologies' nanoparticle formulation.

2.6.2.3 Interferon-gamma

(Table 2.30)

Native IFN-gamma, a glycoprotein, has the same non-specific antiviral properties as other types of interferon but it shows little, if any, chemical homology. IFN-gamma, secreted by T lymphocytes and NK cells, has many immunoregulatory functions. It is a dimerised cytokine that is the only member of the type II class of interferons. Emerging evidence indicates that IFN-gamma may act as a master regulator of immune responses and inflammation; the same cytokine functions as an inducer as well as a regulator for inflammation.

The IFN-gamma product listed in table 2.3, Genentech's Actimmune (interferon gamma-1b), expressed in bacteria, has been approved for the

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treatment of chronic granulomatous disease. Other recombinant IFN-gamma products expressed in bacteria have been approved for the treatment of various forms of cancer. Hayashibara's natural glycosylated IFN-gamma (launched in Japan), is produced from human myeloid cells transplanted into hamsters. A fusion protein, Molmed's interferon Gamma-NGR, is also in development.

2.6.3 Granulocyte-CSF

(Table 2.19)

Granulocyte colony-stimulating factor (G-CSF) stimulates the production of infection-fighting neutrophils (granulocytes). G-CSF is a glycoprotein that exists in two (174- and 180 amino acid long) forms. The more-abundant and more-active 174-amino acid form has been used in the development of recombinant products.

There are two recombinant G-CSF products listed in Table 2.3 – Amgen's Neupogen and Neulasta (a PEGylated, long-lasting version of Neupogen). Recombinant G-CSF is used primarily for the treatment of chemotherapy-induced neutropenia. Key patents covering Neulasta expired in Europe in 2006, and will expire in the US in late 2013.

A number of recombinant G-CSF products are marketed outside the US and the EU. Manufacturers include Dong-A, Dragon Pharmaceutical, Hangzhou, Roche/Sanofi-Aventis and Kyowa Hakko. In Europe, Keryos, which has a recombinant G-CSF product (BK-0023) in Phase II trials, recently asserted that preclinical studies in neutropenia and anaemia to assess pharmacokinetics, pharmacodynamics and toxicology in comparison with Amgen's Neupogen, demonstrated that the concept of a biosimilar drug, as set out in EMEA guidelines, could be applied to BK-0023.

Sygnis Pharma is developing a recombinant G-CSF product for the treatment of ischemic stroke. Most of the products in development are long-acting, PEGylated forms of recombinant G-CSF. Companies in this field include Kirin Brewery/Amgen, Maxygen, Neose Technologies, Keryos, Green Cross and Bolder Biotechnology (cys-PEGylated). Hanmi has a long-acting conjugate product in development.

2.6.4 Interleukin-11

(Table 2.41)

Interleukin-11 (IL-11) is a secreted cytokine with pleiotropic functions in many tissues and cells. Wyeth's recombinant IL-11 product Neumega (oprelvekin) has been launched in the US for the treatment of recurrent severe thrombocytopenia resulting from chemotherapy in patients with solid tumours or non-Hodgkin's lymphoma.

2.6.5 Anakinra

(Table 2.46)

The naturally-occurring interleukin 1 (IL-1) receptor antagonist (IL-1RN) is an anti-inflammatory agent that binds to the IL-1 receptor and inhibits the binding and biological activity of the proinflammatory cytokine IL-1. IL-1R antagonist can be expressed as a secreted glycoprotein (sIL-1Ra) or as an

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intracellular nonglycosylated form (icIL-1Ra). Amgen's Kineret (anakinra) is a recombinant non-glycosylated form of human sIL-1RA for the treatment of rheumatoid arthritis.

2.6.6 Other proteins

Tissue plasminogen activator (t-PA) is a glycosylated serine protease enzyme that converts the proenzyme plasminogen to plasmin, a protease that degrades fibrin. Roche's recombinant non-glycosylated tPA product Retavase (reteplase) demonstrates a diminished affinity to hepatocytes; this property is believed to account for its extended half-life. Recombinant glycosylated t-PA products will be discussed in section 2.8.9.

2.7 Recombinant glycosylated proteins (NDA pathway)

Table 2.4 lists glycosylated protein products, which have been approved through the NDA pathway.

2.7.1 Follitropin

(Table 2.27)

Follitropin is recombinant human follicle stimulating hormone (hFSH). Native hFSH is a glycoprotein hormone synthesised and secreted by the pituitary gland. The protein dimer contains two polypeptide units, labelled alpha and beta subunits. Table 2.4 lists two best-selling recombinant hFSH products, Merck KGaA's Gonal-FRFF (follitropin alfa) and Akzo Nobel's Follistim AQ (follitropin beta). Follitropin alfa is used to treat fertility problems. It is used in combination with another hormone (hCG) to stimulate the ovaries in women or used alone to stimulate sperm production in men. Follitropin beta is used to treat fertility problems in women. It is used in combination with hCG to stimulate the ovaries. Akzo Nobel (Organon) also has a long-lasting formulation of follitropin beta in development. There are also a number of purified human hFSH products on the market.

2.7.2 Thyrotropin

(Table 2.42)

Thyrotropin is recombinant thyroid-stimulating hormone (TSH). Native human TSH is a hormone synthesised and secreted by the pituitary gland, which regulates the endocrine function of the thyroid gland. TSH is a heterodimer of an alpha chain (identical to that found in two other pituitary hormones, FSH and LH) and a unique beta chain that gives TSH its unique properties. Genzyme's recombinant TSH product Thyrogen (thyrotropin alfa) is launched as an adjunct to the detection of recurrent thyroid cancer and is awaiting approval in the US for thyroid cancer ablation. Thyrogen contains all of the sialic acid sugars that human TSH does, but none of the sulfated sugar residues.

2.7.3 Urokinase

(Table 2.26)

Urokinase plasminogen activator (u-PA) is a glycosylated serine protease enzyme that converts the proenzyme plasminogen to plasmin, a protease that degrades fibrin. Wild-type u-PA is composed of two polypeptide chains,

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occurring in a low molecular weight (32 kDa) and high molecular weight (54 kDa) form. The high molecular weight form predominates in u-PA isolated from urine, while the low molecular weight form is found in u-PA obtained from tissue culture of kidney cells. Abbott's Abbokinase (urokinase) is not a recombinant product, but is manufactured from primary human neonatal kidney cells in tissue culture. It has an established use as the primary treatment in the clinical management of coronary artery thrombosis, although in recent years it has been superseded by recombinant t-PA. Following the expiry of Abbokinase's patent in the US, the product was acquired by Imarx in 2006. Imarx is also developing recombinant u-PA (which has a higher molecular weight than Abbokinase), and a recombinant glycosylated pro-urokinase (a single-chain precursor of u-PA that can be activated by plasmin to form active two-chain u-PA).

Microbix has developed the first biosimilar version of Abbokinase in the US, ThromboClear. Manufactured batches of ThromboClear are currently undergoing formal analytical and stability testing to prepare data to be included in the filing of an ANDA with the FDA.

2.7.4 Glucocerebrosidase

(Table 2.36)

Genzyme's recombinant glucocerebrosidase Cerezyme (imiglucerase) is indicated for the treatment of Gaucher's disease, a rare inherited metabolic disorder. Cerezyme was developed to replace the company's purified natural glucocerebrosidase product Ceredase (alglucerase). Genzyme's Cerezyme is a recombinant glucocerebrosidase with an engineered glyco component. The enzymatic cleavage of terminal sialic acid sugar residues from the oligosaccharide chains attached to Cerezyme helps to redistribute the drug from liver to macrophages. Shire Human Genetic Therapies (Shire Pharmaceuticals) is developing gene-activated glucocerebrosidase (glucosylceramidase).

2.7.5 Other products

(Table 2.54)

Wyeth's Mylotarg (gemtuzumab) is a humanised immunotoxin containing a recombinant humanised monoclonal antibody against the myeloid progenitor cell-specific antigen, CD33, linked to the cytotoxic agent calicheamicin. Mylotarg is used in the treatment of relapsed acute myelogenous leukaemia.

2.8 Recombinant glycosylated proteins (BLA pathway)

Table 2.5 lists some glycosylated protein products, which have been licensed through the BLA pathway.

2.8.1 Becaplermin

(Table 2.48)

Novartis's Regranex (becaplermin) is a recombinant platelet-derived growth factor (PDGF) for the treatment of deep diabetic neuropathic foot ulcers. Native human PDGF is a mitogenic peptide growth hormone carried in the alpha-granules of platelets and released when platelets adhere to

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traumatised tissues. PDGF is a dimeric glycoprotein consisting of two homologous polypeptide chains (alpha and beta).

2.8.2 Granulocyte-macrophage-CSF

(Table 2.29)

Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates the production of both neutrophils and macrophages. GM-CSF has diverse actions on mature hemopoietic cells. Recombinant GM-CSF is used for the treatment of chemotherapy-induced neutropenia and for myeloid reconstitution in patients undergoing autologous bone marrow transplants. It may also have potential as a vaccine adjuvant in HIV-infected patients.

Bayer's recombinant GM-CSF product Leukine, originally developed by Immunex, faces patent expiry in the US in 2008. Leukine was recently reformulated with the preservative EDTA to deliver extended shelf life and the new formulation was launched in the US in January 2006.

Wyeth's recombinant GM-CSF is awaiting registration in the US, where orphan drug status has been granted for use in severe thermal injury. Cangene's recombinant GM-CSF is awaiting registration in Canada. Long-lasting GM-CSF formulations are in development by companies such as Bolder Biotechnology and Endo Pharmaceuticals.

2.8.3 Erythropoietin

(Table 2.16)

Erythropoietin (EPO), a 30.4 kDa glycoprotein, is a hematopoietic growth factor and cytokine which stimulates erythropoiesis. Currently, recombinant EPO is used in treating anaemia resulting from chronic renal failure or from cancer chemotherapy. In recent years, EPO has been shown to have important non-hematopoietic functions in the nervous system, and to promote regeneration of adult CNS neurons.

Recombinant human erythropoietins, also known as epoetins, are the number one revenue-generating class of biological products on the market. Approved in 1989, Amgen's Epogen (epoetin alfa) was one of the first biologically-derived human therapeutics. Epogen contains virtually the same amounts of the sugars N-acetylglucosamine, N-acetylneuraminic acid, fucose, and N-acetylgalactosamine as human urinary EPO, but it also contains about eight times as much hexose sugars.

Epogen is manufactured and sold by Amgen only in the US. Procrit (epoetin alfa) is manufactured by Amgen and sold by Ortho Biotech (an affiliate of Johnson & Johnson) under licence from Amgen only in the US. Eprex (epoetin alfa) is manufactured by Ortho Biologics and sold by Janssen-Cilag and its partners (all affiliates of Johnson & Johnson). It is not available in the US. While Epogen/Procrit and Eprex share the same INN nomenclature (epoetin alfa), Eprex is not equivalent to Epogen/Procrit. The products are manufactured by different companies in different facilities, using different methods and formulations.

Because the half-life of circulating epoetins is relatively short, they have to be administered two to three times per week. The demand for longer-acting products allowed Amgen's Aranesp (darbepoetin alfa), a recombinant

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hyperglycosylated variant of EPO, to steadily gain market share in the US since its approval in 2001 and become the top-selling therapeutic protein product (see Table 1.4). Aranesp has a plasma half-life of 25.3 hours (*vs* Epogen's 8.5 hours) and is administered once-weekly.

In the US, the key Eprex patents will expire by the end of 2013, and Aranesp's key patents will expire by the end of 2015. However, in Europe, and in Japan, key Eprex patents expired in 2005. In June 2007, three biosimilar epoetin-alfa products received approval recommendations in the EU – Sandoz's Binocrit, Hexal Biotech's Epoetin alfa Hexal and Medice Arzneimittel Putter's Abseamed.

There are a number of recombinant epoetin alfa products available outside of the US and Europe. Companies marketing them include Dong-A, LG Life Sciences, Dragon Pharmaceutical, Elanex Pharmaceuticals, Shantha Biotechnics and Wyeth. Shire Human Genetic Therapies/Sanofi-Aventis market epoetin delta (produced in human cells by gene activation) outside the US.

There are many engineered EPO-based products with enhanced properties at different stages of clinical and preclinical development. They include Roche's CERA (continuous erythropoietin receptor activator), which incorporates a large glycol polymer chain linked by amide bonds, and demonstrates a half-life substantially longer than that of Aranesp. Amgen itself has a second-generation hyperglycosylated analogue of Aranesp in development.

Affymax's Hematide, a synthetic, modified EPO-mimetic peptide, which stimulates a sustained erythropoiesis, has an amino acid sequence very different from Epogen. Another company developing an EPO-mimetic peptide is Aplagen. Genodyssee Pharma is developing a naturally-occurring variant of EPO. Other companies developing EPO derivatives include Shire and Transtech Pharma. Biogen Idec, Dnaprint Genomics, Novagenetics and Bolder Biotechnology have EPO-based fusion proteins under investigation.

Outside of EPO's current therapeutic applications, Stem Cell Therapeutics is investigating EPO derivatives for use in the treatment of schizophrenia, MS and stroke. Lundbeck and Warren Pharmaceuticals are developing EPO derivatives for neurodegenerative diseases.

The quest to improve the stability of EPO products is continuing with Neose Technologies and Roche developing PEGylated products, Bolder Biotechnology developing a cys-PEGylated product, and Hanmi developing a long-lasting EPO conjugate. There are also nanoencapsulated extended-release formulations (from Flamel Technologies) and oral formulations (from Nautilus Biotech) under investigation.

2.8.4 DNase

(Table 2.50)

DNase I is an endonuclease that non-specifically cleaves DNA to release di-, tri- and oligonucleotide products. Genentech's recombinant product Pulmozyme (dornase alfa) is an aerosolised formulation for the treatment of cystic fibrosis. The pulmonary secretions in CF are complex materials that include mucus glycoproteins, mucopolysaccharides, proteases, actin and DNA. Pulmozyme is effective in reducing the viscoelasticity of pulmonary

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secretions by hydrolysing high-molecular-weight DNA that is present in such secretions. The DNA-hydrolytic activity of DNase I in pulmonary secretions may be reduced, however, as a result of the interaction of the DNase I with actin. In 2002, a US patent was issued to Genentech, describing novel DNase variants, and methods for their recombinant production that have DNA-hydrolytic activity, but which are resistant to inhibition by actin.

2.8.5 Factor VIIa

(Table 2.33)

Factor VII, an enzyme of the serine protease class, is one of the central proteins in the coagulation cascade. Factor VII is synthesised in the liver and secreted as a single-chain glycoprotein of 48 kDa. The major proportion of Factor VII circulates in plasma in zymogen form, and activation of this form results in its cleavage giving rise to Factor VIIa.

Zymogenetics' NovoSeven (recombinant Factor VIIa) was launched by Novo Nordisk for haemophilia patients who have antibodies to Factors VIII and IX. Novo Nordisk is developing a PEGylated Factor VIIa analogue. Also in development is Maxygen's recombinant Factor VIIa with engineered improvements and GTC Biotherapeutics' transgenic Factor VII (produced in rabbits).

2.8.6 Factor IX

(Table 2.24)

Factor IX is one of the serine proteases of the coagulation system. Deficiency of this protein causes haemophilia B. Mature human Factor IX is a 55 kDa glycoprotein with a modular domain structure and numerous post-translational modifications.

Wyeth's BeneFIX (recombinant Factor IX) is expressed in a CHO cell line engineered for high-level protein processing and expression. The company carried out detailed biochemical and biophysical characterisation, which demonstrated that the post-translational modifications and primary, secondary, and tertiary structures of this recombinant glycoprotein are similar to those of plasma-derived Factor IX. Several purified human Factor IX products are also available on the US market.

Factor IX-based products in development include a recombinant and a purified Factor IX, as well as a recombinant Factor IX product engineered to increase t1/2, (from Wyeth/Nautilus Biotech), a long-lasting Factor IX-Fc fusion protein (from Biogen Idec), and a PEGylated Factor IX formulation (from Neose Technologies).

2.8.7 Factor VIII

(Table 2.17)

Coagulation Factor VIII is a heavily glycosylated heterodimeric plasma protein that consists of a heavy (domains A1-A2-B) and light chain (domains A3-C1-C2). Factor VIII participates in the intrinsic pathway of blood coagulation; it acts as a cofactor for Factor IXa which, in the presence of Ca+2 and phospholipids, converts Factor X to the activated form Xa. Defects in the Factor VIII gene result in haemophilia A, a common recessive

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X-linked coagulation disorder.

There are both plasma-derived and recombinant Factor VIII products on the market.

Three recombinant Factor VIII products appear in table 2.5. Talecris Biotherapeutics' Kogenate FS (formulated sucrose), is a second-generation version of Kogenate, developed by Bayer, and then acquired by Talecris. Kogenate FS uses sucrose instead of human albumin as a stabiliser in the purification process and contains one thousand times less albumin than the original product. Wyeth's Recombinate has been licensed to Baxter International. Wyeth's Refacto is a second-generation B-domain deleted recombinant Factor VIII albumin-free formulation. Deletion of the B-domain of Factor VIII has been shown to increase the manufacturing yield of the product without impairing *in vitro* or *in vivo* functionality.

Baxter International's Advate is a 3rd-generation recombinant Factor VIII therapy. It is similar to Recombinate, but all proteins or raw materials derived from humans or animals are excluded to eliminate the risk of infection.

Additional recombinant Factor VIII products are in development, as well as liposomal and PEGylated formulations, and plasma-derived Factor VIII products.

2.8.8 Activated protein C

(Table 2.34)

Protein C, a serine protease enzyme, is a major physiological anticoagulant. Human protein C is made *in vivo* primarily in the liver as a single polypeptide of 461 amino acids. This precursor molecule undergoes multiple post-translational modifications to produce circulating 2-chain zymogen that is activated *in vivo* by thrombin into activated protein C (aPC). The activated form degrades Factor Va and Factor VIIIa. The conversion of protein C to activated protein C is often impaired during sepsis.

Lilly's Xigris (drotrecogin alfa), a glycoprotein with the same amino acid sequence as human plasma-derived aPC, is used in the treatment of severe sepsis. Plasma-derived aPC products are also on the market. Lilly is developing an engineered analogue of recombinant aPC for use in cardiogenic shock which has enhanced anti-inflammatory and anti-thrombotic properties and shows strong binding to endothelial protein C receptor.

2.8.9 Tissue plasminogen activator

(Table 2.25)

Tissue plasminogen activator (tPA) is a serine protease enzyme that converts the proenzyme plasminogen to plasmin, a protease that degrades fibrin. Tissue PA is thought to be primarily responsible for the removal of fibrin from within the vasculature through its specific affinity for fibrin. Tissue-type PA is synthesised as a single chain (with a molecular weight of approximately 65 kDa) which is cleaved by plasmin to a two-chain disulfide linked protein. This enzyme plays a role in cell migration and tissue remodelling. Decreased t-PA activity leads to hypofibrinolysis, which can

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result in thrombosis or embolism. Tissue-type PA is the most widely used thrombolytic agent today. It is used predominantly as a thrombolytic agent in myocardial infarction, and additionally in general thrombosis.

Two recombinant t-PA products appear in Table 2.5 – Genentech's Activase (alteplase – which went off-patent in the US in 2005) and TNKase. In addition, one recombinant t-PA product appears in Table 2.3 – Roche's Retavase (reteplase). Activase, a predominantly single-chain glycosylated form of t-PA expressed in CHO cells, is administered by infusion. In an effort to lengthen the duration of bioavailability of t-PA, the molecule was systematically bioengineered. Initial investigations identified regions in kringle 1 and the protease portion of t-PA that mediated hepatic clearance, fibrin specificity and resistance to plasminogen activator inhibitor. Three sites were modified to create TNKase with a greater half-life (enabling bolus injection) and fibrin specificity. Retavase, similar to TNKase, comprises the kringle 2 and protease domains of t-PA, but is a non-glycosylated product produced in *E.coli* cells. Retavase demonstrates a diminished affinity to hepatocytes; this property is believed to account for its extended half-life.

A range of recombinant t-PA products is on the market in Japan. Menarini plans to file amediplase (licensed from Novartis) for approval in Europe, Japan and the US. This product is a recombinant hybrid plasminogen activator, consisting of kringle 2 from t-PA fused to the protease domain of single-chain uPA.

Recombinant forms of streptokinase (a thrombolytic agent originating from the *Streptococcus* bacterium) have been developed by companies such as Shantha Biotechnics and YM Biosciences. Thrombogenics has a variant recombinant version of staphylokinase in development. Paion's desmoteplase is a recombinant thrombolytic protein derived from the saliva of the vampire bat *Desmodus rotundus*.

2.8.10 Monoclonal antibodies

The FDA defines a monoclonal antibody (mAb) as a clonal product, which may be intact antibody, antibody fragment, conjugate, fusion protein or bispecific antibody. Monoclonal antibodies form the majority of therapeutic proteins currently in clinical and preclinical development.

Thus far, all approved therapeutic recombinant mAbs have been of the IgG class. The therapeutic effect of mAbs is obtained either by blocking a target, or by exerting effector functions residing in the Fc region of the IgG antibody to activate the complement system or cytotoxic cells.

The best-selling mAb products described below are listed in Table 2.5, with the exception of Mylotarg (gemtuzumab), which appears in Table 2.4. These products include chimaeric, humanised and fully-human mAbs. In chimaeric mAbs, the murine Fc region has been replaced with one of human sequence. Humanised mAbs have been created through CDR grafting or variable domain resurfacing. The development of phage display technology, followed by transgenic mice, enabled the development of fully human mAbs. Currently, human mAbs constitute the largest category of mAbs entering clinical study each year. It is now widely accepted that the risk of immunogenicity may be reduced by using fully human antibodies.

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2.8.10.1 Chimaeric mAbs

(Tables 2.43, 2.49, 2.55, 2.60)

Erbitux (cetuximab) is a mAb specific for EGFR (epidermal growth factor receptor), developed by Imclone Systems for the treatment of cancers overexpressing EGFR. Cetuximab inhibits the receptor-associated tyrosine kinase, thus blocking the intracellular signalling pathway that results in cell proliferation. Imclone is also developing a non-chimaeric version of cetuximab.

Remicade (infliximab) is a mAb against TNF-alpha, developed by Centocor (Johnson & Johnson) indicated for Crohn's disease, rheumatoid arthritis, psoriasis and ankylosing spondylitis.

ReoPro (abciximab) is a mAb for the treatment of clot-related cardiovascular disease developed by Johnson & Johnson. It binds to platelet GPIIb/IIIa receptors, blocking the binding of fibrinogen, Von Willebrand factor and other adhesive factors, thereby inhibiting platelet aggregation.

Rituxan (rituximab) is a mAb which targets the leukocyte surface antigen CD20. It was developed by Biogen Idec, Genentech, Roche and Zenyaku Kogyo, for the treatment of B-cell lymphoma and other disorders. Rituximab depletes both normal and malignant B-cells through a complement-mediated process, but does not affect precursor cells which replenish the healthy B-cell population.

2.8.10.2 Humanised mAbs

(Tables 2.38, 2.45, 2.51, 2.56, 2.58, 2.59, 2.61)

Avastin (bevacizumab) is an anti-VEGF mAb, developed by Genentech and Roche for the treatment of cancer. Sirtex is supporting the development of a microencapsulate bevacizumab formulation using its SIR-Spheres technology.

Campath (alemtuzumab) is a mAb targeting the CD52 cell surface antigen. It was developed by Millennium and Genzyme for the treatment of B-cell chronic lymphocytic leukaemia (B-CLL).

Genentech's Herceptin (trastuzumab) is a mAb to HER2, a cell surface oncoprotein, which is overproduced in breast and ovarian cancers.

Synagis (palivizumab) is a mAb against the fusion protein of respiratory syncytial virus (RSV), developed by Medimmune (AstraZeneca) for the treatment and prevention of RSV pneumonia in infants. Medimmune is also developing Numax, an engineered enhanced potency anti-RSV mAb.

Genentech/Xoma's Raptiva (efalizumab) is a mAb directed at the leukocyte surface antigen, used in the treatment of psoriasis. It inhibits T-cells from attacking cells or tissues by preventing their activation.

Tysabri (natalizumab) is a mAb against the leukocyte surface antigen anti-VLA-4. Tysabri blocks the passage of leukocytes across the blood/brain barrier, and was developed by Elan for the treatment of multiple sclerosis.

Xolair (omalizumab) is an anti-IgE mAb, co-developed by Genentech,

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Novartis and Tanox for the treatment of allergic asthma. Xolair is the first approved therapy to address the underlying cause of allergic asthma.

2.8.10.3 Human mAbs and fusion proteins

(Tables 2.44, 2.53)

Amgen's Enbrel (etanercept) is a TNF-alpha receptor-Fc fusion protein for the treatment of rheumatoid arthritis and psoriasis. Enbrel acts by binding the inflammatory cytokine TNF (tumour necrosis factor); this action renders the bound TNF biologically inactive, resulting in significant reduction in inflammatory activity.

Abbott's Humira (adalimumab – developed by Cambridge Antibody Technology and now part of AstraZeneca) is a fully-human anti-TNF mAb for the treatment of rheumatoid arthritis.

2.8.11 Other proteins

Two IFN-beta products listed in Table 2.5 – Biogen Idec's Avonex and Merck KGaA's Rebif, both approved for the treatment of relapsing-remitting multiple sclerosis – were discussed in section 2.6

Bayer's natural product Trasylol (aprotinin) (Table 2.47) is a purified bovine serine proteinase inhibitor, developed for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass surgery.

2.9 Strategies of originator companies

The more established biopharmaceutical companies, with substantial financial resources at their disposal, are employing a number of strategies in an attempt to delay or prevent biosimilar competition.

2.9.1 Increasing product patent protection

Faced with the imminent expiry of key composition-of-matter patents on profitable branded products, originator companies are extending patent protection by patenting preferred manufacturing methods or formulations. For example, the composition-of-matter patent for EPO expired at the end of 2004. However, Amgen was able to extend its patent life by patenting the technique required to produce EPO in mammalian cells; these process patents are enforceable in the US through to 2013.

Although basic patent protection for Novartis's Sandostatin (octreotide) has expired, Sandostatin LAR (long-acting) has patent protection until 2013 and beyond in the US. Bayer's recombinant GM-CSF product Leukine (sargramostim) faces patent expiry in the US in 2008. The product was recently reformulated with the preservative EDTA to deliver extended shelf life and the new formulation was launched in the US in January 2006. Although the patents on Bayer's best-selling Betaferon will start to expire in 2007, the company is developing a higher-dose version of the product in order to secure its place in the market.

2.9.2 Next-generation branded products

The majority of first generation biopharmaceuticals are simple replacement

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proteins displaying an identical amino acid sequence to a native human protein or unmodified monoclonal antibodies. While products of this nature continue to be approved, an increasing number of modern biopharmaceuticals are engineered, second-generation drugs. Protein engineering extends the product lifecycle of existing biopharmaceuticals through development of therapeutically superior second-generation products. Engineering can entail the alteration of amino acid sequences, alteration of the glycocomponent of a glycosylated protein, or the covalent attachment of chemical moieties such as polyethylene glycol (PEG).

Clinically superior second-generation versions of several top-selling biopharmaceuticals have already appeared on the market, and they are replacing their first-generation counterparts as the therapeutic treatments of choice. For example, in 2003, Amgen began to market Aranesp, a longer-lasting variant of its first-generation Epogen product (there is also a next-generation analogue of Aranesp in development), and Neulasta, a longer-acting version of its popular product Neupogen. Likewise, Schering-Plough introduced PEG-Intron in 2001, a second generation version of its top-selling product Intron. Genentech's Activase was systematically bioengineered to create TNKase.

The emergence of second-generation branded products such as insulin analogues is expected to steal some of the market for first-generation biosimilars. Novo Nordisk, for example, is focusing on its patent-protected insulin analogue, as opposed to generic human insulin. The company believes that the new generation of insulins are so clearly superior, and that there is such a change in doctor and patient attitude towards it, that they will not go back to using unmodified human insulin. Novo Nordisk has several years of patent protection left on its newer insulin analogues. The NovoLog rapid-acting insulin analogue has patent protection until 2014, while the slightly newer long-acting insulin analogue Levemir has patents that run through to 2017. By then, the company expects to have a third generation of insulin products on the market.

Many originator companies take the view that the way to protect against generic competition is to continually innovate. Roche, for example, has strengthened its capabilities in biotechnology by acquiring Glycart Biotechnology and partnering with Halozyme Therapeutics. Technology from Glycart has the potential to improve the efficacy of monoclonal antibodies and to increase production yields. At the other end of the chain, Halozyme's technology may allow for the subcutaneous delivery of biologics, which currently can only be administered by infusion.

2.9.3 Development of authorised generics

Branded pharma companies use many tactics to fight off generic competition, but few are as controversial as authorised generics. In the US, under the Hatch-Waxman Act, the first generics firm that successfully challenges a branded drug patent is rewarded 180 days' exclusivity. The Act, however, does not exclude products that have already been approved, so branded drug companies compete by relabelling their existing products and selling them cheaply through a generics company as authorised generics. By launching authorised generics, innovator companies flood distributors with stock, capturing substantial market share and reducing the scope for generics companies to compete. This practice has become widespread since the first launch four years ago.

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It remains to be seen whether this controversial practice will extend to authorised biosimilars. It should also be noted that in July 2007, several US senators introduced a bill that would ban the introduction of authorised generics during the 180-day exclusivity period for unbranded generics.

2.9.4 Price reduction of the branded product

A growing trend among brand name pharmaceutical manufacturers is to drastically reduce the prices of their products when patents expire in order to retain market share. New technologies, for instance, can be used to decrease manufacturing costs. A similar strategy may also be employed in the biosimilars area. For example, Novo Nordisk has indicated that it is prepared to provide human insulin to certain larger clients, such as the US Department of Veterans Affairs, at prices that cannot be met by generic human insulin producers.

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Table 2.1: Peptides (NDA pathway)

Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system
eptifibatide	Integrelin Integrilin intrifiban velofibatide	Millennium	Schering-Plough/ GlaxoSmithKline	GPIIb IIIa receptor antagonist	Angina, unstable	Integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41) integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	7	N/A
*octreotide	Longastatina octreotide pamoate Oncolar Sandostatin Sandostatina Sandostatine SMS-201-995 SMS-995 SMS-995C	Novartis		Somatostatin agonist	Acromegaly	Somatostatin receptor 1 Somatostatin receptor 2 Somatostatin receptor 3 Somatostatin receptor 4 Somatostatin receptor 5	8	N/A
*desmopressin	Adiuretin DDAVP Defirin Desmospray KW-8008 Minirin	Ferring	Kyowa Hakko Valeas Sanofi-Aventis Wyeth Ranbaxy	Vasopressin agonist	Enuresis	Arginine vasopressin receptor 2 (nephrogenic diabetes insipidus)	9	N/A
leuprolide acetate, Atrigel	Eligard Leuprogel leuprolide acetate, QLT SOT-375	QLT	Sanofi-Aventis Hospira Astellas Tecnofarma Medigene Biosintetica Akzo Nobel Key Oncologics Ranbaxy	LHRH agonist	Cancer, prostate	Gonadotropin-releasing hormone receptor	9	N/A

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system
leuprorelin, Takeda	Abbott-43818 Carcinil Enantone Leuplin Leuplin SR leuprolide, Takeda leuprorelin, Abbott leuprorelin, Lederle Lucrin Lucrin Depot Lupron Lupron Depot Procren Depot Procrin Prostap Prostap SR TAP-144-SR Trenantone Gyn	Takeda	Abbott Wyeth	LHRH agonist	Cancer, prostate	Gonadotropin-releasing hormone receptor	9	N/A
goserelin	ICI-118630 Zoladex Zoladex LA Zoladex Plus	AstraZeneca	Kissei Biovail	LHRH agonist	Cancer, prostate	Gonadotropin-releasing hormone receptor	10	N/A
*ciclosporin	cyclosporin-A Neoral OL-27-400 OLO-400 Sandimmun Sandimmun Neoral Sandimmune	Novartis	Daiichi Sankyo	Immunosuppressant	Transplant rejection, general	Peptidylprolyl isomerase A (cyclophilin A)	11	N/A
bivalirudin	Angiomax Angiox BG-8967 Hirulog	The Medicines Company	Nycomed Pharma Oryx Pharmaceuticals Ferrer CSL	Thrombin inhibitor	Thrombosis, general	Coagulation factor II (thrombin)	20	N/A
glucagon	Glucagon for Injection Glucagon R	Lilly		Glucagon agonist	Diabetes, general	Glucagon receptor	29	Yeast, bacteria

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system
glucagon	GlucaGen GlucaGen Hypokit Glucagon G	Zymogenetics	Eisai Novo Nordisk	Glucagon agonist	Hypoglycaemia	Glucagon receptor	29	Yeast, bacteria
*calcitonin, nasal	calcitonin, nasal, Noven Karil Miacalcic Miacalcic Nasal Miacalcin Nasal Spray miacalcin, nasal salcatonin, nasal, Novartis salcatonin, nasal, Noven SMC-051	Novartis	Noven Pharmaceuticals	Calcitonin stimulant	Osteoporosis	Calcitonin receptor	32	N/A
nesiritide citrate	BNP, Johnson brain natriuretic peptide, J&J hBNP, Johnson & Johnson Natrecor Natrecor BNP Noratak	Johnson & Johnson		Brain natriuretic peptide agonist	Heart failure	Natriuretic peptide receptor A/guanylate cyclase A (atrionatriuretic peptide receptor A)	32	Bacteria
teriparatide	Forsteo Forteo Fosteo LY-333334 parathyroid hormone, Emisphere parathyroid hormone, Inhale parathyroid hormone, Lilly PTH, Inhale PTH, Lilly	Lilly		Parathyroid hormone agonist	Osteoporosis	Parathyroid hormone receptor 1	34	Bacteria

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system
enfuvirtide	DP-178 Fuzeon R-698 Ro-29-9800 T-20	Trimeris	Roche	GP41 antagonist	Infection, HIV/AIDS	env, HIV-1	36	N/A
* - with current a-rating								

Source: Pharmaprojects

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Table 2.2: Recombinant non-glycosylated proteins (NDA pathway)

Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
Part I: Non-mammalian expression systems									
insulin aspart	insulin analogue, Novo Nordisk NovoLog NovoRapid	Novo Nordisk		Insulin agonist	Diabetes, type 1	insulin receptor	51	Yeast, bacteria	780
insulin analogue	Humalog Humalog MirioPen Humalog Mix25 Humalog Mix50 Humalog N Humalog25 insulin lispro Liprolog Bio-Lysprol Lispro LY-275585	Lilly		Insulin agonist	Diabetes, type 1	insulin receptor	51	Yeast, bacteria	N/A
insulin, Genentech, recombi	Huminsulin Humulin Humulin L Lente Humulin NPH Humulin Reg Humulin U Ultralente Humulin-C Humulina Humuline Hunulin-N Umuline Umuline Zinc	Genentech	Lilly Shionogi	Insulin agonist	Diabetes, general	insulin receptor	51	Bacteria	861
insulin glargine	Hoe-901 insulin analogue, Sanofi Lantus Lantus SoloStar Optisulin rDNA insulin analogue, Sanofi	Sanofi-Aventis		Insulin agonist	Diabetes, type 1	insulin receptor	53	Bacteria	1,639

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
lepirudin	HBW-023 hirudin, Bayer Schering Pharma Hoe-023 rDNA-Hirudin Refludan Refludin	Bayer	Pharmion	Thrombin inhibitor	Antithrombin III deficiency	Coagulation factor II (thrombin)	65	Yeast	23
somatropin	Genotonorm Genotropin growth hormone, Kabi hGH, Pharmacia somatotropin, Pfizer-2	Pfizer	Gerolymatos Adcock Ingram Green Cross	Growth hormone agonist	Growth hormone deficiency	Growth hormone receptor	191	Bacteria	795
somatropin	BioHGH growth hormone, Lilly hGH, Lilly Humatrope somatotropin, Lilly Umatrope	Lilly		Growth hormone agonist	Dwarfism	Growth hormone receptor	191	Bacteria	468
somatropin	growth hormone, Novo Nordisk hGH, Novo Nordisk Norditropin Norditropin Nordiflex Norditropin S-chu Norditropin SimpleXx Norditropine somatotropin, Novo Nordisk	Novo Nordisk	GlaxoSmithKline Astellas	Growth hormone agonist	Growth hormone deficiency	Growth hormone receptor	191	Bacteria	428
somatropin	growth hormone, Genentech hGH, Genentech Nutropin Nutropin AQ Nutropin AQ Pen Nutropin AQ Pen Cartridge NutropinAq NutropinAq Pen Protropin II somatotropin, Genentech somatropin, Schwarz	Genentech	Ipsen Dainippon Sumitomo Pharma	Growth hormone agonist	Growth hormone deficiency	Growth hormone receptor	191	Bacteria	407

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Part II: Mammalian expression systems									
insulin, monocomponent, Novo	Actraphane Actrapid Actrapid HM Actrapid HM Penfill Actrapid Penfill Monotard HM Novolin Protaphane Ultratard	Zymogenetics	Novo Nordisk Bristol-Myers Squibb Sanofi-Aventis	Insulin agonist	Diabetes, general	insulin receptor	51	Mammalian	1,983
somatropin	growth hormone, Merck Serono r-hGH[m] rhGH, Merck Serono Saizen Saizen Click.Easy Saizen, Click.Easy Saizon, cool.click SeroJet Serostim somatotropin, Merck Serono somatropin, cool.click somatropin, Easyject somatropin, SeroJet somatropin, Viajet 3 Zorbitive	Merck KGaA		Growth hormone agonist	Growth hormone deficiency	Growth hormone receptor	191	Mammalian	218

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Table 2.3: Recombinant non-glycosylated proteins (BLA pathway)

Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
aldesleukin	IL-2, Novartis-3 interleukin, Novartis-3 Leuferon 2 Macrolin IL-2 Proleukin Ro-23-6019	Novartis	Orion Pharma Roche Genesis Pharma Ajinomoto	Interleukin 2 agonist	Cancer, renal	interleukin 2 receptor, alpha	132	Bacteria	130
interferon, Genentech (gamma1b)	Actimmune gamma1b-IFN, Genentech Immukin Immukine Imuforgamma Imukin interferon, InterMune (gamma1b interferon, Toray (gamma1B) interferon,Boehring Ing (gamma interferon,Mondobiotech (gamma	Genentech	Boehringer Ingelheim Intermune Mondobiotech Toray	Interferon gamma 1b agonist	Chronic granulomatous disease	interferon gamma receptor 1	140	Bacteria	N/A
anakinra	Antril IL-1 antagonist, Amgen IL-1ra, Amgen interleukin-1 antagonist, Amge Kineret rhIL-1ra	Amgen	Biovitrum Genesis Pharma	Interleukin 1 receptor antagonist	Arthritis, rheumatoid	interleukin 1 receptor, type I	153	Bacteria	66
interferon, Biogen (alpha2b)	alpha2b-IF, Biogen Cibian Intron A Sch-30500 YM-14090	Biogen Idec	Schering-Plough Astellas	Interferon alpha 2b agonist	Cancer, leukaemia, hairy cell	interferon (alpha, beta and omega) receptor 2	165	Bacteria	1,357
interferon, Novartis (ß1b)	Beneseron Betaferon Betaferon, Beta-assist BetaJect BetaJect Light BetaJect-3 Betaseron IFN-ß1b, Berlex IFN-ß1b, Novartis interferon, Berlex (ß1b) SH-579 ZK-157046	Novartis	Bayer	Interferon beta 1 agonist	Multiple sclerosis, relapsing-remitting	interferon (alpha, beta and omega) receptor 2	165	Bacteria	1,115

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
PEG-interferon alpha-2a, Roche	PEG-IFNalpha-2a, Roche PEG-interferon alpha-2a, Nekta Pegasys PEGylated interferon, Roche R-420 rhIFNalpha-2a, Roche Ro-25-3036 Ro-25-8310	Roche	Nektar Therapeutics Aradigm	Interferon alpha 2A agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2	165	Bacteria	1,995
interferon, Enzon (alpha2b)	alpha2b-IF, Enzon interferon, Schering-Plough PEG-alpha interferon, Enzon PEG-alpha interferon, Schering PEG-interferon-alpha2b, Enzon PEG-interferon-alpha2b, Nektar PEG-interferon-alpha2b, Scheri PEG-Intron PEG-Intron A PEG-Intron Redipen Peginterferon alpha-2b PegIntron ViraFeronPeg	Enzon	Schering-Plough Nektar Therapeutics	Interferon alpha 2b agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2	165	Bacteria	N/A
interferon, Amgen (alpha)	Adopaferon Advaferon alpha-Con1-IF, Amgen alpha-IF, Amgen alpha-IF, Astellas alpha-IF-Con1 CIFN, Amgen CIFN, Astellas Consensus IFN Consensus interferon Infergen Infermax, Amgen Infermax, Astellas interferon alfacon-1 interferon, Amgen (alpha-Con1) interferon, Astellas (alpha) YM-643	Amgen	Astellas Chiesi Valeant	Interferon alpha agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2	166	Bacteria	N/A

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
filgrastim	CSF, Amgen CSF-G, Amgen G-CSF, Amgen Gran Granulokine Grastim, Dr Reddy's hG-CSF, Amgen Neupogen Neutropoietin Nupogen pluripoietin, Amgen r-metHuG-CSF Ro-8315	Amgen	Kirin Brewery Roche Dr Reddy's Genesis Pharma JEIL Pharmaceutical Sidus	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)	175	Bacteria	1,099
pegfilgrastim	filgrastim SD-01 Neulasta Neulastim Neupogen SR Neupogen-PEG Neupopeg PEG-GCSF, Amgen PEG-GCSF, Roche pegfilgrastim, Nektar R-1471 Ro-25-8315 SD-01	Amgen	Genesis Pharma Roche Nektar Therapeutics	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)	175	Bacteria	2,573
oprelvekin	IL-11, Wyeth interleukin-11, Wyeth interleukin-11, Yamanouchi Neumega rhIL-11, Wyeth Sch-53620 YM-294	Wyeth	Yuhan	Interleukin 11 agonist	Chemotherapy-induced injury, bone marrow, thrombocytopenia	interleukin 11 receptor, alpha	177	Bacteria	39

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
reteplase	BM-06022 Ecokinase Rapilysin Retavase Retevase rPA, Centocor	Roche	PDL Biopharma	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue	355	Bacteria	N/A
denileukin diftitox	DAB389IL-2 IL-2 fusion protein, Seragen IL-2 fusion toxin, Seragen LY-335348 ONTAK Onzar	Ligand	Eisai Lilly Ferrer Alfa Wassermann Cephalon	Interleukin 2 receptor antagonist	Cancer, lymphoma, T-cell	eukaryotic translation elongation factor 2 interleukin 2 receptor, alpha	(est 527)	Bacteria	N/A
Note: Filgrastim = $172 million (Gran) + $927 million (Neupogen)									

Source: Pharmaprojects

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Table 2.4: Recombinant glycosylated proteins (NDA pathway)

Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
follitropin alfa, Merck Serono	follitropin alpha, Merck Seron Gonal-F Gonal-F Multi-Dose Gonal-L Gonalef r-follitropin, Merck Serono rhFSH, Merck Serono	Merck KGaA		Follicle-stimulating hormone agonist	Infertility, female	follicle stimulating hormone receptor	203	Mammalian	649
recFSH, Organon	Follistim Follistim AQ follitropin ß hCG, Organon Org-32489 Puregon Puregon pen Recagon Pen rhFSH, Organon	Akzo Nobel		Follicle-stimulating hormone agonist	Infertility, female	follicle stimulating hormone receptor	203	Mammalian	442
thyrotropin alfa, Genzyme	rhTSH, Genzyme Thyrogen thyroid-stimulating hormone,Ge TSH, Genzyme	Genzyme		Thyroid hormone function agonist	Diagnosis, cancer	thyroid stimulating hormone receptor	210	Mammalian	105
urokinase, ImaRx-2	Abbokinase Cultokinase	Imarx	Dainippon Sumitomo Pharma Kyorin	Plasminogen activator stimulant	Thrombosis, general	plasminogen activator, urokinase	(est. 295)	Mammalian	44
imiglucerase	Cerezyme glucocerebrosidase, rec, Genzyme rGCR, Genzyme	Genzyme		Glucosyl-ceramidase stimulant	Gaucher's disease	glucosidase, beta; acid (includes glucosylceramidase)	497	Mammalian	993
gemtuzumab ozogamicin	anti-CD33 MAb, AHP anti-CD33 MAb, UCB CDP-771 CMA-676 Mylotarg P-67	Wyeth	UCB	DNA antagonist	Cancer, leukaemia, acute myelogenous	CD33 molecule	(est 691)	Mammalian	126

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Table 2.5: Recombinant glycosylated proteins (BLA pathway)

Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
Part I: Non-mammalian expression systems									
becaplermin	CTAP-III PDGF, Ethicon PDGF, Novartis Regranex rhPDGF-BB, Abbott rhPDGF-BB, J&J rhPDGF-BB, Novartis RWJ-60235	Novartis	Johnson & Johnson	Platelet growth factor agonist	Ulcer, diabetic	platelet-derived growth factor receptor, beta polypeptide	109	Yeast	N/A
sargramostim	CSF-GM, Bayer GM-CSF, SchAG Interberin Leukine Prokine	Bayer		Granulocyte macrophage colony stimulating factor agonist	Anaemia, aplastic	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	127	Yeast	80
Part II: Mammalian expression systems									
darbepoetin alfa	Aranesp KRN-321 NESP Injection Syringe NESP, Amgen NESP, Genesis NESP, Kirin NESP, Megapharm Novel Erythropoiesis Stimulati	Amgen	Kirin Brewery Genesis Pharma Megapharm Fresenius	Erythropoietin agonist	Anaemia, general	erythropoietin receptor	165	Mammalian	4,733
erythropoietin, Amgen	EPO, Amgen Epoade epoetin alfa Epogen Eprex Erypo erythropoietin, Johnson Espo Globuren KRN-5702E Procrit	Amgen	Dompe Esteve Johnson & Johnson Kirin Brewery Daiichi Sankyo	Erythropoietin agonist	Anaemia, general	erythropoietin receptor	165	Mammalian	5,560

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
interferon, Merck Serono (ß1a)	IFN-ß1a, Merck Serono R-Frone Rebif Rebif 22 Rebif 44 rhIFN-ß1A, Serono ß1A-IF, Merck Serono	Merck KGaA	Pfizer	Interferon beta 1 agonist	Multiple sclerosis, relapsing-remitting	interferon (alpha, beta and omega) receptor 2	166	Mammalian	1,344
interferon, Biogen (ß1a)	Avonex BG-9015 CHO-beta-interferon interferon, Abbott (ß1a interferon, AstraZeneca (ß1a) interferon, CSL (ß1a) interferon, Dompe (ß1a) interferon, Genzyme (ß1a) interferon, Schering-P (ß1a) ß-IF, Biogen	Biogen Idec	AstraZeneca CSL Schering-Plough Abbott Gedeon Richter	Interferon beta 1 agonist	Multiple sclerosis, relapsing-remitting	interferon (alpha, beta and omega) receptor 2	166	Mammalian	1,590
DNase, Genentech	dornase alfa dornase alpha Pulmozyme Pulmozyme CF Pulmozyme, AERx rhDNase	Genentech	Roche	Deoxyribonuclease 1 stimulant	Cystic fibrosis	deoxyribonuclease I	260	Mammalian	297
Factor VIIa, Zymo	eptacog-alpha Factor VIIa, Novo Nordisk NiaStase NN-007 NovoSeven rFVIIa, Novo Nordisk	Zymogenetics	Novo Nordisk	Factor VIIa stimulant	Haemophilia A	coagulation factor VII (serum prothrombin conversion accelerator)	406	Mammalian	828
nonacog alfa	BeneFIX Factor IX, Baxter Factor IX, BTG Factor IX, Wyeth rhFIX	Wyeth	BTG Baxter International	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)	415	Mammalian	360

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
drotrecogin alfa	APC, Lilly LTC-203 LTC-206 protein C, Lilly rhAPC, Lilly Xigris Zovan Zovant	Lilly		Fibrinogen antagonist	Sepsis	protein C (inactivator of coagulation factors Va and VIIIa)	417	Mammalian	233
abciximab	7E3 anti-GPIIb/IIIa MAb c7E3Fab ReoPro	Johnson & Johnson	Lilly	GPIIb IIIa receptor antagonist	Surgery adjunct	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit) integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61) integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41) integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	(est. 433)	Mammalian	373
etanercept	Embrel Enbrel p80 TNFR rhuTNFR:Fc rhvTNFR:Fc soluble TNF receptor, AHP soluble TNF receptor, Amgen STNFR TNF receptor, AHP TNF receptor, Amgen TNFR:Fc TNR-001	Amgen	Wyeth Takeda	Tumour necrosis factor alpha antagonist	Arthritis, rheumatoid	tumour necrosis factor (TNF superfamily, member 2)	467	Mammalian	4,169

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
alteplase	Actase Actilyse Actiplas Activacin Activase Cathflo Activase Grtpa plasminogen activator, Genente tPA, Genentech	Genentech	Boehringer Ingelheim Kyowa Hakko Mitsubishi Pharma Sanofi-Aventis Dompe Millennium Schering-Plough	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue	527	Mammalian	237
tenecteplase	Metalyse plasminogen activator, Boehr plasminogen activator, Genen-2 plasminogen activator, Roche-2 TNK TNK-t-PA TNKase tPA, Boehringer, 2nd-gen tPA, Roche, 2nd-gen tPA-2, Genentech	Genentech	Roche Boehringer Ingelheim	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue	527	Mammalian	N/A
rituximab	anti-CD20 MAb, Genentech anti-CD20 MAb, IDEC anti-CD20 MAb, Roche anti-CD20 MAb, Zenyaku IDEC-C2B8 MAbThera pan-B antibodies, Biogen pan-B antibodies, Genentech pan-B antibodies, Roche pan-B antibodies, Zenyaku R-105 Rituxan	Biogen Idec	Genentech Roche Zenyaku Kogyo	CD20 antagonist	Cancer, lymphoma, non-Hodgkin's	membrane-spanning 4-domains, subfamily A, member 1	664	Mammalian	4,723
adalimumab	D2E7 Humira LU-200134 Raheara	AstraZeneca	Abbott Eisai GTC Biotherapeutics	Tumour necrosis factor antagonist	Arthritis, rheumatoid	tumour necrosis factor (TNF superfamily, member 2)	665	Mammalian	1,574

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
palivizumab	anti-RSV MAb, Abbot anti-RSV MAb, MedImmune MEDI-493 RSV antibodies, Abbott RSV antibodies, MedImmune RSV MAbs, Abbott RSV MAbs, MedImmune Synagis	AstraZeneca	Abbott	Immunostimulant	Infection, respiratory syncytial virus	fusion protein (F), respiratory syncytial virus	(est 672)	Mammalian	1,142
trastuzumab	anti-HER-2 MAb, Genentech anti-HER-2 MAb, Roche HER-2 MAb, Genentech HER-2 MAb, Roche Herceptin R-597 rhuMAb HER2 Ro-45-2317	Genentech	Roche	ErbB-2 inhibitor	Cancer, breast	v-erb-b2 erythroblastic leukaemia viral oncogene homologue 2, neuro/glioblastoma derived oncogene homologue (avian)	675	Mammalian	2,209
bevacizumab	anti-VEGF MAb, Genentech anti-VEGF MAb, Roche Avastin R-435 Ro-4876646	Genentech	Roche	Endothelial growth factor antagonist	Cancer, colorectal	vascular endothelial growth factor A	(est 677)	Mammalian	1,758
natalizumab	AN-100226 Antegren Tysabri	Elan	Biogen Idec	Alpha4beta1 integrin antagonist	Multiple sclerosis, relapsing-remitting	integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) integrin, alpha 4 (antigen CD49d, alpha 4 subunit of VLA-4 receptor)	(est 677)	Mammalian	40
omalizumab	anti-IgE MAb, E25, Tanox anti-IgE MAb, Genen anti-IgE MAb, Novartis CGP-51901 E-25 IGE-025A rhuMAb-E25 Xolair	Genentech	Tanox Novartis	Immunoglobulin E inhibitor	Asthma	immunoglobulin heavy constant epsilon	(est 677)	Mammalian	294

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
infliximab	anti-TNF-alpha MAb, Centocor Avakine cA2 CenTNF Remicade TA-650	Johnson & Johnson	Schering-Plough Tanabe Seiyaku	Tumour necrosis factor alpha antagonist	Crohn's disease	tumour necrosis factor (TNF superfamily, member 2)	(est 677)	Mammalian	4,020
alemtuzumab	alentuzumab Campath Campath-1H LDP-03 MabCampath ZK-217699	BTG	Millennium Genzyme Bayer	Lymphocyte inhibitor	Cancer, leukaemia, chronic lymphocytic	CD52 molecule	(est 682)	Mammalian	117
efalizumab	anti-CD11a MAb, Genentech anti-CD11a MAb, Xoma anti-CD11a monoclonals, Genent anti-CD11a monoclonals, Xoma hu1124 Raptiva Xanelim	Genentech	Xoma Merck KGaA	CD11a antagonist	Psoriasis	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1, alpha polypeptide	(est 682)	Mammalian	146
cetuximab	anti-EGFR MAbs, ImClone C225 Erbitux IMC-C225 MAb C225	Imclone Systems	Merck KGaA Bristol-Myers Squibb	ErbB-1 inhibitor	Cancer, colorectal	epidermal growth factor receptor (erythroblastic leukaemia viral (v-erb-b) oncogene homologue, avian)	(est 691)	Mammalian	845
moroctocog alfa	Factor VIII, Biovitrum Factor VIII, Wyeth-2 ReFacto ReFacto AF ReFacto R2 Kit	Wyeth	Biovitrum	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)	1438	Mammalian	305
Factor VIII-2, Talecris	Factor VIII-2, CSL Helixate Helixate FS Helixate NexGen Kogenate FS Kogenate sucrose formulated	Talecris Biotherapeutics	CSL	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)	2332	Mammalian	821

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Generic name	Synonyms	Originator	Licensee	Pharmacology description	Indication	Target name	Amino acids	Expression system	Sales ($ million)
Factor VIII, Wyeth	Bioclate rAHF Factor VIII, Baxter rDNA Factor VIII, Baxter-2 Factor VIII, CSL rDNA rAHF, Baxter rAHF, Wyeth Recombinate rurioctocog alpha	Wyeth	Baxter International CSL	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)	2332	Mammalian	N/A
Part III: Natural product									
aprotinin, Bayer	Trasylol	Bayer		Kallikrein antagonist	Surgery adjunct	Serine proteases	58	N/A	N/A
Note: EPO, Amgen = $2.93 billion (Procrit/Eprex) + $2.63 billion (Epogen)									

Source: Pharmaprojects

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Table 2.6: Patents - peptides (NDA pathway)

Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
eptifibatide	Integrelin Integrilin intrifiban velofibatide	Millennium	US	5756451	US	07/06/1995
*octreotide	Longastatina octreotide pamoate Oncolar Sandostatin Sandostatina Sandostatine SMS-201-995 SMS-995 SMS-995C	Novartis	European Patent Organisation	29579 (US4395403)	Switzerland	27/11/1979 (US expiry 2005)
*desmopressin	Adiuretin DDAVP Defirin Desmospray KW-8008 Minirin	Ferring	Germany	2948345 (US4221780)	US	04/12/1978 (US expiry 2008)
leuprolide acetate, Atrigel	Eligard Leuprogel leuprolide acetate, QLT SOT-375	QLT	US	6565874	US	13/11/2000
leuprorelin, Takeda	Abbott-43818 Carcinil Enantone Leuplin Leuplin SR leuprolide, Takeda leuprorelin, Abbott leuprorelin, Lederle Lucrin Lucrin Depot Lupron Lupron Depot Procren Depot Procrin Prostap Prostap SR TAP-144-SR Trenantone Gyn	Takeda	US US	4005063 4728721	US Japan	11/10/1973 07/05/1985 (US expiry 2004)
goserelin	ICI-118630 Zoladex Zoladex LA Zoladex Plus	AstraZeneca	US	4100274	UK	11/05/1976 (US Expiry 2005)
*ciclosporin	cyclosporin-A Neoral OL-27-400 OLO-400 Sandimmun Sandimmun Neoral Sandimmune	Novartis	UK	1491509	Switzerland	21/10/1974 (US Expiry 1995)
bivalirudin	Angiomax Angiox BG-8967 Hirulog	The Medicines Company	World Intellectual Property Organization US	9102750 5196404	US US	06/07/1990 18/08/1989
glucagon, Lilly	Glucagon for Injection Glucagon R	Lilly				
glucagon, ZymoGenetics	GlucaGen GlucaGen Hypokit Glucagon G	Zymogenetics				

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Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
*calcitonin, nasal, Novartis	calcitonin, nasal, Noven Karil Miacalcic Miacalcic Nasal Miacalcin Nasal Spray miacalcin, nasal salcatonin, nasal, Novartis salcatonin, nasal, Noven SMC-051	Novartis	US	5733569	UK	05/10/1982
nesiritide citrate	BNP, Johnson brain natriuretic peptide, J&J hBNP, Johnson & Johnson Natrecor Natrecor BNP Noratak	Johnson & Johnson	US	5114923	US	19/01/1988
teriparatide, Lilly	Forsteo Forteo Fosteo LY-333334 parathyroid hormone, Emisphere parathyroid hormone, Inhale parathyroid hormone, Lilly PTH, Inhale PTH, Lilly	Lilly	US	6242495	US	16/06/2000
enfuvirtide	DP-178 Fuzeon R-698 Ro-29-9800 T-20	Trimeris	US	5464933	US	07/06/1993
* - with current a-rating						

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Table 2.7: Patents - recombinant non-glycosylated proteins (NDA pathway)

Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
Part I: Non-mammalian expression systems						
Insulin Aspart	insulin analogue, Novo Nordisk NovoLog NovoRapid	Novo Nordisk	US	5618913	Denmark	30/08/1985 (Expires 2014)
insulin analogue, Lilly	Humalog Humalog MirioPen Humalog Mix25 Humalog Mix50 Humalog N Humalog25 insulin lispro Liprolog Bio-Lysprol Lispro LY-275585	Lilly	US	5514646	US	05/05/1993 (Expires 2013)
insulin, Genentech, recombi	Huminsulin Humulin Humulin L Lente Humulin NPH Humulin Reg Humulin U Ultralente Humulin-C Humulina Humuline Hunulin-N Umuline Umuline Zinc	Genentech				(US expiry 2001)
insulin glargine	Hoe-901 insulin analogue, Sanofi Lantus Lantus SoloStar Optisulin rDNA insulin analogue, Sanofi	Sanofi-Aventis	US European patent	5656722 668292	Germany Germany	08/11/1988 18/02/1994 (Expires 2015)
lepirudin	HBW-023 hirudin, Bayer Schering Pharma Hoe-023 rDNA-Hirudin Refludan Refludin	Bayer	European patent	324712	Hungary	11/04/1985
somatropin, Pfizer	Genotonorm Genotropin growth hormone, Kabi hGH, Pharmacia somatotropin, Pfizer-2	Pfizer				(US expiry 2006)
somatropin, Lilly	BioHGH growth hormone, Lilly hGH, Lilly Humatrope somatotropin, Lilly Umatrope	Lilly	US	3853833	US	27/04/1971 (US expiry 2003)
somatropin, Novo Nordisk	growth hormone, Novo Nordisk hGH, Novo Nordisk Norditropin Norditropin Nordiflex Norditropin S-chu Norditropin SimpleXx Norditropine somatotropin, Novo Nordisk	Novo Nordisk	US	5633352	Denmark	10/12/1982 (Expires 2014)

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Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
somatropin, Genentech	growth hormone, Genentech hGH, Genentech Nutropin Nutropin AQ Nutropin AQ Pen Nutropin AQ Pen Cartridge NutropinAq NutropinAq Pen Protropin II somatotropin, Genentech somatropin, Schwarz	Genentech				(US expiry 2003)
Part II: Mammalian expression systems						
insulin, monocomponent, Novo	Actraphane Actrapid Actrapid HM Actrapid HM Penfill Actrapid Penfill Monotard HM Novolin Protaphane Ultratard	Zymogenetics				(US expiry 2005)
somatropin, Merck Serono	growth hormone, Merck Serono r-hGH[m] rhGH, Merck Serono Saizen Saizen Click.Easy Saizen, Click.Easy Saizon, cool.click SeroJet Serostim somatotropin, Merck Serono somatropin, cool.click somatropin, Easyject somatropin, SeroJet somatropin, Viajet 3 Zorbitive	Merck KGaA				(US expiry 2003)

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***Table 2.8: Patents - recombinant non-glycosylated proteins (BLA* pathway)**

Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
aldesleukin	IL-2, Novartis-3 interleukin, Novartis-3 Leuferon 2 Macrolin IL-2 Proleukin Ro-23-6019	Novartis	US	4752585	US	17/12/1985
interferon, Genentech (gamma1b)	Actimmune gamma1b-IFN, Genentech Immukin Immukine Imuforgamma Imukin interferon, InterMune (gamma1b interferon, Toray (gamma1B) interferon,Boehring Ing (gamma interferon,Mondobiotech (gamma	Genentech	US US	6936694 6936695	US US	06/05/1982 06/05/1982
anakinra	Antril IL-1 antagonist, Amgen IL-1ra, Amgen interleukin-1 antagonist, Amge Kineret rhIL-1ra	Amgen	European patent	343684	US	27/05/1988
interferon, Biogen (alpha2b)	alpha2b-IF, Biogen Cibian Intron A Sch-30500 YM-14090	Biogen Idec	European patent	32134	European patent	08/01/1980 (US expiry 2002)
interferon, Novartis (β1b)	Beneseron Betaferon Betaferon, Beta-assist BetaJect BetaJect Light BetaJect-3 Betaseron IFN-β1b, Berlex IFN-β1b, Novartis interferon, Berlex (β1b) SH-579 ZK-157046	Novartis	US	4588585	US	28/09/1984 (US Expiry 2007)
PEG-interferon alpha-2a, Roche	PEG-IFNalpha-2a, Roche PEG-interferon alpha-2a, Nekta Pegasys PEGylated interferon, Roche R-420 rhIFNalpha-2a, Roche Ro-25-3036 Ro-25-8310	Roche				(US expiry in 2005, Japan expiry in May 2017)

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Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
interferon, Enzon (alpha2b)	alpha2b-IF, Enzon interferon, Schering-Plough PEG-alpha interferon, Enzon PEG-alpha interferon, Schering PEG-interferon-alpha2b, Enzon PEG-interferon-alpha2b, Nektar PEG-interferon-alpha2b, Scheri PEG-Intron PEG-Intron A PEG-Intron Redipen Peginterferon alpha-2b PegIntron ViraFeronPeg	Enzon				(US expiry 2001)
interferon, Amgen (alpha)	Adopaferon Advaferon alpha-Con1-IF, Amgen alpha-IF, Amgen alpha-IF, Astellas alpha-IF-Con1 CIFN, Amgen CIFN, Astellas Consensus IFN Consensus interferon Infergen Infermax, Amgen Infermax, Astellas interferon alfacon-1 interferon, Amgen (alpha-Con1) interferon, Astellas (alpha) YM-643	Amgen	US	5661009	US	26/07/1996 (US expiry 2007)
filgrastim	CSF, Amgen CSF-G, Amgen G-CSF, Amgen Gran Granulokine Grastim, Dr Reddy's hG-CSF, Amgen Neupogen Neutropoietin Nupogen pluripoietin, Amgen r-metHuG-CSF Ro-8315	Amgen	US	4810643	US	23/08/1985

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Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
pegfilgrastim	filgrastim SD-01 Neulasta Neulastim Neupogen SR Neupogen-PEG Neupopeg PEG-GCSF, Amgen PEG-GCSF, Roche pegfilgrastim, Nektar R-1471 Ro-25-8315 SD-01	Amgen	European patent	733067	US	12/10/1994 (US expiry 2006)
oprelvekin	IL-11, Wyeth interleukin-11, Wyeth interleukin-11, Yamanouchi Neumega rhIL-11, Wyeth Sch-53620 YM-294	Wyeth	US	5646016	US	06/02/1991
reteplase	BM-06022 Ecokinase Rapilysin Retavase Retevase rPA, Centocor	Roche	Germany	3903581 (US5223256)	Germany	07/02/1989
denileukin diftitox	DAB389IL-2 IL-2 fusion protein, Seragen IL-2 fusion toxin, Seragen LY-335348 ONTAK Onzar	Ligand				

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***Table 2.9: Patents - recombinant glycosylated proteins (NDA* pathway)**

Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
follitropin alfa, Merck Serono	follitropin alpha, Merck Seron Gonal-F Gonal-F Multi-Dose Gonal-L Gonalef r-follitropin, Merck Serono rhFSH, Merck Serono	Merck KGaA	US	4923805	US	02/11/1983
recFSH, Organon	Follistim Follistim AQ follitropin β hCG, Organon Org-32489 Puregon Puregon pen Recagon Pen rhFSH, Organon	Akzo Nobel	US	5270057	European patent	20/03/1990
thyrotropin alfa, Genzyme	rhTSH, Genzyme Thyrogen thyroid-stimulating hormone, Ge TSH, Genzyme	Genzyme	US	5240832	US	20/06/1989
urokinase, ImaRx-2	Abbokinase Cultokinase	Imarx				(US expiry 2005)
imiglucerase	Cerezyme glucocerebrosidase, rec, Genzyme rGCR, Genzyme	Genzyme	US	5236838	US	22/12/1989 (US expiry 2001)
gemtuzumab ozogamicin	anti-CD33 MAb, AHP anti-CD33 MAb, UCB CDP-771 CMA-676 Mylotarg P-67	Wyeth	US	5739116	US	05/06/1995

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Table 2.10: Patents - recombinant glycosylated proteins (BLA pathway)

Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
Part I: Non-mammalian expression systems						
becaplermin	CTAP-III PDGF, Ethicon PDGF, Novartis Regranex rhPDGF-BB, Abbott rhPDGF-BB, J&J rhPDGF-BB, Novartis RWJ-60235	Novartis				
sargramostim	CSF-GM, Bayer GM-CSF, SchAG Interberin Leukine Prokine	Bayer	US	5229496	US	06/08/1985 (US expiry 2008)
Part II: Mammalian expression systems						
darbepoetin alfa	Aranesp KRN-321 NESP Injection Syringe NESP, Amgen NESP, Genesis NESP, Kirin NESP, Megapharm Novel Erythropoiesis Stimulati	Amgen	European patent	640619	US	17/08/1993 (Expires 2016)
erythropoietin, Amgen	EPO, Amgen Epoade epoetin alfa Epogen Eprex Erypo erythropoietin, Johnson Espo Globuren KRN-5702E Procrit	Amgen	US	5441868	US	23/10/1987
interferon,Merck Serono (β1a)	IFN-β1a, Merck Serono R-Frone Rebif Rebif 22 Rebif 44 rhIFN-β1A, Merck Serono β1A-IF, Merck Serono	Merck KGaA				(US Expiry 2005)
interferon, Biogen (β1a)	Avonex BG-9015 CHO-beta-interferon interferon, Abbott (β1a interferon, AstraZeneca (β1a) interferon, CSL (β1a) interferon, Dompe (β1a) interferon, Genzyme (β1a) interferon, Schering-P (β1a) β-IF, Biogen	Biogen Idec	European patent	41313	UK	03/04/1980 (US expiry 2003)
DNase, Genentech	dornase alfa dornase alpha Pulmozyme Pulmozyme CF Pulmozyme, AERx rhDNase	Genentech				

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Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
Factor VIIa, Zymo	eptacog-alpha Factor VIIa, Novo Nordisk NiaStase NN-007 NovoSeven rFVIIa, Novo Nordisk	Zymogenetics				
nonacog alfa	BeneFIX Factor IX, Baxter Factor IX, BTG Factor IX, Wyeth rhFIX	Wyeth	GB	2125409	GB	04/08/1982
drotrecogin alfa	APC, Lilly LTC-203 LTC-206 protein C, Lilly rhAPC, Lilly Xigris Zovan Zovant	Lilly	European patent	191606	US	08/02/1985
abciximab	7E3 anti-GPIIb/IIIa MAb c7E3Fab ReoPro	Johnson & Johnson				
etanercept	Embrel Enbrel p80 TNFR rhuTNFR:Fc rhvTNFR:Fc soluble TNF receptor, AHP soluble TNF receptor, Amgen STNFR TNF receptor, AHP TNF receptor, Amgen TNFR:Fc TNR-001	Amgen	US	5605690	US	08/02/1995
alteplase	Actase Actilyse Actiplas Activacin Activase Cathflo Activase Grtpa plasminogen activator, Genente tPA, Genentech	Genentech	European patent	93619	US	05/05/1982 (US expiry 2005)
tenecteplase	Metalyse plasminogen activator, Boehr plasminogen activator, Genen-2 plasminogen activator, Roche-2 TNK TNK-t-PA TNKase tPA, Boehringer, 2nd-gen tPA, Roche, 2nd-gen tPA-2, Genentech	Genentech				

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Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
rituximab	anti-CD20 MAb, Genentech anti-CD20 MAb, IDEC anti-CD20 MAb, Roche anti-CD20 MAb, Zenyaku IDEC-C2B8 MAbThera pan-B antibodies, Biogen pan-B antibodies, Genentech pan-B antibodies, Roche pan-B antibodies, Zenyaku R-105 Rituxan	Biogen Idec				Japan expiry in September 2014
adalimumab	D2E7 Humira LU-200134 Raheara	AstraZeneca				
palivizumab	anti-RSV MAb, Abbot anti-RSV MAb, MedImmune MEDI-493 RSV antibodies, Abbott RSV antibodies, MedImmune RSV MAbs, Abbott RSV MAbs, MedImmune Synagis	AstraZeneca				
trastuzumab	anti-HER-2 MAb, Genentech anti-HER-2 MAb, Roche HER-2 MAb, Genentech HER-2 MAb, Roche Herceptin R-597 rhuMAb HER2 Ro-45-2317	Genentech				Japan expiry in February 2010
bevacizumab	anti-VEGF MAb, Genentech anti-VEGF MAb, Roche Avastin R-435 Ro-4876646	Genentech				
natalizumab	AN-100226 Antegren Tysabri	Elan				
omalizumab	anti-IgE MAb, E25, Tanox anti-IgE MAb, Genen anti-IgE MAb, Novartis CGP-51901 E-25 IGE-025A rhuMAb-E25 Xolair	Genentech	US European patent US	5428133 407392 5422258	US US US	31/12/1987 31/12/1987 31/12/1987
infliximab	anti-TNF-alpha MAb, Centocor Avakine cA2 CenTNF Remicade TA-650	Johnson & Johnson				
alemtuzumab	alentuzumab Campath Campath-1H LDP-03 MabCampath ZK-217699	BTG				

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Generic name	Synonyms	Originator	Patent country	Patent number	Priority country	Priority date
efalizumab	anti-CD11a MAb, Genentech anti-CD11a MAb, Xoma anti-CD11a monoclonals, Genent anti-CD11a monoclonals, Xoma hu1124 Raptiva Xanelim	Genentech				
cetuximab	anti-EGFR MAbs, ImClone C225 Erbitux IMC-C225 MAb C225	Imclone Systems	US	5770195	US	12/01/1988
moroctocog alfa	Factor VIII, Biovitrum Factor VIII, Wyeth-2 ReFacto ReFacto AF ReFacto R2 Kit	Wyeth	European patent	381640	Sweden	10/01/1989
Factor VIII-2, Talecris	Factor VIII-2, CSL Helixate Helixate FS Helixate NexGen Kogenate FS Kogenate sucrose formulated	Talecris Biotherapeutics	US	5763401	US	12/07/1996
Factor VIII, Wyeth	Bioclate rAHF Factor VIII, Baxter rDNA Factor VIII, Baxter-2 Factor VIII, CSL rDNA rAHF, Baxter rAHF, Wyeth Recombinate rurioctocog alpha	Wyeth	US US	4757006 4868112	US US	28/10/1983 12/04/1985
Part III: Natural product						
aprotinin, Bayer	Trasylol	Bayer				

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Table 2.11: Commercialisation of candidate biosimilars

Rank	Number of drugs	Drug class
1	46	Interferon Alpha
2	45	Insulin
3	32	Erythropoietin
4	31	Somatotropin
5	20	Factor VIII
6	18	Cyclosporin
7	17	Granulocyte Stimulating Factor
8	17	Interferon Beta
9	16	Calcitonin
10	14	LHRH
11	12	Interleukin 2
12	10	Factor IX
13	9	Tissue Plasminogen Activator
14	9	Urokinase Plasminogen Activator
15	8	Follitropin
16	6	Granulocyte Macrophage Colony Stimulating Factor
17	6	Interferon Gamma
18	5	Octreotide
19	4	Desmopressin
20	4	Factor VIIa
21	4	Protein C
22	4	Teriparatide
23	3	Glucocerebrosidase
24	3	Hirudin
25	2	Bevacizumab
26	2	Enfuvirtide
27	2	Glucagon
28	2	Interleukin 11
29	1	Thyrotropin
30	1	Abciximab
31	1	Adalimumab
32	1	Alemtuzumab
33	1	Anakinra
34	1	Aprotinin
35	1	Becaplermin
36	1	Cetuximab
37	1	DNase
38	1	Efalizumab
39	1	Eptifibatide
40	1	Etanercept
41	1	Gemtuzumab
42	1	Infliximab
43	1	Natalizumab
44	1	Nesiritide
45	1	Omalizumab
46	1	Palivizumab
47	1	Rituximab
48	1	Trastuzumab
--	371	Total

Source: Pharmaprojects

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Table 2.12: Candidate biosimilars by gene target

Rank	Number of drugs	Percent	Target
1	58	16.9	interferon (alpha, beta and omega) receptor 2
2	44	12.8	insulin receptor
3	31	9.0	erythropoietin receptor
4	31	9.0	growth hormone receptor
5	18	5.2	coagulation factor VIII, procoagulant component (haemophilia A)
6	18	5.2	colony stimulating factor 3 receptor (granulocyte)
7	17	4.9	peptidylprolyl isomerase A (cyclophilin A)
8	16	4.7	calcitonin receptor
9	14	4.1	gonadotropin-releasing hormone receptor
10	12	3.5	interleukin 2 receptor, alpha
11	10	2.9	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
12	8	2.3	follicle stimulating hormone receptor
13	8	2.3	plasminogen activator, tissue
14	7	2.0	plasminogen activator, urokinase
15	6	1.7	interferon gamma receptor 1
16	5	1.5	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)
17	4	1.2	arginine vasopressin receptor 2 (nephrogenic diabetes insipidus)
18	4	1.2	coagulation factor VII (serum prothrombin conversion accelerator)
19	4	1.2	parathyroid hormone receptor 1
20	4	1.2	protein C (inactivator of coagulation factors Va and VIIIa)
21	4	1.2	von Willebrand factor
22	3	0.9	coagulation factor II (thrombin)
23	3	0.9	glucosidase, beta; acid (includes glucosylceramidase)
24	3	0.9	tumour necrosis factor (TNF superfamily, member 2)
25	2	0.6	calcitonin receptor-like
26	2	0.6	env, HIV-1
27	2	0.6	glucagon receptor
28	2	0.6	integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41)
29	2	0.6	integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)
30	2	0.6	interferon (alpha, beta and omega) receptor 1
31	2	0.6	interleukin 11 receptor, alpha
32	2	0.6	luteinizing hormone/choriogonadotropin receptor
33	2	0.6	vascular endothelial growth factor A
34	1	0.3	androgen receptor (dihydrotestosterone receptor; testicular feminization; spinal and bulbar muscular atrophy; Kennedy disease)
35	1	0.3	ATP-binding cassette, subfamily B (MDR/TAP), member 1
36	1	0.3	CD33 molecule
37	1	0.3	CD52 molecule
38	1	0.3	deoxyribonuclease I
39	1	0.3	epidermal growth factor receptor (erythroblastic leukaemia viral (v-erb-b) oncogene homologue, avian)
40	1	0.3	eukaryotic translation elongation factor 2
41	1	0.3	fusion protein (F), respiratory syncytial virus
42	1	0.3	immunoglobulin heavy constant epsilon
43	1	0.3	integrin, alpha 4 (antigen CD49d, alpha 4 subunit of VLA-4 receptor)
44	1	0.3	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1, alpha polypeptide
45	1	0.3	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)
46	1	0.3	integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)

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Rank	Number of drugs	Percent	Target
47	1	0.3	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)
48	1	0.3	interleukin 1 receptor, type I
49	1	0.3	membrane-spanning 4-domains, subfamily A, member 1
50	1	0.3	natriuretic peptide receptor A/guanylate cyclase A (atrionatriuretic peptide receptor A)
51	1	0.3	platelet-derived growth factor receptor, beta polypeptide
52	1	0.3	Somatostatin receptor
53	1	0.3	thyroid stimulating hormone receptor
54	1	0.3	tumour-associated calcium signal transducer 1
55	1	0.3	v-erb-b2 erythroblastic leukaemia viral oncogene homologue 2, neuro/glioblastoma derived oncogene homologue (avian)
--	11	3.2	Unspecified
--	368	100.0	Total

Source: Pharmaprojects, Entrez Gene

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***Table 2.13: Launched peptides and proteins by primary* pharmacology description**

Number	BS[1]	Primary pharmacology description
18	*	Insulin agonist
12	*	Plasminogen activator stimulant
11	*	Factor VIII agonist
11	*	Growth hormone agonist
10	*	Calcitonin stimulant
10	*	Erythropoietin agonist
9	*	Interferon alpha agonist
7	*	Follicle-stimulating hormone agonist
7	*	Granulocyte stimulating factor agonist
7	*	Thrombin inhibitor
5	*	DNA antagonist
5	*	Factor IX stimulant
5	*	Interferon beta agonist
5	*	LHRH agonist
4	*	Interferon alpha 2 agonist
4	*	Interleukin 2 agonist
3		Epidermal growth factor agonist
3	*	Fibrinogen antagonist
3	*	GPIIb IIIa receptor antagonist
3	*	Granulocyte macrophage colony stimulating factor agonist
3		Insulin like growth factor 1 agonist
3	*	Interferon alpha 2A agonist
3	*	Interferon alpha 2b agonist
3	*	Interferon beta 1 agonist
3	*	Interferon gamma agonist
3	*	Interleukin 2 receptor antagonist
3	*	Parathyroid hormone agonist
3		Sermorelin agonist
3		T cell inhibitor
3	*	Vasopressin agonist
2		Acetylcholine release inhibitor
2		Alpha 1 antitrypsin agonist
2		Alpha-galactosidase stimulant
2		Bone stimulating morphogenic protein factor stimulant
2		Colony stimulating factor agonist
2		Cysteine protease stimulant
2	*	Endothelial growth factor antagonist
2	*	ErbB-1 inhibitor
2		Fibrinogen stimulant
2	*	Glucagon agonist
2	*	Glucosylceramidase stimulant
2		Growth hormone antagonist
2		Growth hormone releasing factor antagonist
2		Hyaluronidase stimulant
2	*	LHRH antagonist
2		mTOR kinase inhibitor
2		Plasmin stimulant
2	*	Platelet growth factor agonist
2		Secretin agonist
2	*	Somatostatin agonist
2		Superoxide dismutase stimulant
2		Thyrotropin releasing hormone agonist
2	*	Tumour necrosis factor alpha antagonist
1		Adenosine deaminase stimulant
1		Alpha glucosidase stimulant
1	*	Alpha4beta1 integrin antagonist
1		Amylase stimulant
1		Amylin agonist

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Number	BS[1]	Primary pharmacology description
1		Angiotensin II agonist
1		Angiotensin II antagonist
1		Asparaginase stimulant
1		Atrial natriuretic peptide agonist
1		Bone growth factor stimulant
1	*	Brain natriuretic peptide agonist
1		Calcium channel agonist
1		CCK agonist
1	*	CD11a antagonist
1		CD2 antagonist
1	*	CD20 antagonist
1		CD28 antagonist
1		CD3 antagonist
1		Collagen agonist
1		Collagenase stimulant
1		Complement factor C5 inhibitor
1		Corticotropin releasing factor agonist
1		Cyclic AMP agonist
1	*	Deoxyribonuclease 1 stimulant
1	*	ErbB-2 inhibitor
1	*	Factor VIIa stimulant
1		Factor XIII stimulant
1		Fibroblast growth factor 2 agonist
1		Fibroblast growth factor 7 agonist
1		Glucagon-like peptide 1 agonist
1	*	GP41 antagonist
1		Growth hormone releasing factor agonist
1		Haemophilia A
1	*	hCG agonist
1		Iduronate 2 sulfatase stimulant
1	*	Immunoglobulin E inhibitor
1	*	Interferon agonist
1	*	Interferon alpha 1b agonist
1	*	Interferon alpha 2c agonist
1	*	Interferon alpha N1 agonist
1	*	Interferon alpha N3 agonist
1	*	Interferon gamma 1a agonist
1	*	Interferon gamma 1b agonist
1	*	Interleukin 1 receptor antagonist
1	*	Interleukin 11 agonist
1		Interleukin 6 receptor antagonist
1		Interleukin 8 antagonist
1	*	Kallikrein antagonist
1		Leucotriene agonist
1		Leucotriene C4 antagonist
1	*	LH agonist
1		L-iduronidase stimulator
1	*	Lymphocyte inhibitor
1		Metallic radical formation inhibitor
1		N Acetylgalactosamine 4 sulfatase stimulant
1		Nerve growth factor agonist
1		Stem cell growth factor agonist
1		Sucrose \a-glucosidase stimulant
1		Thymosin fraction A1 agonist
1	*	Thyroid hormone function agonist
1		Tumour necrosis factor alpha agonist
1	*	Tumour necrosis factor antagonist
1		Urate oxidase stimulant
281	-	Subtotal
98	-	Others[2]
379	-	Total

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Number	**BS[1]**	**Primary pharmacology description**
Notes: 1. At least one agent in "best-selling" category 2. Nonspecific descriptions such as Unidentified, Not Applicable, Immunostimulant, Immunosuppressant, Peptide agonist.		

Source: Pharmaprojects

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Table 2.14: Candidate biosimilars (interferon alpha)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Amgen (alpha)	Adopaferon Advaferon alpha-Con1-IF, Amgen alpha-IF, Amgen alpha-IF, Astellas alpha-IF-Con1 CIFN, Amgen CIFN, Astellas Consensus IFN Consensus interferon Infergen Infermax, Amgen Infermax, Astellas interferon alfacon-1 interferon, Amgen (alpha-Con1) interferon, Astellas (alpha) YM-643	Launched	Amgen	Astellas Chiesi Valeant	Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon, Biogen (alpha2b)	alpha2b-IF, Biogen Cibian Intron A Sch-30500 YM-14090	Launched	Biogen Idec	Schering-Plough Astellas	Recombinant interferon	Interferon alpha 2b agonist	Cancer, leukaemia, hairy cell	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Enzon (alpha2b)	alpha2b-IF, Enzon interferon, Schering-Plough PEG-alpha interferon, Enzon PEG-alpha interferon, Schering PEG-interferon-alpha2b, Enzon PEG-interferon-alpha2b, Nektar PEG-interferon-alpha2b, Scheri PEG-Intron PEG-Intron A PEG-Intron Redipen Peginterferon alpha-2b PegIntron ViraFeronPeg	Launched	Enzon	Schering-Plough Nektar Therapeutics	Formulation, conjugate, pegylated	Interferon alpha 2b agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
PEG-interferon alpha-2a, Roche	PEG-IFNalpha-2a, Roche PEG-interferon alpha-2a, Nekta Pegasys PEGylated interferon, Roche R-420 rhIFNalpha-2a, Roche Ro-25-3036 Ro-25-8310	Launched	Roche	Nektar Therapeutics Aradigm	Formulation, conjugate, pegylated	Interferon alpha 2A agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon, BI (alpha2c)	Berofor alpha 2	Launched	Boehringer Ingelheim		Recombinant interferon	Interferon alpha 2c agonist	Infection, herpes virus, general	interferon (alpha, beta and omega) receptor 2
interferon, CJCorp (alpha2)	alpha2-IF, Cheil Alphaferon Eye Drops	Launched	CJ Corp		Recombinant interferon	Interferon alpha 2 agonist	Cancer, melanoma	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Dong-A (alpha2)	alpha2-IF, Dong-A Inter-alpha, Dong-A	Launched	Dong-A		Recombinant interferon	Interferon alpha 2 agonist	Cancer, melanoma	interferon (alpha, beta and omega) receptor 2
interferon, Dynavax	alpha-IF, Dynavax	Launched	Dynavax Technologies		Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-B virus	interferon (alpha, beta and omega) receptor 2
interferon, Genentech (alpha2a)	alpha2a-IF, Genentech alpha2a-IF, Gilead alpha2a-IF, Roche alpha2a-IF, Stiefel alpha2a-IF, Takeda Canferon Canferon-A interferon, Gilead (alpha2a) interferon, Roche (alpha2a) interferon, Stiefel (alpha2a) interferon, Takeda (alpha2a) Laroferon Ro-22-8181 Roferon Roferon-A	Launched	Genentech	Roche Takeda Gilead Sciences	Recombinant interferon	Interferon alpha 2A agonist	Cancer, leukaemia, hairy cell	interferon (alpha, beta and omega) receptor 2
interferon, LG Life (alpha)	alpha-IF, LG Life Sciences IFN-alpha, Life Sciences Intermax-alpha rec-IFN-alpha, LG life Science	Launched	LG Life Sciences		Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-B virus	interferon (alpha, beta and omega) receptor 2
interferon, Shantha (alpha2a)	interferon, Pfizer (alpha2a) Shanferon	Launched	Shantha Biotechnics	Pfizer	Recombinant interferon	Interferon alpha 2A agonist	Infection, hepatitis-B virus	interferon (alpha, beta and omega) receptor 2
interferon, Sidus (alpha2)	alpha2-IF, Sidus Bioferon	Launched	Sidus		Recombinant interferon	Interferon alpha 2 agonist	Infection, general	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Beijing (alpha1b)	Hapgen	Launched	Beijing Tri-Prime Genetic		Recombinant interferon	Interferon alpha 1b agonist	Unspecified	Unspecified
interferon, AW (alpha)	Alfaferone alpha-IF, Alfa Wassermann alpha-IF, Cilag alpha-interferon, AW alpha-interferon, BioNative alpha-interferon, Cilag interferon, AlfaNative (alpha) interferon, Cilag (alpha)	Launched	Alfa Wassermann	Viragen Johnson & Johnson	Antiviral, interferon	Interferon alpha agonist	Infection, hepatitis-B virus	interferon (alpha, beta and omega) receptor 2
interferon, Boehringer In (alpha)	alpha-IF, Boehringer Ingelheim Berofor	Launched	Boehringer Ingelheim		Antiviral, interferon	Interferon alpha agonist	Infection, herpes virus, general	interferon (alpha, beta and omega) receptor 2
interferon, EGIS (alpha)	alpha-IF, EGIS Egiferon	Launched	Servier		Cytokine	Interferon alpha agonist	Cancer, leukaemia, hairy cell	interferon (alpha, beta and omega) receptor 2
interferon, GlaxoSmithK(alpha-N1)	alpha-N1-IF, GlaxoSmithKline alpha-N1-IF, Pacific alpha-N1-IF, Sigma-Tau alpha-N1-IF, Sumitomo Humoferon interferon, Pacific (alpha-N1) interferon, Sigma-Tau (alpha-N interferon, Sumitomo (alpha-N1 NSC-339140 Sumiferon Wellferon	Launched	GlaxoSmithKline	Dainippon Sumitomo Pharma Pacific Pharmaceuticals (Canada)	Anticancer, interferon	Interferon alpha N1 agonist	Cancer, leukaemia, chronic myelogenous	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Hayashibara (alpha)	alpha-IF, Hayashibara interferon, Mochida (alpha) interferon, Otsuka (alpha) MOR-22 OIF	Launched	Hayashibara		Anticancer, interferon	Interferon alpha agonist	Cancer, renal	interferon (alpha, beta and omega) receptor 2
interferon, Hemispherx	Alfa-n3-IF, Andromaco Alfa-n3-IF, ISI Alferon Alferon A Alferon Gel Alferon LDO Alferon N Alferon N Gel Alferon N Injection Altemol Cellferon Cytoferon interferon,Hemispherx(Alfa-n3)	Launched	Hemispherx Biopharma		Antiviral, interferon	Interferon alpha N3 agonist	Infection, human papilloma virus	interferon (alpha, beta and omega) receptor 2
interferon, MediCuba (alpha2)	alpha2-IF, MediCuba Leuferon	Launched	Nycomed Pharma		Antiviral, interferon	Interferon alpha 2 agonist	Infection, general	interferon (alpha, beta and omega) receptor 2
interferon, Sidus (alpha)	alpha-IF, Sidus I.L	Launched	Sidus		Antiviral, interferon	Interferon alpha agonist	Infection, herpes simplex virus	interferon (alpha, beta and omega) receptor 2
interferon, Viragen	alpha-IF, ViraNative Alphaferon IFNalpha Le Interferon Alfanative interferon, Viragen (alpha)-3 interferon, ViraNative Multiferon, ViraNative Multiform nIFN	Launched	Viragen	Key Oncologics CJ Corp Fresenius Swedish Orphan	Cytokine	Interferon alpha agonist	Cancer, leukaemia, hairy cell	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Schering-P (alpha2b)	alpha2b-IF, Schering-Plough Viraferon Virtron	Launched	Schering-Plough		Formulation, parenteral, other	Interferon alpha 2b agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon, Hayashibara(alpha),or	interferon, Amarillo (alpha) interferon, Atrix (alpha) interferon, Biopharma (alpha) interferon, Key Oncol (alpha) interferon, North China (alpha interferon,-alpha, oral Veldona	Registered	Hayashibara	Amarillo Biosciences QLT Biopharm GmbH North China Pharmaceutical Key Oncologics Nobel	Formulation, oral, other	Interferon alpha agonist	Infection, influenza virus prophylaxis	interferon (alpha, beta and omega) receptor 2
interferon, HGS (alpha)	ABF-656 Albuferon Albuferon alfa Albuferon-alpha	Phase III	Human Genome Sciences	Novartis	Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon, Scigen (alpha2a)	Sci-Feron A	Phase II	Scigen		Recombinant interferon	Interferon alpha 2A agonist	Infection, hepatitis virus, general	interferon (alpha, beta and omega) receptor 2
interferon, SciGen (alpha2b)	Sci-Feron B	Phase II	Scigen		Recombinant interferon	Interferon alpha 2b agonist	Infection, hepatitis virus, general	interferon (alpha, beta and omega) receptor 2
interferon, Biolex (alpha2b) CR	BLX-883 CR interferon, OctoPlus (alpha2b) interferon, PolyActive (alpha2 Locteron	Phase II	Biolex	Octoplus	Formulation, modified-release, >24hr	Interferon alpha 2b agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon, Biphasix, (alpha2b)	interferon, Helix (alpha2b) interferon-alpha cream, Helix topical interferon alpha-2b, H	Phase II	Helix Biopharma		Formulation, dermal, topical	Interferon alpha 2b agonist	Infection, human papilloma virus	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Flamel (alpha2b)	IFN alpha-XL IFN-alpha2b XL interferon, Medusa (alpha2b)	Phase II	Flamel Technologies		Formulation, optimised, nanoparticles	Interferon alpha 2b agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon, KeyBay (alpha), oral	KB-201	Phase II	Keybay Pharma	Amarillo Biosciences	Formulation, oral, other	Interferon alpha agonist	Fibrosis, pulmonary	interferon (alpha, beta and omega) receptor 2
interferon, Nautilus (alpha)	Belerofon IFN-alpha, Nautilus	Phase I	Nautilus Biotech	Hanall Pharmaceutical	Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon, LG Life (alpha), SR	SR-IFN-alpha, LG Life Sciences	Phase I	LG Life Sciences		Formulation, modified-release, other	Interferon alpha agonist	Unspecified	interferon (alpha, beta and omega) receptor 2
PEG-interferon-alpha, Maxygen	interferon, Maxygen (alpha) interferon, Roche (alpha) Maxy-24 Maxy-alpha PEG-interferon-alpha, Roche R-7025	Phase I	Maxygen	Roche	Formulation, conjugate, pegylated	Interferon alpha agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon-alpha8, RioTech	IFN-alpha8, RioTech	Preclinical	Riotech		Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 1
BK-0033	alpha2b-IFN, Keryos IFN-alpha2b, Keryos interferon, Keryos (alpha2b) interferon-alpha2b, Keryos	Preclinical	Keryos		Recombinant interferon	Interferon alpha 2b agonist	Unspecified	interferon (alpha, beta and omega) receptor 2
GEA-0071	IFN71 interferon-alpha variants,GenO	Preclinical	Genodyssee Pharmaceuticals	Debiopharm	Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
GEA-0092	interferon-alpha variants,GenO	Preclinical	Genodyssee Pharmaceuticals		Recombinant interferon	Interferon alpha agonist	Unspecified	interferon (alpha, beta and omega) receptor 2
interferon, conj,Hanmi (alpha)	HM-10660 HM-10660A IFN, conj, Hanmi (alpha)	Preclinical	Hanmi		Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
interferon,Bolder (alpha),cys-PEG	alpha-IF, cys-PEG, Bolder BBT-006 cys-PEG interferon,Bolder (/a) interferon (alpha), cys-PEG, B	Preclinical	Bolder Biotechnology		Recombinant interferon	Interferon alpha agonist	Unspecified	interferon (alpha, beta and omega) receptor 2
interferon, MTT (alpha)	Greenferon	Preclinical	Molecular Targeting Technology		Recombinant interferon	Interferon alpha agonist	Infection, hepatitis-C virus prophylaxis	Unspecified
interferon, Digna (alpha5)	IFN, Digna (alpha5) NAHE001	Preclinical	Digna Biotech		Antiviral, interferon	Interferon alpha 5 agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2
GlycoPEG-interferon-alpha, Neose	interferon, Neose (alpha)	Preclinical	Neose Technologies		Formulation, conjugate, pegylated	Interferon alpha agonist	Infection, general	interferon (alpha, beta and omega) receptor 2
interferon, Biogen (alpha)	IFN-alpha-Fc, Biogen	Preclinical	Biogen Idec		Formulation, inhalable, systemic	Interferon alpha agonist	Unspecified	interferon (alpha, beta and omega) receptor 2
interferon, SkyePharma (alpha2b)	DepoIFN interferon, DepoFoam (alpha2b) interferon, GeneMedix (alpha2b	Preclinical	Skyepharma		Formulation, modified-release, >24hr	Interferon alpha 2b agonist	Infection, hepatitis-C virus	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
pegylated interferon-alpha, Ambrx	PEG-IFN-alpha, Ambrx PEG-IFN-alpha, Roche pegylated interferon-alpha, Ro	Preclinical	Ambrx	Roche	Formulation, conjugate, pegylated	Interferon alpha agonist	Infection, hepatitis-B virus	Unspecified

Source: Pharmaprojects

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Table 2.15: Candidate biosimilars (insulin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
insulin analogue, Lilly	Humalog Humalog MirioPen Humalog Mix25 Humalog Mix50 Humalog N Humalog25 insulin lispro Liprolog Bio- Lysprol Lispro LY-275585	Launched	Lilly		Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor
Insulin Aspart	insulin analogue, Novo Nordisk NovoLog NovoRapid	Launched	Novo Nordisk		Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor
insulin glargine	Hoe-901 insulin analogue, Sanofi Lantus Lantus SoloStar Optisulin rDNA insulin analogue, Sanofi	Launched	Sanofi-Aventis		Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Genentech, recombi	Huminsulin Humulin Humulin L Lente Humulin NPH Humulin Reg Humulin U Ultralente Humulin-C Humulina Humuline Hunulin-N Umuline Umuline Zinc	Launched	Genentech	Lilly Shionogi	Recombinant hormone	Insulin agonist	Diabetes, general	insulin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
insulin, monocomponent, Novo	Actraphane Actrapid Actrapid HM Actrapid HM Penfill Actrapid Penfill Monotard HM Novolin Protaphane Ultratard	Launched	Zymogenetics	Novo Nordisk Bristol-Myers Squibb Sanofi-Aventis	Insulin	Insulin agonist	Diabetes, general	insulin receptor
insulin, Novo Nordisk	Combitard Initard Insulard Insulatard Mixtard Semisyn Unitard Velosulin Velosulin BR Velosuline	Launched	Novo Nordisk	GlaxoSmithKline Merck & Co	Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Chiron	proinsulin, Chiron	Launched	Novartis	Novo Nordisk	Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Ferring Pharma	insulin, Abbot insulin, SciGen SciLin	Launched	Ferring	Scigen Abbott	Recombinant hormone	Insulin agonist	Diabetes, general	insulin receptor
insulin, recombinant, Aventis	HGT pSW3M HR-1799 insulin, HGT insulin, HPR Insuman Insuman Basal Insuman Comb Insuman Infusat Insuman Rapid r-human insulin, Aventis rDNA insulin, Aventis	Launched	Sanofi-Aventis		Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Zymo, recombinant	insulin, Novo, recombinant	Launched	Novo Nordisk	Zymogenetics	Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
insulin detemir	Levemir long-acting insulin, Novo NN-304	Launched	Novo Nordisk		Insulin	Insulin agonist	Diabetes, type 2	insulin receptor
insulin glulisine	1964 Apidra fast-acting insulin, Aventis HMR-1964	Launched	Sanofi-Aventis		Insulin	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Hoechst, semisynth	Depot-H-Insulin H-Insulin	Launched	Sanofi-Aventis		Insulin	Insulin agonist		insulin receptor
insulin, Organon	Orgasuline Orgasuline 30/70 Orgasuline NL/ordinaire Orgasuline Retard	Launched	Akzo Nobel		Insulin	Insulin agonist		insulin receptor
insulin, semisynthetic, Biobra	Biohulin	Launched	Novo Nordisk		Insulin	Insulin agonist		insulin receptor
insulin Aspart, biphasic, Novo	Novolog Mix 70/30 NovoMix 30 NovoMix 30 FlexPen	Launched	Novo Nordisk		Formulation, modified-release, multi	Insulin agonist	Diabetes, type 2	insulin receptor
insulin, buccal, Generex	insulin, RapidMist Oral-lyn Oralgen Oralin	Launched	Generex		Formulation, transmucosal, systemic	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Nektar, inhaled	Exubera Exubera 2nd-Generation Devi HMR-4006 insulin inhaled, Pfizer insulin inhaled, Sanofi-Aventi insulin, inhaled, Nektar insulin, Pfizer, inhaled insulin, Sanofi-Aventis inhale PEG-insulin	Launched	Nektar Therapeutics	Pfizer	Formulation, inhalable, dry powder	Insulin agonist	Diabetes, type 2	insulin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
Insulin Aspart, biphasic-2, No	NovoMix 50 NovoMix 70	Registered	Novo Nordisk		Formulation, modified-release, multi	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Biodel-1	VIAject	Phase III	Biodel		Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, AutoImmune	AI-401	Phase III	Autoimmune		Recombinant hormone	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, AERx	AERx iDMS inhaled, insulin insulin, Aradigm insulin, inhaled, Aradigm insulin, inhaled, Novo NN-1998 Novo insulin Novo Nordisk, inhaled	Phase III	Novo Nordisk		Formulation, inhalable, systemic	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Alkermes, inhaled	AIR Insulin insulin, AIR insulin, inhaled, Alkermes	Phase III	Alkermes	Lilly	Formulation, inhalable, systemic	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Technosphere, Mannkind	insulin, pulmonary, Mannkind pulmonary insulin, Mannkind Technosphere Insulin System Technosphere insulin, Mannkind	Phase III	Mannkind		Formulation, inhalable, dry powder	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Kos, inhaled	insulin, inhaled, Kos KI-02-212	Phase II	Abbott		Formulation, inhalable, systemic	Insulin agonist	Diabetes, type 2	insulin receptor
insulin, Bentley, intranasal	Nasulin	Phase II	Bentley	Biocon	Formulation, transmucosal, nasal	Insulin agonist	Diabetes, type 2	insulin receptor
insulin, Emisphere	insulin, eligen	Phase II	Emisphere Technologies		Formulation, oral, other	Insulin agonist	Diabetes, type 2	insulin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
insulin, Flamel	Basulin insulin, CR, Novo insulin, Medusa LABI NN-1215	Phase II	Flamel Technologies		Formulation, optimised, nanoparticles	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, oral, Biocon-2	hexyl insulin monoconj, Biocon HIM2 IN-105 NIN-058	Phase II	Biocon		Formulation, oral, other	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Biodel-2	VIAtab	Phase I	Biodel		Recombinant hormone	Insulin agonist	Diabetes, general	insulin receptor
NN-5401		Phase I	Novo Nordisk		Antidiabetic	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, Altea	AT-1391 insulin, MicroPor	Phase I	Altea		Formulation, parenteral, targeted	Insulin agonist	Diabetes, general	insulin receptor
insulin, Innovata	AND-398 insulin, Inhalation Therapeuti insulin, QDose	Phase I	Vectura	Bristol-Myers Squibb	Formulation, optimised, microencapsulate	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, nasal, Nastech		Phase I	Nastech		Formulation, transmucosal, nasal	Insulin agonist	Diabetes, general	insulin receptor
insulin, oral, Oramed		Phase I	Oramed Pharmaceuticals		Formulation, oral, targeted	Insulin agonist	Diabetes, general	insulin receptor
insulin, Phosphagenics	TPM-02 TPM-02/insulin	Phase I	Phosphagenics		Formulation, transdermal, systemic	Insulin agonist	Diabetes, type 1	insulin receptor
insulin, ProMaxx	insulin, pulmonary, Baxter RHIIP	Phase I	Baxter International		Formulation, optimised, microparticles	Insulin agonist	Diabetes, general	insulin receptor
insulin, Sembiosys		Preclinical	Sembiosys Genetics		Recombinant hormone	Insulin agonist	Diabetes, general	insulin receptor
EN-122002		Preclinical	Protemix		Antidiabetic	Insulin agonist	Diabetes, type 2	insulin receptor
insulin, MAP	Tempo Insulin	Preclinical	MAP Pharmaceuticals		Formulation, inhalable, dry powder	Insulin agonist	Diabetes, general	insulin receptor
insulin, Mystic, Ventaira	insulin, EHD, Ventaira	Preclinical	Ventaira		Formulation, inhalable, systemic	Insulin agonist	Diabetes, general	insulin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
insulin, Organon-2	insulin, CarboCarrier Org-211559	Preclinical	Akzo Nobel		Formulation, modified-release, >24hr	Insulin agonist	Unspecified	insulin receptor
insulin, Advancell	ADV-P2	Preclinical	Advancell		Formulation, optimised, nanoparticles	Insulin agonist	Diabetes, general	insulin receptor
insulin, Medivas		Preclinical	Medivas		Formulation, oral, other	Insulin agonist	Diabetes, general	insulin receptor
insulin, oral, Apollo	insulin, Oradel	Preclinical	Apollo Life Sciences		Formulation, optimised, microencapsulate	Insulin agonist	Diabetes, general	insulin receptor

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Table 2.16: Candidate biosimilars (erythropoietin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
darbepoetin alfa	Aranesp KRN-321 NESP Injection Syringe NESP, Amgen NESP, Genesis NESP, Kirin NESP, Megapharm Novel Erythropoiesis Stimulati	Launched	Amgen	Kirin Brewery Genesis Pharma Megapharm Fresenius	Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, Amgen	EPO, Amgen Epoade epoetin alfa Epogen Eprex Erypo erythropoietin, Johnson Espo Globuren KRN-5702E Procrit	Launched	Amgen	Dompe Esteve Johnson & Johnson Kirin Brewery Daiichi Sankyo	Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
epoetin delta	Dynepo EPO gene activation, Aventis EPO gene activation, Shire erythropoietin gene activation erythropoietin, Shire GA-EPO gene activated EPO, Aventis gene activated EPO, Shire HMR-4396 MDL-104396	Launched	Shire	Sanofi-Aventis	Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, Dong-A	DA-3285 EPO, Dong-A Eporon	Launched	Dong-A		Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, Dragon	EPO, Dragon Ning Hong Xin Proclat Vintor	Launched	Dragon Pharmaceutical		Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, Elanex	EPO, Elanex EPO, ratiopharm epoetin omega EPOMAX erythropoietin, ratiopharm Hemax	Launched	Elanex Pharmaceuticals	Baxter International Sidus	Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, LGLS	EPO, LGLS	Launched	LG Life Sciences		Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, Shantha	Shanpoietin	Launched	Shantha Biotechnics		Recombinant growth factor	Erythropoietin agonist	Anaemia, aplastic	erythropoietin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
erythropoietin, Wyeth	EPO, Wyeth Epoch epoetin beta Epogin Eritrogen erythropoietin, Chugai erythropoietin, Roche Marogen Neo-Recormon NeoRecormon Recormon Recormon-S Recornorm	Launched	Wyeth	Roche	Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
ior EPOCIM	erythropoietin, CIM hrEPO	Launched	Center of Molecular Immunology		Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
R-744	CERA EPO derivative, Roche Mircera	Pre-registration	Roche	Nektar Therapeutics	Urological	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, JCR	EPO, JCR JR-013	Phase II	JCR Pharmaceuticals	Kissei	Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
NTx-265	erythropoietin + hCG, StemCell hCG+erythropoietin, StemCell T	Phase II	Stem Cell Therapeutics		Recombinant hormone	hCG agonist	Ischaemia, cerebral	luteinizing hormone/chorionadotropin receptor erythropoietin receptor
NTx-028	schizophrenia therapy, SCT	Phase II	Stem Cell Therapeutics		Neuroleptic	Erythropoietin agonist	Schizophrenia	erythropoietin receptor
NTx-268	multiple sclerosis ther, SCT	Phase II	Stem Cell Therapeutics		Multiple sclerosis treatment	Erythropoietin agonist	Multiple sclerosis, chronic progressive	erythropoietin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
erythropoietin, Neose	EPO, Neose GlycoPEG-EPO NE-180 PEG-EPO, Neose	Phase II	Neose Technologies		Formulation, conjugate, pegylated	Erythropoietin agonist	Chemotherapy-induced injury, bone marrow, anaemia	erythropoietin receptor
Hematide	AF-37702 Pharmaprojects No. 4972	Phase II	Affymax	Johnson & Johnson Takeda Nektar Therapeutics	Formulation, conjugate, pegylated	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
AMG-114		Phase I	Amgen		Recombinant growth factor	Erythropoietin agonist	Chemotherapy-induced injury, bone marrow, anaemia	erythropoietin receptor
erythropoietin, Biogen 2	EPO-Fc, Biogen	Phase I	Biogen Idec		Formulation, inhalable, systemic	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin conj, Hanmi	EPO conjugate, Hanmi HM-10760 HM-10760A	Preclinical	Hanmi		Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, DNAPrint	PT-401 Super EPO	Preclinical	DNAPrint Genomics		Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, Protein Scienc	EPO, Protein Sciences rEPO, Protein Sciences	Preclinical	Protein Sciences		Recombinant growth factor	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
Nova-EPO	erythropoietin, Novagenetics	Preclinical	Novagenetics		Recombinant hormone	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
AG-EM-0040	EMP, Aplagen EPO mimetic, AplaGen	Preclinical	Aplagen Biopharmaceuticals		Recombinant, other	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
EPO derivative, Lundbeck	erythropoietin deriv, Lundbeck	Preclinical	Lundbeck	Warren Pharmaceuticals	Neuroprotective	Erythropoietin agonist	Unspecified	erythropoietin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
EPO derivative, Shire	erythropoietin deriv, Shire renal therapy, Shire SPD-500	Preclinical	Shire	Warren Pharmaceuticals	Urological	Erythropoietin agonist	Unspecified	erythropoietin receptor
erythropoietin deriv, Trans	EPO derivative, TransTech EPO mimetics, TransTech	Preclinical	Transtech Pharma		Anticancer, other	Erythropoietin agonist	Unspecified	erythropoietin receptor
erythropoietin, Nautilus	Eporal erythropoietin, HanAll	Preclinical	Nautilus Biotech	Hanall Pharmaceutical	Antianaemic	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
GO-EPO	erythropoietin-alpha variant,G	Preclinical	Genodyssee Pharmaceuticals		Antianaemic	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, Warren	WP-170	Preclinical	Warren Pharmaceuticals	Lundbeck	Neuroprotective	Erythropoietin agonist	Unspecified	Unspecified
EPO-stimulating protein, Bolde	cys-PEG EPO, Bolder cys-PEG erythropoietin, Bolder EPO + IgG1-Fc, Bolder EPO, cys-PEG, Bolder erythropoietin + IgG1-Fc,Bolde erythropoietin, cys-PEG, Bolde	Preclinical	Bolder Biotechnology		Formulation, conjugate, pegylated	Erythropoietin agonist	Anaemia, general	erythropoietin receptor
erythropoietin, Flamel	EPO XL, Flamel EPO XL, Medusa erythropoietin, Medusa	Preclinical	Flamel Technologies		Formulation, optimised, nanoparticles	Erythropoietin agonist	Anaemia, general	erythropoietin receptor

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Table 2.17: Candidate biosimilars (factor VIII)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
Factor VIII, Genentech	Bay-w-6240 Factor VIII, Bayer Kogenate	Launched	Genentech	Bayer	Recombinant, other	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII, Wyeth	Bioclate rAHF Factor VIII, Baxter rDNA Factor VIII, Baxter-2 Factor VIII, CSL rDNA rAHF, Baxter rAHF, Wyeth Recombinate rurioctocog alpha	Launched	Wyeth	Baxter International CSL	Recombinant, other	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
moroctocog alfa	Factor VIII, Biovitrum Factor VIII, Wyeth-2 ReFacto ReFacto AF ReFacto R2 Kit	Launched	Wyeth	Biovitrum	Recombinant, other	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII, Aventis	BI-8021	Launched	Sanofi-Aventis		Blood fraction	Factor VIII agonist		coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII, Baxter	Haemofil Method M Monoclonal purified	Launched	Baxter International		Blood fraction	Factor VIII agonist		coagulation factor VIII, procoagulant component (haemophilia A)

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
Factor VIII, Baxter-3	Advate Advate ultra-high octocog alfa rAHF, next-gen, Baxter rAHF-PFM	Launched	Baxter International		Recombinant, other	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII-2, Talecris	Factor VIII-2, CSL Helixate Helixate FS Helixate NexGen Kogenate FS Kogenate sucrose formulated	Launched	Talecris Biotherapeutics	CSL	Recombinant, other	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII, Talecris-3	Koate-DVI	Launched	Talecris Biotherapeutics	Gador	Blood fraction	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A) von Willebrand factor
Factor VIII:c, ZLB Behring	Monoclate Monoclate-P	Launched	CSL		Blood fraction	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII, Ipsen	Factor VIIIc, Ipsen Hyate Hyate C	Launched	Ipsen	Sanofi-Aventis	Blood fraction	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A) von Willebrand factor
Factor VIII, Grifols	Alphanate	Launched	Grifols		Blood fraction	Factor VIII agonist	Haemophilia A	von Willebrand factor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
V.F.	Vueffe	Launched	Baldacci		Haemostatic	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII, Green Cross	Greengene	Phase III	Green Cross		Recombinant, other	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
OBI-1	Factor VIII, Ipsen-2	Phase II	Ipsen		Recombinant, other	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII, liposomal, Bayer	PEG-Factor VIII, Bayer-2	Phase II	Bayer		Formulation, optimized, liposomes	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
Factor VIII-Fc, Biogen		Preclinical	Biogen Idec		Recombinant, other	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
von Willebrand factor, Baxter		Preclinical	Baxter International		Recombinant, other	Factor VIII agonist	von Willebrand's disease	von Willebrand factor
Factor VIII, Neose	Factor VIII, Novo-2	Preclinical	Neose Technologies	Novo Nordisk	Haemostatic	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
iATX FVIII		Preclinical	Apitope Technology		Haemostatic	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)
pegylated clotting proteins,Ba	pegylated clotting proteins,Ne	Preclinical	Baxter International	Nektar Therapeutics	Formulation, conjugate, pegylated	Factor VIII agonist	Haemophilia A	coagulation factor VIII, procoagulant component (haemophilia A)

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Table 2.18: Candidate biosimilars (cyclosporin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
ciclosporin	cyclosporin-A Neoral OL-27-400 OLO-400 Sandimmun Sandimmun Neoral Sandimmune	Launched	Novartis	Daiichi Sankyo	Immunosuppressant	Immunosuppressant	Transplant rejection, general	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin A, ophthalmic	ciclosporin A, Allergan cyclosporin, Allergan Refresh Plus Restasis	Launched	Allergan	NPS Pharmaceuticals Inspire	Formulation, mucosal, topical	Immunosuppressant	Dry eye syndrome	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin-A, Genzyme-2	ciclosporin-A, CycloTech Sang-2000 Sang-35 SangCya	Launched	Genzyme	Abbott	Formulation, other	Immunosuppressant	Transplant rejection, general	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin A, Chong Kun Dang	Cipol-N CKD-461 KD-461	Launched	Chong Kun Dang		Formulation, optimised, microemulsion	Immunosuppressant	Transplant rejection, general	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin, Abbott	Gengraf	Launched	Abbott	Genzyme	Formulation, other	Immunosuppressant	Transplant rejection, general	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin, ophthalmic, Santen	DE-076 Papilock Mini	Launched	Santen		Formulation, mucosal, topical	Immunosuppressant	Keratoconjunctivitis	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin, Dexcel	ciclosporin, Recordati	Launched	Dexcel Pharma	Recordati	Formulation, oral, other	Immunosuppressant	Transplant rejection, general	peptidylprolyl isomerase A (cyclophilin A)

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
ciclosporin, inhaled, Novartis	ACsA, Novartis cyclosporin, inhaled, Novartis Pulminiq	Pre-registration	Novartis	Research Corporation Tech	Formulation, inhalable, other	P glycoprotein inhibitor	Transplant rejection, general	peptidylprolyl isomerase A (cyclophilin A) ATP-binding cassette, subfamily B (MDR/TAP), member 1
ciclosporin, Novagali-1	NOVA-22007 NOVA-22008	Phase III	Novagali Pharma		Formulation, optimised, microparticles	Immunosuppressant	Keratoconjunctivitis	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin-A, Sirion	ciclosporin-A, ophthalmic ciclosporin-A, Sophia ST-603, Sirion	Phase III	Sirion Therapeutics		Formulation, other	Immunosuppressant	Dry eye syndrome	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin A, Lux	LX-201	Phase III	Lux Biosciences		Formulation, implant	Immunosuppressant	Transplant rejection, general	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin A, Novagali	Vekacia	Phase III	Novagali Pharma		Formulation, optimised, microparticles	Immunosuppressant	Keratoconjunctivitis	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin A, Maas BiolAB	Mitogard	Preclinical	Maas BiolAB		Neuroprotective	Apoptosis antagonist	Head trauma	peptidylprolyl isomerase A (cyclophilin A)
immunosuppressives, Albany	ciclosporin analogues, Albany	Preclinical	Albany Molecular Research		Immunosuppressant	Immunosuppressant	Unspecified	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin A, iv, NeuroPharma	NeuroSTAT	Preclinical	Maas BiolAB		Neuroprotective	Apoptosis antagonist	Head trauma	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin analogues, NeuroPh		Preclinical	Maas BiolAB		Neuroprotective	Apoptosis antagonist	Unspecified	Unspecified

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
ciclosporin A, Advancell	ADV-P3 ciclosporin A, Isdin Py-04	Preclinical	Advancell	Esteve	Formulation, optimised, nanoparticles	Immunostimulant	Psoriasis	peptidylprolyl isomerase A (cyclophilin A)
ciclosporin-A, Ophthalmophar		Preclinical	Ophthalmopharma		Formulation, other	Immunosuppressant	Dry eye syndrome	peptidylprolyl isomerase A (cyclophilin A)

Source: Pharmaprojects

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Table 2.19: Candidate biosimilars (granulocyte stimulating factor)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
filgrastim	CSF, Amgen CSF-G, Amgen G-CSF, Amgen Gran Granulokine Grastim, Dr Reddy's hG-CSF, Amgen Neupogen Neutropoietin Nupogen pluripoietin, Amgen r-metHuG-CSF Ro-8315	Launched	Amgen	Kirin Brewery Roche Dr Reddy's Genesis Pharma JEIL Pharmaceutical Sidus	Recombinant growth factor	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)
pegfilgrastim	filgrastim SD-01 Neulasta Neulastim Neupogen SR Neupogen-PEG Neupopeg PEG-GCSF, Amgen PEG-GCSF, Roche pegfilgrastim, Nektar R-1471 Ro-25-8315 SD-01	Launched	Amgen	Genesis Pharma Roche Nektar Therapeutics	Formulation, conjugate, pegylated	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)
CSF-G, Dong-A	G-CSF, Dong-A	Launched	Dong-A		Recombinant growth factor	Granulocyte stimulating factor agonist	Neutropenia, general	colony stimulating factor 3 receptor (granulocyte)
CSF-G, Dragon	G-CSF, Dragon	Launched	Dragon Pharmaceutical		Recombinant growth factor	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)
CSF-G, Hangzhou	Jilifen rhG-CSF, Hangzhou	Launched	Hangzhou Jiuyuan Gene Engineerin		Recombinant growth factor	Granulocyte stimulating factor agonist	Leucopenia, general	colony stimulating factor 3 receptor (granulocyte)

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
lenograstim	CSF, Chugai G-CSF, AMRAD G-CSF, Aventis G-CSF, Chugai G-CSF, Italfarmaco G-CSF, Rhone-Poulenc Rorer Granocyte hG-CSF, Chugai Myelostim Neutrogin	Launched	Roche	Sanofi-Aventis Almirall-Prodesfarma Sidus	Recombinant growth factor	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, leucopenia	colony stimulating factor 3 receptor (granulocyte)
nartograstim	CSF, Kyowa Hakko G-CSF, Kyowa Hakko KW-2228 naltograstim Naltoplastim Neu-Up	Launched	Kyowa Hakko		Recombinant growth factor	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, leucopenia	colony stimulating factor 3 receptor (granulocyte)
BK-0023	CSF-ß filgrastim, Keryos G-CSF, Keryos pluripoietin, Keryos rec-G-CSF rG-CSF, Keryos	Phase II	Keryos		Recombinant growth factor	Granulocyte stimulating factor agonist	Neutropenia, general	colony stimulating factor 3 receptor (granulocyte)
GCSF, Sygnis	AX-200 CSF-G, Sygnis	Phase II	Sygnis Pharma		Cytokine	Granulocyte stimulating factor agonist	Ischaemia, cerebral	colony stimulating factor 3 receptor (granulocyte)
KRN-125	filgrastim, 2nd-gen, Amgen filgrastim, 2nd-gen, Kirin pegfilgrastim, 2nd-gen, Amgen pegfilgrastim, Kirin	Phase II	Kirin Brewery	Amgen	Formulation, conjugate, pegylated	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)
CSF-G, Maxygen	G-CSF, Maxygen Maxy-996 Maxy-G34 PEG-G-CSF, Maxygen	Phase I	Maxygen		Formulation, conjugate, pegylated	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
CSF-G, Neose	G-CSF, Neose GlycoPEG-GCSF	Phase I	Neose Technologies	ratiopharm	Formulation, conjugate, pegylated	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)
G-CSF conjugate, Hanmi	HM-10460A	Preclinical	Hanmi		Recombinant growth factor	Granulocyte stimulating factor agonist	Neutropenia, general	colony stimulating factor 3 receptor (granulocyte)
CSF-G agonists, Affymax	G-CSF mimetics, Affymax Gematide	Preclinical	Affymax		Radio/chemoprotective	Granulocyte stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 3 receptor (granulocyte)
BK-0026	CSF- G retard, Keryos CSF-G SR, Keryos G-CSF retard, Keryos G-CSF SR, Keryos Met-G-CSF-PEG PEG-filgrastim pluripoietin SR, Keryos rG-CSF SR, Keryos rMet-G-CSF-PEG	Preclinical	Keryos		Formulation, modified-release, >24hr	Granulocyte stimulating factor agonist	Anaemia, general	colony stimulating factor 3 receptor (granulocyte)
CSF-G, Bolder	BBT-002 CSF-GM, Bolder cys-PEG G-CSF, Bolder G-CSF, cys-PEG, Bolder GM-CSF, Bolder PEG-GM-CSF, Bolder	Preclinical	Bolder Biotechnology		Formulation, conjugate, pegylated	Granulocyte stimulating factor agonist	Neutropenia, general	colony stimulating factor 3 receptor (granulocyte)
pegylated G-CSF, Green Cross	G-CSF, pegylated, Green Cross PEG-GCSF, Green Cross	Preclinical	Green Cross		Formulation, conjugate, pegylated	Granulocyte stimulating factor agonist	Unspecified	colony stimulating factor 3 receptor (granulocyte)

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Table 2.20: Candidate biosimilars (interferon beta)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Biogen (ß1a)	Avonex BG-9015 CHO-beta-interferon interferon, Abbott (ß1a interferon, AstraZeneca (ß1a) interferon, CSL (ß1a) interferon, Dompe (ß1a) interferon, Genzyme (ß1a) interferon, Schering-P (ß1a) ß-IF, Biogen	Launched	Biogen Idec	AstraZeneca CSL Schering-Plough Abbott Gedeon Richter	Recombinant interferon	Interferon beta 1 agonist	Multiple sclerosis, relapsing-remitting	interferon (alpha, beta and omega) receptor 2
interferon, Novartis (ß1b)	Beneseron Betaferon Betaferon, Beta-assist BetaJect BetaJect Light BetaJect-3 Betaseron IFN-ß1b, Berlex IFN-ß1b, Novartis interferon, Berlex (ß1b) SH-579 ZK-157046	Launched	Novartis	Bayer	Recombinant interferon	Interferon beta 1 agonist	Multiple sclerosis, relapsing-remitting	interferon (alpha, beta and omega) receptor 2
interferon,Merck Serono (ß1a)	IFN-ß1a, Merck Serono R-Frone Rebif Rebif 22 Rebif 44 rhIFN-ß1A, Serono ß1A-IF, Merck Serono	Launched	Merck KGaA	Pfizer	Recombinant interferon	Interferon beta 1 agonist	Multiple sclerosis, relapsing-remitting	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
PEG-interferon,Merck Ser(ß1A)	PEG-interferon, Nektar (ß1a) Rebif, Nektar	Phase I	Merck KGaA	Nektar Therapeutics	Formulation, conjugate, pegylated	Interferon beta 1 agonist	Unspecified	interferon (alpha, beta and omega) receptor 1
interferon, Bioferon (ß)	Fiblaferon R ß-IF, Bioferon	Launched	Rentschler	Lacer Menarini	Antiviral, interferon	Interferon beta agonist	Inflammation, brain	interferon (alpha, beta and omega) receptor 2
interferon, Mochida (ß)	IFNß Mochida ß-IF, Mochida	Launched	Mochida		Anticancer, interferon	Interferon beta agonist	Infection, hepatitis-B virus	interferon (alpha, beta and omega) receptor 2
interferon, Sclavo (ß)	Naferon ß-IF, Sclavo	Launched	Sclavo		Cytokine	Interferon beta agonist	Cancer, general	interferon (alpha, beta and omega) receptor 2
interferon, Toray (ß)	BM-532 DL-8234 Feron ß-IF, Toray	Launched	Toray	Daiichi Sankyo	Anticancer, interferon	Interferon beta agonist	Cancer, skin, general	interferon (alpha, beta and omega) receptor 2
interferon, Yeda (ß)	Frone interferon, Merck Serono (ß) Serobif ß-IF, Merck Serono ß-IF, Yeda	Launched	Yeda	Merck KGaA	Antiviral, interferon	Interferon beta agonist	Keratoconjunctivitis	interferon (alpha, beta and omega) receptor 2
interferon, Rentschler (ß)-2		Phase III	Rentschler	Biopartners	Recombinant interferon	Interferon beta agonist	Multiple sclerosis, general	interferon (alpha, beta and omega) receptor 2
interferon, Synairgen (ß)	IFN-ß, Synairgen SYN-101 SYN-102 project SYN-102 project-1	Phase I	Synairgen		Recombinant interferon	Interferon beta agonist	Infection, rhinovirus	interferon (alpha, beta and omega) receptor 2
interferon, Bolder (ß)		Preclinical	Bolder Biotechnology		Recombinant interferon	Interferon beta agonist	Multiple sclerosis, general	interferon (alpha, beta and omega) receptor 2
interferon, Keryos (ß1b)	BK-0034 IFN-ß1b, Keryos	Preclinical	Keryos		Recombinant interferon	Interferon beta 1 agonist	Multiple sclerosis, general	interferon (alpha, beta and omega) receptor 2
interferon, Sidus (ß)	ß-interferon, Sidus	Preclinical	Sidus		Recombinant interferon	Interferon beta agonist	Multiple sclerosis, general	interferon (alpha, beta and omega) receptor 2
interferon, Vakzine (ß)	Soluferon VPM-5-001	Preclinical	Vakzine Projekt Management		Recombinant interferon	Interferon beta agonist	Multiple sclerosis, general	interferon (alpha, beta and omega) receptor 2

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Biogen (ß)	IFN-ß-Fc, Biogen IFN-ß-Fc, Serono interferon,Merck Serono-2 (ß)	Preclinical	Biogen Idec	Merck KGaA	Formulation, inhalable, systemic	Interferon beta agonist	Multiple sclerosis, general	interferon (alpha, beta and omega) receptor 2
interferon, Flamel (ß)	IFN ß XL, Flamel Interferon ß XL	Preclinical	Flamel Technologies		Formulation, optimised, nanoparticles	Interferon beta agonist	Multiple sclerosis, general	interferon (alpha, beta and omega) receptor 2

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Table 2.21: Candidate biosimilars (calcitonin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
calcitonin, nasal, Novartis	calcitonin, nasal, Noven Karil Miacalcic Miacalcic Nasal Miacalcin Nasal Spray miacalcin, nasal salcatonin, nasal, Novartis salcatonin, nasal, Noven SMC-051	Launched	Novartis	Noven Pharmaceuticals	Formulation, transmucosal, nasal	Calcitonin stimulant	Osteoporosis	calcitonin receptor
calcitonin, Armour	calcitonin, Yamanouchi Salmotonin Salmotoruin YM-11221	Launched	Sanofi-Aventis	Astellas	Hormone	Calcitonin stimulant		calcitonin receptor
calcitonin, Novartis	Cibacalcin	Launched	Novartis		Hormone	Calcitonin stimulant	Osteoporosis	calcitonin receptor
calcitonin, Teikoku	calcitonin, Prodesfarma Calcitoran Calogen salcatonin TZ-CT	Launched	Aska Pharmaceutical	Almirall-Prodesfarma UCB	Hormone	Calcitonin stimulant	Osteoporosis	calcitonin receptor
elcatonin	Carbicalcin Diatin Elactonin Elcatonina Elcimen Elcitonin HC-58 Laskarton Turbocalcin	Launched	Asahi Kasei Pharma	Nycomed Pharma UCB Ferrer Chong Kun Dang	Hormone	Calcitonin stimulant	Hypercalcaemia, general	calcitonin receptor
calcitonin, Unigene	Forcaltonin Fortical Injection	Launched	Unigene	Prostrakan	Formulation, parenteral, other	Calcitonin stimulant	Paget's disease	calcitonin receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
elcatonin, Therapicon	carbacalcitonin, Therapicon elcatonin injectable, Therapic elcatonin nasal, Therapicon	Launched	Therapicon		Formulation, transmucosal, nasal	Calcitonin stimulant	Osteoporosis	calcitonin receptor
salmon calcitonin, Therapicon	salcatonin injectable, Therapi salcatonin nasal, Therapicon	Launched	Therapicon		Formulation, transmucosal, nasal	Calcitonin stimulant	Osteoporosis	calcitonin receptor
calcitonin, Aventis	Calcimar Calcin Calcymar Calsynar Prontocalcin RG-83630	Launched	Sanofi-Aventis		Formulation, transmucosal, nasal	Calcitonin stimulant	Osteoporosis	calcitonin receptor
calcitonin, nasal, Unigene	Fortical	Launched	Unigene		Formulation, transmucosal, nasal	Calcitonin stimulant	Osteoporosis	calcitonin receptor
calcitonin, oral, Emisphere	calcitonin, oral, Novartis Miacalcic, oral sCT, Emisphere; sCT, Novartis SMC-021	Phase III	Emisphere Technologies	Novartis Nordic Bioscience	Formulation, oral, other	Calcitonin stimulant	Osteoporosis	calcitonin receptor
calcitonin, oral, Bone Medical	BN-002, Bone Medical Capsitonin	Phase II	Bone Medical		Formulation, modified-release, other	Calcitonin stimulant	Osteoporosis	calcitonin receptor
calcitonin, oral, Unigene		Phase II	Unigene		Formulation, oral, other	Calcitonin stimulant	Osteoporosis	calcitonin receptor
CGRP, LAB	LAB CGRP	Phase II	LAB International		Formulation, inhalable, dry powder	Calcitonin gene-related peptide agonist	Asthma	calcitonin receptor-like
calcitonin, oral, Biocon	NCT-025 Oratonin	Phase I	Biocon		Formulation, oral, other	Calcitonin stimulant	Osteoporosis	calcitonin receptor
CGRP, VasoGenix	Vasonex Vasonex CR	Preclinical	Vasogenix		Cardiovascular	Calcitonin gene-related peptide agonist	Ischaemia, general	calcitonin receptor-like

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Table 2.22: Candidate biosimilars (LHRH)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
goserelin	ICI-118630 Zoladex Zoladex LA Zoladex Plus	Launched	AstraZeneca	Kissei Biovail	Releasing hormone	LHRH agonist	Cancer, prostate	gonadotropin-releasing hormone receptor
leuprorelin, Takeda	Abbott-43818 Carcinil Enantone Leuplin Leuplin SR leuprolide, Takeda leuprorelin, Abbott leuprorelin, Lederle Lucrin Lucrin Depot Lupron Lupron Depot Procren Depot Procrin Prostap Prostap SR TAP-144-SR Trenantone Gyn	Launched	Takeda	Abbott Wyeth	Formulation, implant	LHRH agonist	Cancer, prostate	gonadotropin-releasing hormone receptor
leuprolide acetate, Atrigel	Eligard Leuprogel leuprolide acetate, QLT SOT-375	Launched	QLT	Sanofi-Aventis Hospira Astellas Tecnofarma Medigene Biosintetica Akzo Nobel Key Oncologics Ranbaxy	Formulation, implant	LHRH agonist	Cancer, prostate	gonadotropin-releasing hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
abarelix	abarelix-depot abarelix-depot-F abarelix-depot-M Plenaxis PPI-149 R-3827	Launched	GlaxoSmithKline		Anticancer, hormonal	LHRH antagonist	Cancer, prostate	gonadotropin-releasing hormone receptor androgen receptor (dihydrotestosterone receptor; testicular feminization; spinal and bulbar muscular atrophy; Kennedy disease)
gonadorelin preparations	Ay-24031 Cystorelin Factrel HRF Lutamin Relefact LH-RH Relistorm-L Stimu-LH	Launched	Wyeth	Sanofi-Aventis Roche Tanabe Seiyaku Daiichi Sankyo Merck KGaA Shire	Releasing hormone	LHRH agonist	Hormone replacement therapy	gonadotropin-releasing hormone receptor
leuprorelin, DUROS	leuprolide, Alza leuprolide, DUROS leuprorelin, Alza leuprorelin, Bayer Viadur	Launched	Johnson & Johnson	Bayer	Formulation, implant	LHRH agonist	Cancer, prostate	gonadotropin-releasing hormone receptor
leuprolide acetate, Voyager	leuprolide acetate, Durect leuprolide acetate, Durin luprolide acetate, Voyager Memryte VP-4896	Phase III	Voyager Pharmaceutical	Durect	Formulation, implant	LHRH agonist	Alzheimer's disease	gonadotropin-releasing hormone receptor
avorelin	EP-23904 Meterelin MF-6001	Phase II	Mediolanum		Releasing hormone	LHRH agonist	Cancer, prostate	gonadotropin-releasing hormone receptor
leuprorelin, Norwood	GnRH analogues, Norwood	Phase II	Norwood Abbey		Immunostimulant, anti-AIDS	LHRH agonist	Infection, HIV/AIDS	gonadotropin-releasing hormone receptor
leuprorelin, Archimedes	leuprolide, Archimedes	Phase II	Archimedes		Formulation, transmucosal, nasal	LHRH agonist	Endometriosis	gonadotropin-releasing hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
goserelin, Ambrilia		Preclinical	Ambrilia Biopharma		Formulation, modified-release, >24hr	LHRH agonist	Cancer, prostate	gonadotropin-releasing hormone receptor
leuprolide, oral, DOR BioPharm	LPM-leuprolide	Preclinical	DOR BioPharm		Formulation, oral, other	LHRH agonist	Cancer, prostate	gonadotropin-releasing hormone receptor
leuprorelin, Merrion	leuprolide acetate, GIPET leuprolide acetate, Merrion leuprorelin, GIPET MER-104	Preclinical	Merrion Pharmaceuticals		Formulation, oral, other	LHRH agonist	Cancer, prostate	gonadotropin-releasing hormone receptor
leuprorelin, oral, Unigene	leuprolide, oral, Unigene	Preclinical	Unigene		Formulation, oral, other	LHRH antagonist	Cancer, prostate	gonadotropin-releasing hormone receptor

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Table 2.23: Candidate biosimilars (interleukin 2)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
denileukin diftitox	DAB389IL-2 IL-2 fusion protein, Seragen IL-2 fusion toxin, Seragen LY-335348 ONTAK Onzar	Launched	Ligand	Eisai Lilly Ferrer Alfa Wassermann Cephalon	Recombinant, other	Interleukin 2 receptor antagonist	Cancer, lymphoma, T-cell	eukaryotic translation elongation factor 2 interleukin 2 receptor, alpha
aldesleukin	IL-2, Novartis-3 interleukin, Novartis-3 Leuferon 2 Macrolin IL-2 Proleukin Ro-23-6019	Launched	Novartis	Orion Pharma Roche Genesis Pharma Ajinomoto	Recombinant interleukin	Interleukin 2 agonist	Cancer, renal	interleukin 2 receptor, alpha
celmoleukin	Celeuk IL-2, Takeda interleukin-2, Takeda TGP-3	Launched	Takeda		Recombinant interleukin	Interleukin 2 agonist	Cancer, sarcoma, general	interleukin 2 receptor, alpha
interleukin-2, Ajinomoto	IL-2, Ajinomoto IL-2, Roche IL-2, Seragen interleukin-2, Roche	Launched	Ajinomoto	Roche Takeda	Recombinant interleukin	Interleukin 2 agonist	Cancer, renal	interleukin 2 receptor, alpha
teceleukin	BG-8301 Bioleukin IL-2, Biogen IL-2, Shionogi Imunase interleukin-2, Biogen interleukin-2, Shionogi S-6820	Launched	Biogen Idec	Shionogi	Recombinant interleukin	Interleukin 2 agonist	Cancer, sarcoma, general	interleukin 2 receptor, alpha
Bay-50-4798	IL-2 agonist, Bayer	Phase II	Bayer		Recombinant interleukin	Interleukin 2 agonist	Infection, HIV/AIDS	interleukin 2 receptor, alpha

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
EMD-273063	ch14.18-IL-2 hu14.18-IL2 IL-2 fusion protein, Lexigen immunocytokine 14.18-IL2 Pharmaprojects No. 5827	Phase II	Merck KGaA		Immunoconjugate, other	Interleukin 2 agonist	Cancer, melanoma	interleukin 2 receptor, alpha
interleukins, Cel-Sci	BC-IL IL-2, Cel-Sci ILs, Cel-Sci interleukin-2, Cel-Sci Multikine	Phase II	Cel-Sci		Anticancer, immunological	Interleukin 2 agonist	Cancer, head and neck	interleukin 2 receptor, alpha
tucotuzumab celmoleukin	EMD-273066 huKS-IL2 KS-IL2	Phase II	Merck KGaA		Immunoconjugate, other	Interleukin 2 agonist	Cancer, lung, non-small cell	interleukin 2 receptor, alpha tumour-associated calcium signal transducer 1
interleukin-2, Flamel	IL-2 XL, Flamel IL-2, Medusa	Phase II	Flamel Technologies		Formulation, optimized, nanoparticles	Interleukin 2 agonist	Cancer, renal	interleukin 2 receptor, alpha
L19-IL2		Preclinical	Bayer	Philogen	Recombinant, other	Interleukin 2 agonist	Cancer, renal	interleukin 2 receptor, alpha
interleukin-2 mimetic, AplaGen	IL-2, AplaGen	Preclinical	AplaGen Biopharmaceuticals		Anticancer, immunological	Interleukin 2 agonist	Unspecified	interleukin 2 receptor, alpha

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Table 2.24: Candidate biosimilars (factor IX)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
nonacog alfa	BeneFIX Factor IX, Baxter Factor IX, BTG Factor IX, Wyeth rhFIX	Launched	Wyeth	BTG Baxter International	Recombinant, other	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
Factor IX, Alpha Therapeutics	AlphaNine AlphaNine SD	Launched	Mitsubishi Pharma		Blood fraction	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
Factor IX, Armour	Mono-IX Mononine	Launched	Sanofi-Aventis		Blood fraction	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
Factor IX, CSL	monocomponent Factor IX MonoFIX MonoFIX-VF	Launched	CSL		Blood fraction	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
Factor IX-2, Baxter	Bebulin Immunine	Launched	Baxter International		Blood fraction	Factor IX stimulant		coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
Factor IX, Green Cross		Preclinical	Green Cross		Recombinant, other	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
Factor IX, Univ Nebraska		Preclinical	Non-industrial source	Biosante	Recombinant, other	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
Factor IX, Wyeth-2	Factor IX, Nautilus	Preclinical	Wyeth	Nautilus Biotech	Recombinant, other	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
Factor IX-Fc, Biogen	Factor IX-Fc, Biovitrum FIX:Fc, Biogen FIX:Fc, Biovitrum	Preclinical	Biogen Idec	Biovitrum	Recombinant, other	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)
Factor IX, Neose	PEG-Factor IX, Neose	Preclinical	Neose Technologies	Novo Nordisk	Formulation, conjugate, pegylated	Factor IX stimulant	Haemophilia B	coagulation factor IX (plasma thromboplastic component, Christmas disease, haemophilia B)

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Table 2.25: Candidate biosimilars (tissue plasminogen activator)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
alteplase	Actase Actilyse Actiplas Activacin Activase Cathflo Activase Grtpa plasminogen activator, Genente tPA, Genentech	Launched	Genentech	Boehringer Ingelheim Kyowa Hakko Mitsubishi Pharma Sanofi-Aventis Dompe Millennium Schering-Plough	Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue
tenecteplase	Metalyse plasminogen activator, Boehr plasminogen activator, Genen-2 plasminogen activator, Roche-2 TNK TNK-t-PA TNKase tPA, Boehringer, 2nd-gen tPA, Roche, 2nd-gen tPA-2, Genentech	Launched	Genentech	Roche Boehringer Ingelheim	Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue
reteplase	BM-06022 Ecokinase Rapilysin Retavase Retevase rPA, Centocor	Launched	Roche	PDL BioPharma	Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue
monteplase	Cleactor Creactor E-6010 Mf-tPA plasminogen activator, Eisai tPA, Eisai	Launched	Eisai		Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
nateplase	Milyzer MMR-701 plasminogen activator, Mitsui plasminogen activator, Mochida Tepase tPA, Mitsui tPA, Mochida	Launched	Bayer	Mochida	Recombinant, other	Plasminogen activator stimulant	Thrombosis, general	plasminogen activator, tissue
pamiteplase	Solinase tPA analogues, Yama YM-22866 YM-866	Launched	Astellas		Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue
plasminogen activator, Asahi	AK-124 Hapase plasminogen activator, Kowa plasminogen activator, Kowa Co Plasvata tisokinase tPA, Asahi tPA, Kowa	Launched	Asahi Kasei Pharma	Kowa	Fibrinolytic	Plasminogen activator stimulant	Infarction, myocardial	Unspecified
amediplase	CGP-2935 K2tuPA MEN-9036 plaminogen activator-2, Menari tPA-2, Menarini	Phase III	Menarini		Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue
alteplase + mesna, Angiogen	mesna + alteplase, Angiogen	Phase II	Angiogen		Formulation, fixed-dose combinations	Plasminogen activator stimulant	Unspecified	plasminogen activator, tissue

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***Table 2.26: Candidate biosimilars (urokinase plasminogen* activator)**

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
urokinase, ImaRx-2	Abbokinase Cultokinase	Launched	Imarx	Dainippon Sumitomo Pharma Kyorin	Fibrinolytic	Plasminogen activator stimulant	Thrombosis, general	plasminogen activator, urokinase
pro-urokinase, Mitsubishi	KPA, Mitsubishi nasaruplase PPA, Mitsubishi PUK, Mitsubishi Thrombolyse Tomieze Tomize	Launched	Mitsubishi Pharma		Fibrinolytic	Plasminogen activator stimulant		plasminogen activator, urokinase
streptokinase, Shantha	Shankinase	Launched	Shantha Biotechnics		Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, urokinase
pro-urokinase, Mitsubishi	KPA, Mitsubishi nasaruplase PPA, Mitsubishi PUK, Mitsubishi Thrombolyse Tomieze Tomize	Launched	Mitsubishi Pharma		Fibrinolytic	Plasminogen activator stimulant		plasminogen activator, urokinase
urokinase, Bharat	Endurase	Launched	Bharat Biotech		Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, urokinase
amediplase	CGP-2935 K2tuPA MEN-9036 plaminogen activator-2, Menari tPA-2, Menarini	Phase III	Menarini		Recombinant, other	Plasminogen activator stimulant	Infarction, myocardial	plasminogen activator, tissue
nasaruplase ß	A-74187 ABT-187 MRX-515 pro-urokinase, ImaRx ProLyse r-Pro UK	Phase III	Imarx		Recombinant, other	Plasminogen activator stimulant	Ischaemia, cerebral	plasminogen activator, urokinase

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
urokinase, ImaRx	MRX-530 Open-Cath-R rUK, ImaRx ssa	Phase III	Imarx		Recombinant, other	Plasminogen activator stimulant	Thrombosis, general	plasminogen activator, urokinase
plasminogen activator, Shiseid	Fu-PA	Preclinical	Shiseido		Fibrinolytic	Plasminogen activator stimulant	Thrombosis, general	plasminogen activator, urokinase

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Table 2.27: Candidate biosimilars (follitropin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
follitropin alfa, Merck Serono	follitropin alpha, Merck Seron Gonal-F Gonal-F Multi-Dose Gonal-L Gonalef r-follitropin, Merck Serono rhFSH, Merck Serono	Launched	Merck KGaA		Recombinant hormone	Follicle-stimulating hormone agonist	Infertility, female	follicle stimulating hormone receptor
recFSH, Organon	Follistim Follistim AQ follitropin ß hCG, Organon Org-32489 Puregon Puregon pen Recagon Pen rhFSH, Organon	Launched	Akzo Nobel		Recombinant hormone	Follicle-stimulating hormone agonist	Infertility, female	follicle stimulating hormone receptor
urofollitropin	Fertinorm follitropin, Merck Serono FSH, Merck Serono Metrodin Metrodin R Metrodine H	Launched	Merck KGaA		Fertility enhancer	Follicle-stimulating hormone agonist	Polycystic ovarian syndrome	follicle stimulating hormone receptor
urofollitropin, Merck Serono-2	Fertinex Metrodin HP urofollitrophin, MerckSerono-2	Launched	Merck KGaA		Fertility enhancer	Follicle-stimulating hormone agonist	Infertility, female	follicle stimulating hormone receptor
urofollitropin, Ferring	Bravelle FSH, Ferring hpFSH, Ferring	Launched	Ferring		Formulation, other	Follicle-stimulating hormone agonist	Infertility, female	follicle stimulating hormone receptor
follitropin, Dong-A	DA-3801 FSH, Dong-A	Pre-registration	Dong-A		Recombinant hormone	Follicle-stimulating hormone agonist	Infertility, female	follicle stimulating hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
lutropin alfa+follitropin alfa	follitropin alfa+leutropin alf FSH + LH, Merck Serono LH + FSH, Merck Serono Pergoveris	Pre-registration	Merck KGaA		Formulation, fixed-dose combinations	LH agonist	Infertility, female	luteinizing hormone/choriogonadotropin receptor follicle stimulating hormone receptor
corifollitropin alfa	FSH-CTP Org-36286	Phase III	Akzo Nobel		Recombinant hormone	Follicle-stimulating hormone agonist	Infertility, female	follicle stimulating hormone receptor

Source: Pharmaprojects

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Table 2.28: Candidate biosimilars (somatotropin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatropin, Genentech	growth hormone, Genentech hGH, Genentech Nutropin Nutropin AQ Nutropin AQ Pen Nutropin AQ Pen Cartridge NutropinAq NutropinAq Pen Protropin II somatotropin, Genentech somatropin, Schwarz	Launched	Genentech	Ipsen Dainippon Sumitomo Pharma	Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Lilly	BioHGH growth hormone, Lilly hGH, Lilly Humatrope somatotropin, Lilly Umatrope	Launched	Lilly		Recombinant hormone	Growth hormone agonist	Dwarfism	growth hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatropin, Merck Serono	growth hormone, Merck Serono r-hGH[m] rhGH, Merck Serono Saizen Saizen Click.Easy Saizen, Click.Easy Saizon, cool.click SeroJet Serostim somatotropin, Merck Serono somatropin, cool.click somatropin, Easyject somatropin, SeroJet somatropin, Viajet 3 Zorbitive	Launched	Merck KGaA		Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatropin, Novo Nordisk	growth hormone, Novo Nordisk hGH, Novo Nordisk Norditropin Norditropin Nordiflex Norditropin S-chu Norditropin SimpleXx Norditropine somatotropin, Novo Nordisk	Launched	Novo Nordisk	GlaxoSmithKline Astellas	Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Pfizer	Genotonorm Genotropin growth hormone, Kabi hGH, Pharmacia somatotropin, Pfizer-2	Launched	Pfizer	Gerolymatos Adcock Ingram Green Cross	Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Dong-A	growth hormone, Dong-A Growtropin II hGH, Dong-A somatotropin, Dong-A	Launched	Dong-A		Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatrem, Dong-A	growth hormone (met), Dong-A Growtropin hGH (met), Dong-A somatrotropin (met), Dong-A	Launched	Dong-A		Recombinant hormone	Growth hormone agonist	Dwarfism	growth hormone receptor</ TD< TR>
somatropin, Sanofi-Synthelabo	growth hormone, Sanofi-Synthel hGH, Sanofi-Synthelabo Maxomat somatotropin, Sanofi-Synthelab	Launched	Sanofi-Aventis		Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatropin, Savient	Abitropin Bio-Tropin Biotropin Cryotropin Eskatrope Growject growth hormone, Savient hGH, Ferring hGH, Savient hGH, Teva Sci-Tropin somatotropin, Savient somatropin, Ferring somatropin, IVAX somatropin, Teva Tev-Tropin Zomacton	Launched	Ferring	JCR Pharmaceuticals Dainippon Sumitomo Pharma Scigen Teva	Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, LG Life	Eutropin growth hormone, LG Life rec-hGH, LG Chem somatropin, Biopartners Valtropin	Launched	LG Life Sciences	Biopartners Nycomed Pharma	Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin,Antares,needle-free	EZ-II Twin-Jector	Launched	Antares Pharma	JCR Pharmaceuticals	Formulation, parenteral, needle-free	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatropin, SR, LG	Declage LB-03002 sr-hGH, LG Life Valtropin, SR	Registered	LG Life Sciences	Biopartners	Formulation, modified-release, >24hr	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
human growth hormone, Daewoong	Caretropin	Pre-registration	Daewoong		Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Cangene	Accretropin hGH, Cangene human growth hormone, Cangene rhGH, Cangene	Pre-registration	Cangene	ratiopharm Apotex	Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
ARX-201	human growth hormone, Ambrx PEG-hGH	Phase II	Ambrx	Merck KGaA	Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Altus	ALT-238 ALTU-238	Phase II	Altus Pharmaceuticals	Genentech	Growth hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Pfizer, pegylated	PEG-hGH, Pfizer PH-794428 PHA-794428	Phase II	Pfizer		Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Emisphere	growth hormone, Emisphere HGH-191 rhGH, Emisphere somatropin, eligen	Phase I	Emisphere Technologies	Novartis	Formulation, oral, other	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatropin, OctoDEX	hGH, OctoDEX human growth hormone, DexHEMA human growth hormone, OctoDEX OctoDEX-hGH somatropin, DexHEMA	Phase I	Octoplus		Formulation, optimised, microencapsulate	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Skyepharma	growth hormone, SkyePharma hGH, SkyePharma somatropin, Biosphere	Phase I	Skyepharma		Formulation, modified-release, >24hr	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
AOD-9604	hGH 177-191 variant, Metabolic	Preclinical	Metabolic Pharmaceuticals		Growth hormone	Growth hormone agonist	Osteoporosis	growth hormone receptor
BBT-005	cys-PEG growth hormone, Bolder growth hormone, cys-PEG, Bolde	Preclinical	Bolder Biotechnology		Formulation, conjugate, pegylated	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
NNZ-3006	GH variant, Neuren growth hormone variant, Neuren somatropin variant, Neuren	Preclinical	Neuren		Growth hormone	Growth hormone agonist	Unspecified	growth hormone receptor
PEG-GH, PharmaEssentia	somatropin, pegylated, PharmaE	Preclinical	Pharmaessentia		Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatropin, conjugate, Hanmi	growth hormone, conj, Hanmi hGH, conjugate, Hanmi HM-10560A	Preclinical	Hanmi		Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Medusa	hGH XL, Flamel hGH XL, Medusa somatropin, Flamel	Preclinical	Flamel Technologies		Formulation, optimised, nanoparticles	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Modigene	hGH-CTP MOD-401	Preclinical	Modigene		Growth hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, Nautilus	GH, Merck Serono-2 GH, Nautilus growth hormone, MerckSerono-2 growth hormone, Nautilus hGH, Merck Serono-2 hGH, Nautilus somatropin, Merck Serono-2 Vitatropin	Preclinical	Nautilus Biotech	Merck KGaA Hanall Pharmaceutical	Recombinant hormone	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, SABER	hGH, SABER somatropin, Durect	Preclinical	Durect		Formulation, modified-release, >24hr	Growth hormone agonist	Unspecified	growth hormone receptor

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
somatropin, SR, Genentech	somatropin, SR, Ipsen	Preclinical	Genentech	Ipsen	Formulation, modified-release, >24hr	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor
somatropin, SR, Keryos	NP-2001, sustained-release rhGH, sustained-release,Keryos	Preclinical	Keryos		Formulation, modified-release, >24hr	Growth hormone agonist	Growth hormone deficiency	growth hormone receptor

Source: Pharmaprojects

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***Table 2.29: Candidate biosimilars (granulocyte macrophage colony* stimulating factor)**

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
sargramostim	CSF-GM, Bayer GM-CSF, SchAG Interberin Leukine Prokine	Launched	Bayer		Recombinant growth factor	Granulocyte macrophage colony stimulating factor agonist	Anaemia, aplastic	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)
CSF-GM, LGLS	GM-CSF, LGLS Leucogen	Launched	LG Life Sciences		Recombinant growth factor	Granulocyte macrophage colony stimulating factor agonist	Chemotherapy-induced injury, bone marrow, general	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)
molgramostim	CSF, Novartis CSF, Schering-Plough CSF, Wyeth CSF-GM, Novartis CSF-GM, Schering-Plough CSF-GM, Wyeth GM-CSF, Novartis GM-CSF, Schering-Plough GM-CSF, Wyeth Leucomax Mielogen	Launched	Wyeth	Schering-Plough	Recombinant growth factor	Granulocyte macrophage colony stimulating factor agonist	Granulocytopenia	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)
CSF-GM, Cangene	CSF-GM, Cheil Jedang GM-CSF, Cangene GM-CSF, Cheil Jedang Leucotropin	Pre-registration	Cangene	Apotex CJ Corp	Recombinant growth factor	Granulocyte macrophage colony stimulating factor agonist	Chemotherapy-induced injury, bone marrow, neutropenia	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
BBT-007	cys-PEG GM-CSF, Bolder GM-CSF, cys-PEG, Bolder	Preclinical	Bolder Biotechnology		Formulation, conjugate, pegylated	Granulocyte macrophage colony stimulating factor agonist	Neutropenia, general	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)
HemaGel	HemaGel G-CSF	Preclinical	Endo Pharmaceuticals		Formulation, other	Granulocyte macrophage colony stimulating factor agonist	Unspecified	colony stimulating factor 3 receptor (granulocyte)

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Table 2.30: Candidate biosimilars (interferon gamma)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Genentech (gamma1b)	Actimmune gamma1b-IFN, Genentech Immukin Immukine Imuforgamma Imukin interferon, InterMune (gamma1b interferon, Toray (gamma1B) interferon,Boehring Ing (gamma interferon,Mondobiotech (gamma	Launched	Genentech	Boehringer Ingelheim Intermune Mondobiotech Toray	Recombinant interferon	Interferon gamma 1b agonist	Chronic granulomatous disease	interferon gamma receptor 1
interferon, Biogen (gamma)	gamma-IF, Biogen Immuneron Immunomax Immunomax Gamma interferon, Shionogi (gamma) Polyferon, Biogen S-6810	Launched	Biogen Idec	Shionogi	Recombinant interferon	Interferon gamma agonist	Cancer, renal	interferon gamma receptor 1
interferon, Daiichi (gamma1a)	Biogamma gamma1a-IF, Daiichi gamma1a-IF, Maruho interferon, Maruho (gamma1a) Sch-36850 SUN 4800	Launched	Daiichi Sankyo	Maruho	Recombinant interferon	Interferon gamma 1a agonist	Cancer, skin, general	interferon gamma receptor 1
interferon, LGLS	gamma-IF, LGLS Intermax gamma rec-IFN-gamma, LGLS	Launched	LG Life Sciences		Recombinant interferon	Interferon gamma agonist	Cancer, leukaemia, chronic myelogenous	interferon gamma receptor 1

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Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
interferon, Hayashibara (gamma)	Gamma 100 gamma-IF, Hayashibara Ogamma OH-6000	Launched	Hayashibara	Otsuka	Anticancer, interferon	Interferon gamma agonist	Cancer, lymphoma, T-cell	interferon gamma receptor 1
NGR-IFNgamma	IFNgamma-NGR	Preclinical	Molmed		Recombinant, other	Interferon gamma agonist	Unspecified	interferon gamma receptor 1

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Table 2.31: Candidate biosimilars (octreotide)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
octreotide	Longastatina octreotide pamoate Oncolar Sandostatin Sandostatina Sandostatine SMS-201-995 SMS-995 SMS-995C	Launched	Novartis		Somatostatin	Somatostatin agonist	Acromegaly	Unspecified
octreotide, Ambrilia		Phase III	Ambrilia Biopharma	Tyco Healthcare	Formulation, modified-release, >24hr	Somatostatin agonist	Acromegaly	Unspecified
octreotide, Indevus	VP-003	Phase II	Indevus		Formulation, implant	Somatostatin agonist	Acromegaly	Unspecified
edotreotide	90Y-octreotide OctreoTher Onalta SMT-487 Y-90 SMT-487	Preclinical	Molecular Insight		Anticancer, hormonal	DNA antagonist	Cancer, pancreatic	Unspecified
octreotide, PR Pharmaceuticals	SomaLAR	Preclinical	PR Pharmaceuticals		Formulation, modified-release, >24hr	Somatostatin agonist	Retinopathy, diabetic	Unspecified

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Table 2.32: Candidate biosimilars (desmopressin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
desmopressin	Adiuretin DDAVP Defirin Desmospray KW-8008 Minirin	Launched	Ferring	Kyowa Hakko Valeas Sanofi-Aventis Wyeth Ranbaxy	Hormone	Vasopressin agonist	Enuresis	arginine vasopressin receptor 2 (nephrogenic diabetes insipidus)
desmopressin, Columbia		Phase I	Columbia Laboratories		Formulation, transmucosal, systemic	Vasopressin agonist	Unspecified	arginine vasopressin receptor 2 (nephrogenic diabetes insipidus)
desmopressin, Orexo	OX-19, Orexo urogenital therapeutics, Orexo	Preclinical	Orexo		Formulation, transmucosal, systemic	Vasopressin agonist	Incontinence	arginine vasopressin receptor 2 (nephrogenic diabetes insipidus)
desmopressin, Unigene	DDVAP, Unigene	Preclinical	Unigene		Formulation, oral, other	Vasopressin agonist	Unspecified	arginine vasopressin receptor 2 (nephrogenic diabetes insipidus)

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Table 2.33: Candidate biosimilars (factor VIIa)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
Factor VIIa, Zymo	eptacog-alpha Factor VIIa, Novo Nordisk NiaStase NN-007 NovoSeven rFVIIa, Novo Nordisk	Launched	Zymogenetics	Novo Nordisk	Recombinant, other	Factor VIIa stimulant	Haemophilia A	coagulation factor VII (serum prothrombin conversion accelerator)
NN-1731	Factor VIIa analogue, Neose Factor VIIa analogue, Novo rFVIIa analogue, Neose rFVIIa analogue, Novo	Phase I	Novo Nordisk	Neose Technologies	Recombinant, other	Factor VIIa stimulant	Unspecified	coagulation factor VII (serum prothrombin conversion accelerator)
Factor VIIa, Maxygen	Factor VIIa, Roche Maxy-968 Maxy-Factor VII Maxy-VII rFVIIa, Maxygen rFVIIa, Roche	Preclinical	Maxygen		Recombinant, other	Factor VIIa stimulant	Traumatic shock	coagulation factor VII (serum prothrombin conversion accelerator)
Factor VIIa, GTC	Factor VIIa, LFB	Preclinical	GTC Biotherapeutics	LFB Biotechnologies	Recombinant, other	Factor VIIa stimulant	Haemophilia, general	coagulation factor VII (serum prothrombin conversion accelerator)

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Table 2.34: Candidate biosimilars (protein C)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
drotrecogin alfa	APC, Lilly LTC-203 LTC-206 protein C, Lilly rhAPC, Lilly Xigris Zovan Zovant	Launched	Lilly		Recombinant, other	Fibrinogen antagonist	Sepsis	protein C (inactivator of coagulation factors Va and VIIIa)
CTC-111	activated protein C, Teijin activated protein C,Kaketsuken Anact C	Launched	Kaketsuken	Teijin	Anticoagulant	Fibrinogen antagonist	Thrombosis, general	protein C (inactivator of coagulation factors Va and VIIIa)
protein C, Baxter	Ceprotin	Launched	Baxter International		Antithrombotic	Fibrinogen antagonist	Thrombosis, general	protein C (inactivator of coagulation factors Va and VIIIa)
LY-458202	GED-aPC	Preclinical	Lilly	Cardiome	Recombinant, other	Protein C subunit activator	Traumatic shock	protein C (inactivator of coagulation factors Va and VIIIa)

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Table 2.35: Candidate biosimilars (teriparatide)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
teriparatide, Lilly	Forsteo Forteo Fosteo LY-333334 parathyroid hormone, Emisphere parathyroid hormone, Inhale parathyroid hormone, Lilly PTH, Inhale PTH, Lilly	Launched	Lilly		Recombinant hormone	Parathyroid hormone agonist	Osteoporosis	parathyroid hormone receptor 1
teriparatide	1-34hPTH MN-10T PTH fragment, Asahi	Launched	Asahi Kasei Pharma		Hormone	Parathyroid hormone agonist	Diagnosis, general	parathyroid hormone receptor 1
teriparatide, oral, Emisphere	PTH1-34, eligen, Emisphere PTH1-34, oral, Emisphere	Phase I	Emisphere Technologies	Novartis	Formulation, oral, other	Parathyroid hormone agonist	Osteoporosis	parathyroid hormone receptor 1
teriparatide, inhaled, Lilly	PTH, inhaled, Lilly	Preclinical	Lilly	Alkermes	Formulation, inhalable, other	Parathyroid hormone agonist	Osteoporosis	parathyroid hormone receptor 1

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Table 2.36: Candidate biosimilars (glucocerebrosidase)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
imiglucerase	Cerezyme glucocerebrosidase,rec, Genzyme rGCR, Genzyme	Launched	Genzyme		Recombinant, other	Glucosylceramidase stimulant	Gaucher's disease	glucosidase, beta; acid (includes glucosylceramidase)
alglucerase	Ceredase glucocerebrosidase, Genzyme ß-glucosidase	Launched	Genzyme		Metabolic and enzyme disorders	Glucosylceramidase stimulant	Gaucher's disease	glucosidase, beta; acid (includes glucosylceramidase)
glucocerebrosidase, Shire	DRX-008A GA-GCB GCB, Shire GCR glucosylceramidase Pharmaprojects No. 6026	Phase III	Shire		Recombinant, other	Glucosylceramidase stimulant	Gaucher's disease	glucosidase, beta; acid (includes glucosylceramidase)

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Table 2.37: Candidate biosimilars (hirudin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
bivalirudin	Angiomax Angiox BG-8967 Hirulog	Launched	The Medicines Company	Nycomed Pharma Oryx Pharmaceuticals Ferrer CSL	Anticoagulant	Thrombin inhibitor	Thrombosis, general	coagulation factor II (thrombin)
lepirudin	HBW-023 hirudin, Bayer Schering Pharma Hoe-023 rDNA-Hirudin Refludan Refludin	Launched	Bayer	Pharmion	Recombinant, other	Thrombin inhibitor	Antithrombin III deficiency	coagulation factor II (thrombin)
desirudin	CGP-39393 desulfatohirudin HIR-393 hirudin, Novartis Revasc Revasc-Ciba	Launched	Novartis	Sanofi-Aventis	Recombinant, other	Thrombin inhibitor	Thrombosis, venous	coagulation factor II (thrombin)

Source: Pharmaprojects

Table 2.38: Candidate biosimilars (bevacizumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
bevacizumab	anti-VEGF MAb, Genentech anti-VEGF MAb, Roche Avastin R-435 Ro-4876646	Launched	Genentech	Roche	Monoclonal antibody, humanised	Endothelial growth factor antagonist	Cancer, colorectal	vascular endothelial growth factor A
bevacizumab SIR-Spheres,Sirtex		Preclinical	Sirtex Medical		Formulation, optimised, microencapsulate	Endothelial growth factor agonist	Unspecified	vascular endothelial growth factor A

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Table 2.39: Candidate biosimilars (enfuvirtide)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
enfuvirtide	DP-178 Fuzeon R-698 Ro-29-9800 T-20	Launched	Trimeris	Roche	Antiviral, anti-HIV	GP41 antagonist	Infection, HIV/AIDS	env, HIV-1
enfuvirtide, needle-free	Fuzeon, needle-free	Pre-registration	Trimeris	Roche	Formulation, parenteral, needle-free	GP41 antagonist	Infection, HIV/AIDS	env, HIV-1

Source: Pharmaprojects

Table 2.40: Candidate biosimilars (glucagon)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
glucagon, Lilly	Glucagon for Injection Glucagon R	Launched	Lilly		Recombinant hormone	Glucagon agonist	Diabetes, general	glucagon receptor
glucagon, ZymoGenetics	GlucaGen GlucaGen Hypokit Glucagon G	Launched	Zymogenetics	Eisai Novo Nordisk	Recombinant hormone	Glucagon agonist	Hypoglycaemia	glucagon receptor

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Table 2.41: Candidate biosimilars (interleukin 11)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
oprelvekin	IL-11, Wyeth interleukin-11, Wyeth interleukin-11, Yamanouchi Neumega rhIL-11, Wyeth Sch-53620 YM-294	Launched	Wyeth	Yuhan	Recombinant interleukin	Interleukin 11 agonist	Chemotherapy-induced injury, bone marrow, thrombocytopenia	interleukin 11 receptor, alpha
interleukin-11, Bolder	IL-11, Bolder	Preclinical	Bolder Biotechnology		Recombinant interleukin	Interleukin 11 agonist	Chemotherapy-induced injury, bone marrow, thrombocytopenia	interleukin 11 receptor, alpha

Source: Pharmaprojects

Table 2.42: Candidate biosimilars (thyrotropin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
thyrotropin alfa, Genzyme	rhTSH, Genzyme Thyrogen thyroid-stimulating hormone,Ge TSH, Genzyme	Launched	Genzyme		Recombinant hormone	Thyroid hormone function agonist	Diagnosis, cancer	thyroid stimulating hormone receptor

Source: Pharmaprojects

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Table 2.43: Candidate biosimilars (abciximab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
abciximab	7E3 anti-GPIIb/IIIa MAb c7E3Fab ReoPro	Launched	Johnson & Johnson	Lilly	Monoclonal antibody, chimaeric	GPIIb IIIa receptor antagonist	Surgery adjunct	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit) integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61) integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41) integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)

Source: Pharmaprojects

Table 2.44: Candidate biosimilars (adalimumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
adalimumab	D2E7 Humira LU-200134 Raheara	Launched	AstraZeneca	Abbott Eisai GTC Biotherapeutics	Monoclonal antibody, human	Tumour necrosis factor antagonist	Arthritis, rheumatoid	tumour necrosis factor (TNF superfamily, member 2)

Source: Pharmaprojects

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Table 2.45: Candidate biosimilars (alemtuzumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
alemtuzumab	alentuzumab Campath Campath-1H LDP-03 MabCampath ZK-217699	Launched	BTG	Millennium Genzyme Bayer	Monoclonal antibody, humanized	Lymphocyte inhibitor	Cancer, leukaemia, chronic lymphocytic	CD52 molecule

Source: Pharmaprojects

Table 2.46: Candidate biosimilars (anakinra)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
anakinra	Antril IL-1 antagonist, Amgen IL-1ra, Amgen interleukin-1 antagonist, Amge Kineret rhIL-1ra	Launched	Amgen	Biovitrum Genesis Pharma	Recombinant, other	Interleukin 1 receptor antagonist	Arthritis, rheumatoid	interleukin 1 receptor, type I

Source: Pharmaprojects

Table 2.47: Candidate biosimilars (aprotinin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
aprotinin, Bayer	Trasylol	Launched	Bayer		Haemostatic	Kallikrein antagonist	Surgery adjunct	Unspecified

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Table 2.48: Candidate biosimilars (becaplermin)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
becaplermin	CTAP-III PDGF, Ethicon PDGF, Novartis Regranex rhPDGF-BB, Abbott rhPDGF-BB, J&J rhPDGF-BB, Novartis RWJ-60235	Launched	Novartis	Johnson & Johnson	Recombinant growth factor	Platelet growth factor agonist	Ulcer, diabetic	platelet-derived growth factor receptor, beta polypeptide

Source: Pharmaprojects

Table 2.49: Candidate biosimilars (cetuximab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
cetuximab	anti-EGFR MAbs, ImClone C225 Erbitux IMC-C225 MAb C225	Launched	Imclone Systems	Merck KGaA Bristol-Myers Squibb	Monoclonal antibody, chimaeric	ErbB-1 inhibitor	Cancer, colorectal	epidermal growth factor receptor (erythroblastic leukaemia viral (v-erb-b) oncogene homologue, avian)

Source: Pharmaprojects

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Table 2.50: Candidate biosimilars (DNase)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
Nase, Genentech	dornase alfa dornase alpha Pulmozyme Pulmozyme CF Pulmozyme, AERx rhDNase	Launched	Genentech	Roche	Recombinant, other	Deoxyribonuclease 1 stimulant	Cystic fibrosis	deoxyribonuclease I

Source: Pharmaprojects

Table 2.51: Candidate biosimilars (efalizumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
efalizumab	anti-CD11a MAb, Genentech anti-CD11a MAb, Xoma anti-CD11a monoclonals, Genent anti-CD11a monoclonals, Xoma hu1124 Raptiva Xanelim	Launched	Genentech	Xoma Merck KGaA	Monoclonal antibody, humanised	CD11a antagonist	Psoriasis	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1, alpha polypeptide

Source: Pharmaprojects

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Table 2.52: Candidate biosimilars (eptifibatide)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
eptifibatide	Integrelin Integrilin intrifiban velofibatide	Launched	Millennium	Schering-Plough GlaxoSmithKline	Antianginal	GPIIb IIIa receptor antagonist	Angina, unstable	integrin, alpha 2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41) integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)

Source: Pharmaprojects

Table 2.53: Candidate biosimilars (etanercept)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
etanercept	Embrel Enbrel p80 TNFR rhuTNFR:Fc rhvTNFR:Fc soluble TNF receptor, AHP soluble TNF receptor, Amgen STNFR TNF receptor, AHP TNF receptor, Amgen TNFR:Fc TNR-001	Launched	Amgen	Wyeth Takeda	Immunoconjugate, other	Tumour necrosis factor alpha antagonist	Arthritis, rheumatoid	tumour necrosis factor (TNF superfamily, member 2)

Source: Pharmaprojects

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Table 2.54: Candidate biosimilars (gemtuzumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
gemtuzumab ozogamicin	anti-CD33 MAb, AHP anti-CD33 MAb, UCB CDP-771 CMA-676 Mylotarg P-67	Launched	Wyeth	UCB	Immunotoxin	DNA antagonist	Cancer, leukaemia, acute myelogenous	CD33 molecule

Source: Pharmaprojects

Table 2.55: Candidate biosimilars (infliximab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
infliximab	anti-TNF-alpha MAb, Centocor Avakine cA2 CenTNF Remicade TA-650	Launched	Johnson & Johnson	Schering-Plough Tanabe Seiyaku	Monoclonal antibody, chimaeric	Tumour necrosis factor alpha antagonist	Crohn's disease	tumour necrosis factor (TNF superfamily, member 2)

Source: Pharmaprojects

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Table 2.56: Candidate biosimilars (natalizumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
natalizumab	AN-100226 Antegren Tysabri	Launched	Elan	Biogen Idec	Monoclonal antibody, humanised	Alpha4beta1 integrin antagonist	Multiple sclerosis, relapsing-remitting	integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) integrin, alpha 4 (antigen CD49d, alpha 4 subunit of VLA-4 receptor)

Source: Pharmaprojects

Table 2.57: Candidate biosimilars (nesiritide)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
nesiritide citrate	BNP, Johnson brain natriuretic peptide, J&J hBNP, Johnson & Johnson Natrecor Natrecor BNP Noratak	Launched	Johnson & Johnson		Recombinant, other	Brain natriuretic peptide agonist	Heart failure	natriuretic peptide receptor A/guanylate cyclase A (atrionatriuretic peptide receptor A)

Source: Pharmaprojects

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Table 2.58: Candidate biosimilars (omalizumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
omalizumab	anti-IgE MAb, E25, Tanox anti-IgE MAb, Genen anti-IgE MAb, Novartis CGP-51901 E-25 IGE-025A rhuMAb-E25 Xolair	Launched	Genentech	Tanox Novartis	Monoclonal antibody, humanised	Immunoglobulin E inhibitor	Asthma	immunoglobulin heavy constant epsilon

Source: Pharmaprojects

Table 2.59: Candidate biosimilars (palivizumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
palivizumab	anti-RSV MAb, Abbot anti-RSV MAb, MedImmune MEDI-493 RSV antibodies, Abbott RSV antibodies, MedImmune RSV MAbs, Abbott RSV MAbs, MedImmune Synagis	Launched	AstraZeneca	Abbott	Monoclonal antibody, humanised	Immunostimulant	Infection, respiratory syncytial virus	fusion protein (F), respiratory syncytial virus

Source: Pharmaprojects

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Table 2.60: Candidate biosimilars (rituximab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
rituximab	anti-CD20 MAb, Genentech anti-CD20 MAb, IDEC anti-CD20 MAb, Roche anti-CD20 MAb, Zenyaku IDEC-C2B8 MAbThera pan-B antibodies, Biogen pan-B antibodies, Genentech pan-B antibodies, Roche pan-B antibodies, Zenyaku R-105 Rituxan	Launched	Biogen Idec	Genentech Roche Zenyaku Kogyo	Monoclonal antibody, chimaeric	CD20 antagonist	Cancer, lymphoma, non-Hodgkin's	membrane-spanning 4-domains, subfamily A, member 1

Source: Pharmaprojects

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Table 2.61: Candidate biosimilars (trastuzumab)

Generic name	Synonyms	World status	Originator	Licensee	Therapy description	Pharmacology description	Indication	Target name
trastuzumab	anti-HER-2 MAb, Genentech anti-HER-2 MAb, Roche HER-2 MAb, Genentech HER-2 MAb, Roche Herceptin R-597 rhuMAb HER2 Ro-45-2317	Launched	Genentech	Roche	Monoclonal antibody, humanised	ErbB-2 inhibitor	Cancer, breast	v-erb-b2 erythroblastic leukaemia viral oncogene homologue 2, neuro/glioblastoma derived oncogene homologue (avian)

Source: Pharmaprojects

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CHAPTER 3
APPROACHES TO THE CHARACTERISATION OF BIOSIMILARS

3.1 Introduction

Since the original developers of a protein drug are not obliged to disclose their production processes, biosimilar competitors have to start by developing new manufacturing methods. They must then establish, using various analytical methods, that their products exhibit sufficient structural and functional similarity to an original protein to be able to substitute for it.

In this chapter we examine the scientific issues involved in assessing the similarity of biosimilars and describe the more important analytical methodologies available for this purpose. Demonstrating comparability of large molecules requires an understanding of molecular structure, heterogeneity profile, impurities and degradation patterns. Biosimilar developers need to deploy an array of sophisticated analytical techniques to characterise their products, including techniques with an established role in protein analysis such as high performance liquid chromatography and optical spectroscopy, as well as emerging techniques like nuclear magnetic resonance spectroscopy and the various forms of macromolecular mass spectrometry.

Regulatory requirements are likely to be more demanding for products bearing post-translational modifications, since relatively minor structural changes can alter therapeutically relevant characteristics. We also examine the issue of immunogenicity. European regulatory guidelines require clinical data demonstrating comparable immunogenicity, unless such problems can be excluded by other means.

3.2 Problems in characterising biologics

3.2.1 Definitions

Over the past 20 years or so, a number of definitions of biological products ("biologics") have been proposed for regulatory purposes. These often stress the fact that the chemical composition of a biologic is not completely deterministic. The WHO has defined a biological substance as "a substance which cannot be completely characterised by physicochemical means alone and which therefore requires the use of some form of bioassay". Bioassays involve a comparison of the biological response to the test substance with that towards a reference material. Since the 1920s, the WHO has supplied biological reference materials for such procedures. The UK Biological Standards Act states that biologics are substances "whose purity or potency cannot be adequately tested by chemical or physical means".

3.2.2 Types of biologic

3.2.2.1 Peptides

Peptides are normally regarded as containing 10-40 amino acid residues. They function as antibiotics, growth promoters, immunomodulators (both stimulants and suppressants), and agents to treat diabetes, pain, hypertension and infertility. Examples include oxytocin, desmopressin, glucagons, secretin, calcitonins, leuprolide, somatostatin and cyclosporin.

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The major synthetic sources are chemical, biochemical (eg. fermentation), and rDNA technology. Chemical synthesis is the most common approach, divided approximately evenly between solution-phase and solid-phase methods. It must be controlled carefully to remove the products of intermediate steps such as side-chain blocking, and degradation products. Because synthesis occurs through a series of steps, the yield progressively decreases, and longer peptides are more likely to contain incorrect sequences. Common degradation products include conversion of asparagine to aspartic or isoaspartic acid, conversion of aspartic acid to succinimide, and pyroglutamide formation from N-terminal glutamines. Racemisation also occurs, and stereospecificity is a major advantage of biosynthesis. rDNA synthesis is generally used for larger peptides such as growth hormone and insulin. Peptides can be made in bacteria, yeast or mammalian cells. Translational fidelity with occasional errors in amino acid incorporation can be a problem. Undesired post-translational modifications may also occur. Because of the relatively small number of amino acid residues, peptides can be more thoroughly characterised than proteins. Although such analyses are more straightforward than for proteins, they may still not be sufficient to predict biologic toxicity and immunogenicity.

3.2.2.2 Non-glycosylated proteins

Many of the problems associated with peptides also occur with non-glycosylated proteins, and additional issues arise as well. Variants of the desired molecule can be produced during synthesis, by chemical or physical reaction with manufacturing materials or components, or through degradation. For this reason, non-glycosylated proteins arising from rDNA synthesis tend to be heterogeneous. Because interactions of proteins with their receptors are often complex, small chemical changes may seriously affect activity, eg. deamidation of an amino acid, substitution of an amino acid (if not available in sufficient amounts during synthesis), acetylation (as acetate levels in the fermentation process rise), oxidation, misincorporation of amino acids (when mammalian codons are used in bacterial plasmids), misfolding (which is affected by disulphide bond formation), and carbamylation from process buffers such as urea (which may contain cyanate).

Though powerful, analytical procedures still have limitations, for example high-performance liquid chromatography may not detect an amino acid change buried within a protein, separation steps for mass spectrometry may affect protein characteristics, peptide maps may not always detect a change because of co-elution, proteins such as growth hormone with multiple effects may require multiple bioassays, and bioassays may not correlate well with human responses. Thus analytical procedures alone, including bioassay, may not adequately predict the effects of slight chemical variations on clinical outcomes.

3.2.2.3 Glycosylated proteins

Glycosylation is a post-translation event that adds complex sugar (glycan) structures to specific amino acid sequences. Different glycan structures are added depending on the expression system used. If a protein is expressed in *E.coli*, no carbohydrate is added. If yeast is used, glycosylation will add only oligomannosyl oligosaccharide moieties. These moieties are not added in mammalian cell culture. Insect and plant cells have other characteristics. Because changes in glycosylation patterns can affect many characteristics of a protein drug, analytical glycobiology is an important parameter when

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assessing changes in manufacturing processes for glycosylated proteins. Because glycan composition varies with cell line, nutrients, purification process and other factors, glycosylation pattern is also a useful process consistency marker during routine manufacturing. Despite its general importance, glycosylation has varying degrees of impact. It may affect activity directly, indirectly (eg. through changes in pharmacokinetics), or not at all. As with non-glycosylated proteins, full characterisation of a glycoprotein may not be possible, requiring non-clinical and clinical studies to assess consistency in therapeutic outcomes following a manufacturing change.

3.2.2.4 Monoclonal antibodies

Many therapeutic monoclonal antibodies, which are normally glycoproteins, are now available. Understanding of immunoglobulin structure and function, in particular the complementarity-determining regions and constant domains, has improved in recent years. Uses of monoclonal antibodies fall into one of several groups: (1) binding to a cell surface target, leading to immune-mediated target cell lysis; (2) binding to a cell surface receptor causing apoptosis; (3) cross-linking to a cytotoxic reagent; (4) receptor blocking; and (5) catalysis. All the usual protein analytical methods are applicable to monoclonal antibodies. Testing may require limited proteolysis to assess the activity of individual domains. As elsewhere, oligosaccharide residues on a monoclonal antibody add complexity and can be involved in activity. Changes in a manufacturing process can require both physicochemical characterisation studies and bioassays. As with other proteins, full characterisation of a monoclonal antibody may not be possible, requiring non-clinical and clinical studies to assess therapeutic outcomes in the presence of manufacturing changes.

3.2.3 Equivalence issues

Given that the detailed composition of a biological product may vary, at least three types of equivalence issue arise when dealing with it. The first is batch-to-batch consistency when no change in method of manufacture or ingredients has occurred. The second occurs when a manufacturer makes one or more specific changes to the ingredients or method of manufacture. This type of equivalence may be termed comparability. The third is when one manufacturer attempts to create a duplicate of another manufacturer's product, using different procedures, and sometimes different specifications, as with biosimilars. Statistical tests can be used to determine whether comparative data support the claim that two preparations are actually equivalent within a stated confidence interval (eg. 90%).

The term "bioequivalence" is often encountered in pharmacology and may cause confusion in relation to candidate biosimilars. It relates only to one type of equivalence, where two compounds become bioavailable at the same rate and to the same extent after administration at the same concentration. Because many biological products are simple solution formulations given by injection, bioequivalence in this sense is generally taken for granted (although it will of course vary according to the route of injection). Differential receptor binding, stability, immunogenicity, and so forth are issues of pharmaceutical equivalence.

Because no drug or biological is 100% safe, the management of risks becomes a crucial factor in demonstrating equivalence. The use of appropriate animal models during development and manufacture of these

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products may provide supportive data for an equivalence determination, as it does now for conventional pharmaceuticals.

3.2.4 Post-translational modifications

Post-translational modifications (PTMs) are the leading cause of heterogeneity in proteins with apparently similar amino acid sequences. There are at least 150 different kinds of covalent modifications of proteins. Although these may be small, they may serve a physiological role and can cause substantial conformational changes. Such changes can in turn alter the immunogenicity of the molecule, which will often also influence the biological activity, owing to sequestration by antibodies. PTMs are frequently necessary for biological activity, but in other cases are needed only for correct synthesis and secretion. Some 40 PTMs with varying degrees of ubiquity and importance are listed in Table 3.1.

Some PTMs involve alterations to the length of a protein by adding or removing amino acids (or polypeptides), but most involve modifications of existing amino acids *in situ*. Some modifications, most notably disulfidation but also the incorporation of entities such as haem groups, cause intrachain linkages within the protein, which strongly influence its conformation. Modifications generally occur at amino acids that are both physically exposed and chemically susceptible. For example, glycosylation occurs at asparagine, hydroxylysine, serine or threonine residues, phosphorylation usually occurs at serine, tyrosine, threonine or histidine residues, and biotinylation occurs at certain lysine residues. It is possible, to a limited extent, to predict PTMs from the amino acid sequence of a protein, but these algorithms have not progressed to an extent that would make them pharmaceutically useful. X-ray crystallographers, who can only determine the structures of chemically pure molecules that form crystals, often try to improve the homogeneity and cystallisability of their proteins by obtaining variants that lack key PTM target sites, eg. following point mutation or deletion, while retaining their biological activity. In the future, if the pharma industry could attempt the same tactic it would certainly simplify regulatory and production issues.

3.2.5 Effect of microheterogeneity

Even in a purified sample of, for example, erythropoietin it may be found that differences exist between individual molecules, eg. in terms of electrical charge (including the attachment of metal ligands) or conformation. The protein may co-exist with precursors, metabolites or variant forms of slightly different length. The amount and composition of any attached carbohydrate residues may vary. This situation is called microheterogeneity. It is affected by many factors, including preparation and storage conditions.

Experience over the past two decades has shown that the consequences of change in the manufacture of a natural-source or rDNA protein, which would obviously occur if a different manufacturer started to produce it using a different process, are not always predictable using non-clinical studies. Owing to the microheterogeneity of glycoproteins in particular, even drug batches from the same manufacturer will often differ slightly from each other. It is impossible to describe all microheterogeneic structures. The objective of a biosimilar manufacturer can only be to copy the safety and efficacy profile of the reference product. Sometimes, the significance of a change can be assessed using assay/model systems that have in the past been shown to be sensitive to the types of change that are likely to occur.

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However, biosimilar manufacturers have to recognise that substantial one-off studies, including clinical trials, will often be necessary to document equivalence. Where a product can be fully characterised and shown to differ from an existing product only in minor respects, the regulatory burden would clearly be less. Reference standards based on existing products are commonly held by regulatory agencies such as the US Pharmacopoeia (USP). Such standards will generally have been donated by the original manufacturers, and subjected to further detailed study. Additional standards may also be available, eg. process intermediates (which should be absent from the finished product), assay reagents and bioassay materials. The final decision as to how much characterisation will be required rests of course with the regulatory agency.

3.2.6 Pharmacokinetics

Pharmacokinetic studies assess variability in absorption, distribution and elimination, and can help in establishing pharmaceutical equivalence. They are useful in assessing the impact of a change in the manufacture of a natural-source or rDNA-derived protein. Although most proteins are administered by injection, absorption can vary depending on whether the injection is subcutaneous, intramuscular or intravenous. Formulation also affects pharmacokinetics, even where the same route of administration is used. Many factors, including glycosylation state and other physicochemical characteristics, can affect distribution. Both oxidation and glycosylation are known to impact pharmacokinetics. Elimination is affected by protein molecular weight, leading to many-fold differences in half-life. For proteins that are rapidly cleared by the liver, hepatic blood flow (which increases during exercise) can influence both the pharmacokinetics and pharmacologic effects.

3.2.7 Pharmacodynamics

Pharmacodynamics is the study of the biochemical and physiological effects of drugs and the mechanisms of drug action. One often reads that pharmacodynamics studies what a drug does to the body, whereas pharmacokinetics studies what the body does to a drug. Pharmacodynamic studies usually focus on a surrogate or biomarker of interest, eg. platelet aggregation following administration of anti-platelet therapy in the treatment of myocardial infarction. In this way, they allow comparisons between unchanged and changed dosage forms. Pharmacodynamic studies more directly reflect clinical outcomes and can change even when pharmacokinetic measures do not. However, such studies are also affected by many problems, such as multiple mechanisms of drug action and high variability in and between subjects, as occur with intravenous immunoglobulins for example. Because the focus of a pharmacodynamic study is a specific endpoint related to the natural source or rDNA biological, it is not appropriate to generalise further.

3.2.8 Clinical efficacy

Clinical studies may be used to assess equivalence using both safety and efficacy endpoints. If a new drug or regimen has benefits with respect to a primary or secondary endpoint in comparison to the existing drug or regimen, it is not necessary for the new regimen to be superior to the existing regimen with respect to all the endpoints. For example, if survival is the primary endpoint, a new regimen which is safer need only be similar with respect to survival in order to be the preferred regimen. In other

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words, non-inferiority is the minimum requirement. This approach is applicable to equivalence testing for a natural or rDNA-derived protein, where relevant clinical outcomes should stay within the equivalence interval. Biosimilars should be neither markedly superior nor markedly inferior to the reference product.

3.2.9 Immunogenicity

Many exogenously administered proteins produce an antibody response, but this usually causes few or no clinical problems. Because significant immune responses occur infrequently, clinical trials may not reveal them, and some type of market surveillance may be needed instead. Many factors affect the immunogenicity of protein therapeutics, including structural and chemical alterations, storage conditions, production/purification techniques, formulation, route of administration, dose and frequency of administration, and various patient characteristics. Immunogenicity may have no clinical impact, if the response is small or transient, or it may produce a spectrum of responses including hypersensitivity and neutralisation of biological effects. Neutralisation may also extend to endogenous proteins related to the therapeutic, as with the incidents of pure red cell aplasia among patients receiving recombinant erythropoeitin. Antibodies may also accelerate or retard clearance of the therapeutic protein. It is important to fully characterise an immune response using both immunoassays, which detect antibodies that bind to the drug, and biological assays, which detect neutralisation of biological effects by antibodies. Human immune responses cannot be predicted from animal testing.

3.3 Analytical methods

3.3.1 Introduction

The ultimate structural characterisation of a protein can be achieved with either nuclear magnetic resonance (NMR) spectroscopy or X-ray crystallography. X-ray structures are the "gold standard" in protein biology because a map of every single atom in a protein can (in principle) be obtained, but X-ray studies take a long time to complete and cannot be done at all for many proteins. Hence we do not discuss it further in this Report. Although computationally intensive, NMR is probably the more practical of these two methods. A variety of other techniques are important in detecting amino acid sequence alterations, differential glycosylation, etc.

Table 3.2 summarises the type of information contributed by the most widely used analytical procedures. In this section we review selected techniques in greater depth.

3.3.2 Chromatography

The general principle of chromatography relies on a matrix, for example consisting of dextran or silica beads, that chemically or physically binds and retains a molecule of interest; contaminating proteins and other impurities interact with the matrix less strongly (or not at all) and become separated in the solvent (also called the eluant). Most chromatography procedures are performed in a long column containing the matrix. This improves the selectivity by repeatedly retarding desired protein relative to its contaminants. Initially, ion-exchange chromatography was available to separate out proteins based on their ionic charge as a function of pH and salt concentration. Newer developments include gel-filtration

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chromatography, which separates proteins by molecular weight; affinity chromatography, which selects a protein by its unique ability to chemically interact with the matrix, eg. because the matrix includes antibodies; and high performance, or high pressure, liquid chromatography (HPLC), which relies on hydrophobicity and structural interaction with the matrix. Variants of HPLC, in particular reversed phase-HPLC (which incorporates a non-polar matrix and a variably polar eluant), have become central techniques in the characterisation of peptides and proteins. In RP-HPLC, relatively polar eluants increase the hydrophobic interaction of non-polar solutes with the separation matrix, which in turn increases the retention time. HPLC produces sharp reliable resolution of even quite closely related proteins. It is also an economically effective process, which is employed in the manufacture and purification of many recombinant therapeutics including erythropoietin, insulins, interferons, interleukins and human growth hormone. Multiple chromatography procedures may be combined in series, improving the overall purity of the final product: for example, reversed phase HPLC is often used near the end of a purification process to remove remaining trace impurities.

Peptide mapping is routinely used for the structural characterisation of native and recombinant proteins. With this technique, peptides derived from the proteolytic fragmentation of a protein are separated by RP-HPLC. The availability of sufficient amounts of protein is often a limiting factor in peptide mapping. For this reason, low volume narrow-bore and microbore reversed-phase HPLC columns are used increasingly. The sensitivity of the peptide map to even the smallest change in the covalent structure of the protein makes it a valuable "fingerprint" for identity testing and process monitoring. Peptide maps are generally inspected visually. It is possible to detect anticipated sequence variations by running samples that include them as standards or references.

3.3.3 Protein sequencing

Obtaining the amino acid sequence of a protein is a crucial early step in characterisation because it confirms the presence of the desired protein, ensures that no unwanted mutations arose during any preceding gene manipulation, and is a key determinant of the three-dimensional structure. The sequence of a purified protein can be investigated with a number of chemical and physical analyses, most prominently electrospray ionisation mass spectrometry (ESI-MS) and the Edman degredation. Both are applicable to peptides up to around 50 amino acids in length. Longer proteins must first be partially digested with a suitable protease (such as trypsin) or a reagent such as cyanogen bromide (which cleaves peptide bonds at the C-terminus of methionine residues). Disulphide linkages must also be broken. After the fragments have been purified and sequenced, the sequence of the original protein can be reconstructed from those of the overlapping fragments. ESI-MS is discussed in the section dealing with mass spectrometry. Automated Edman sequencers are in widespread use, and are now rapid enough to be integrated with production and purification processes.

The Edman degredation consists of a series of steps that are repeated for each amino acid. The peptide to be sequenced is adsorbed onto a solid surface. One common substrate is glass fibre coated with polybrene, a cationic polymer. The Edman reagent, phenylisothiocyanate (PTC), is added to the adsorbed peptide, together with a mildly basic buffer solution of 12% trimethylamine. This reacts with the amine group of the N-terminal amino

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acid. The N-terminal amino acid derivative can then be selectively detached by the addition of anhydrous acid. The derivative then isomerises to give a substituted phenylthiohydantoin which can be washed off and identified by chromatography, and the cycle can be repeated. The efficiency of each step is about 98%, which allows about 50 amino acids to be reliably determined. Because the Edman degradation proceeds from the N-terminus of the protein, it will not work if the N-terminal amino acid has been chemically modified or if it is concealed within the body of the protein. It also requires a separate procedure to determine the positions of disulphide bridges. Because the first round of the Edman degradation is often contaminated by impurities, it does not give an accurate determination of the N-terminal amino acid. Various reagents are available to label the N-terminus; these include Sanger's reagent (2,4-dinitrofluorobenzene) and dansyl derivatives such as dansyl chloride. Phenylisothiocyanate, the Edman reagent, can also be used. These reagents give qualitative results, ie. a colour change specific for each amino acid.

3.3.4 Mass spectrometry

Mass spectrometry (MS) and its variants, which offer excellent sensitivity and accuracy, can also be used to determine amino acid sequences. Mass spectrometry involves evaporating a protein molecule from a solution, bombarding it with electron beams to cause molecular fragmentation and ionisation, and then separating and identifying the fragments according to their charge-to-mass ratio. All mass spectrometers possess an ion source to produce ions, an analyser to sort them in some way by their masses, and a detector to measure the relative intensities of different masses. Ions derived from the sample are accelerated to a high speed by an electric field after which they are directed into a magnetic field. The latter applies a force to the ions, which deflects them to differing degrees depending on their mass-to-charge ratio. For any given charge, the lighter ions are deflected more than the heavier ions because of their lower momentum. The detector measures the deflection of each resulting ion beam. From this measurement, the mass-to-charge ratios of all the ions produced in the source can be determined. This information can be used to determine the chemical composition of the original sample and, where appropriate, the isotopic compositions of its constituents. For example, time-of-flight (TOF) mass spectrometers measure the time taken for ions to reach the detector; for a given charge-to-mass ratio and kinetic energy, small particles travel faster.

There are numerous methods for ionising samples; the most biologically important are electrospray ionisation (ESI) and matrix-assisted laser desorption/ionisation (MALDI). These methods minimise the unwanted tendency of large molecules to fragment when ionised. In ESI, a highly dilute liquid sample is forced through a small charged (usually metal) capillary. The solvent is normally electroneutral and more volatile than the analyte, which exists as an ion in solution (usually either protonated, ie. positive, or deprotonated, ie. negative). On emerging from the capillary into an electric field, the sample forms an aerosol consisting of small droplets about 10 um across. As the solvent evaporates, the sample ions repel each other to yield a spray of single ions which can be directed into the mass analyser of a mass spectrometer. Although John Fenn received a share of the 2002 Nobel Prize in Chemistry for ESI, the exact mechanism of lone ion formation remains obscure.

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In MALDI, ionisation is triggered by a laser beam (normally a nitrogen laser). A matrix is used to protect the biomolecule from being destroyed by the direct laser beam and to facilitate vaporisation and ionisation. Matrices must be soluble in water, acidic (so that they can provide positive charges to an analyte), and must absorb laser light at the wavelengths used (in the ultra-violet). The three most commonly used compounds are 3,5-dimethoxy-4-hydroxycinnamic acid (sinapinic acid), alpha-cyano-4-hydroxycinnamic acid, and 2,5-dihydroxybenzoic acid (DHB). A solution of one of these substances is made, commonly in a mixture of highly purified water and an organic solvent such as acetonitrile or ethanol. Trifluoroacetic acid may also be added. The matrix solution is mixed with the analyte, which will generally be a protein-containing sample. The organic solvent allows hydrophobic molecules to dissolve into the solution, while the water allows for water-soluble (hydrophilic) molecules to do the same. This solution is spotted onto a specially designed metal plate. The solvents vaporise, leaving only the crystallised matrix, which contains analyte molecules distributed throughout it. The laser is fired at these crystals in pulses, which ionises the matrix. This may occur in a vacuum or at atmospheric pressure. The matrix is then thought to transfer part of its charge to the analyte molecules, thus ionising them without exposing them to the direct energy of the laser. Ions originating during this process are created by the gain or loss of protons, as with ESI. MALDI generally produces singly-charged ions. The type of mass spectrometer most widely used with MALDI is the TOF (time-of-flight) instrument, mainly due to its large mass range. Using MALDI, whole proteins such as albumin can be ionised. MALDI is used for the identification of proteins isolated through gel electrophoresis.

One method of protein characterisation used with MS is peptide mass fingerprinting. The unknown protein is cleaved into peptides by a protease such as trypsin. The collection of peptides resulting from this cleavage uniquely identify the unknown protein. The absolute masses of the peptides in the digest are accurately measured with an MS technique such as MALDI-TOF or ESI-TOF. This produces a so-called peak list of molecular fragments, the masses of which are scanned against the genome *in silico*. A computer queries protein databases such as SWISS-PROT and virtually 'cuts' the proteins into peptides with the same protease. It then calculates the absolute masses of the peptides from each protein and compares the masses of the peptides from the unknown protein to the theoretical peptide masses derived from each protein in the databases searched. The results are statistically analysed to find the best match. In a related process called de novo sequencing, peptide sequences are derived from the masses of their fragments as shown on a mass spectrum without using a protein sequence database. Hence this method should work with previously undescribed proteins.

3.3.5 Nuclear magnetic resonance

All atomic nuclei that contain odd numbers of protons or neutrons have a quantum mechanical 'spin', together with an intrinsic magnetic moment and angular momentum. From the standpoint of biological NMR, the most important such nuclei are 1-H and 13-C. Both isotopes are stable and occur naturally, but 13-C only accounts for about 1% of all carbon. However, samples can be labelled with it if necessary. In NMR studies, magnetic nuclei are aligned with a very powerful external magnetic field and perturbed with an electromagnetic field. The response to these perturbations is exploited in NMR spectroscopy. When placed in a magnetic

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field, NMR active nuclei absorb or resonate at a radiofrequency characteristic of the isotope. The energy of the absorption and the intensity of the signal are proportional to the strength of the magnetic field. For example, in a 21 tesla magnetic field, protons resonate at 900 MHz. Depending on the local chemical environment, different protons in a molecule resonate at slightly different frequencies. It is this frequency shift that provides the chemical information. It is reported as a relative measure from a reference resonance frequency. For the nuclei 1-H and 13-C (and 29-Si), tetramethylsilane (TMS) is the most common reference. The difference between the signal and reference frequencies is divided by frequency of the reference signal to give the so-called chemical shift. Such frequency shifts are small (100s of Hz) in comparison to the nuclear resonance frequency (100s of MHz) and so are generally expressed as parts per million (ppm). For example, in the 1H-NMR spectrum for ethanol (CH_3CH_2OH) one would expect to see three specific chemical shifts or signals, one for the CH_3 group (typically 1ppm), one for the CH_2 group (4ppm) and one for the OH (2-3ppm). Shifts also depend on the solvent used. Only one signal is obtained from the three methyl protons (albeit at three times the intensity of one proton) because they average out at room temperature.

Protein nuclear magnetic resonance is performed on aqueous samples of highly purified protein. Usually the sample consists of 300-600 microlitres of solvent with a protein concentration in the range 0.1-3.0 mM. In large molecules such as proteins, the number of individual chemical shifts can typically be several thousand, and a one-dimensional spectrum inevitably has many overlaps. Various tactics have been devised to improve resolution. For example, the use of radiofrequency pulse sequences and delays in correlation spectroscopy allows relationships between different nuclei to be detected. Depending on the concentration of the sample, the magnetic field strength of the spectrometer, and the type of investigation, a single NMR experiment on a protein sample may take hours or even several days to obtain suitable signal-to-noise ratio through signal averaging and other manipulations. Resolution can also be improved by heteronuclear labelling, ie. the introduction of NMR-active isotopes other than 1-H, such as 13-C or 15-N. Researchers often start by obtaining a two-dimensional heteronuclear single quantum correlation (HSQC) spectrum. In theory the HSQC spectrum has one peak for each H bound to a heteronucleus. Thus in the 15-N-HSQC, one signal is expected for each amino acid residue (except proline which has no amide hydrogens). Tryptophan and certain other residues with N-containing side-chains also give rise to additional signals. The 15-N-HSQC is often referred to as the fingerprint of a protein because each has a unique pattern of signal positions. Analysis of the 15-N-HSQC allows researchers to evaluate whether the expected number of peaks is present and thus to identify possible problems due to multiple conformations or sample heterogeneity.

To assign particular resonances to particular atoms, some more advanced form of correlation spectroscopy (COSY) is used. Examples include total correlation spectroscopy (TOCSY) and nuclear Overhauser effect spectroscopy (NOESY). These are two-dimensional NMR experiments. They involve a series of one-dimensional experiments, each of which consists of measuring NMR effects following a sequence of radio frequency pulses with delay periods in between them. It is the timing, frequencies and intensities of these pulses that distinguish different NMR experiments from one another. During some of the delays, the nuclear spins are allowed to freely precess (rotate) for a determined period, known as the evolution time. The

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frequencies of the nuclei are detected after the final pulse. By incrementing the evolution time in successive experiments, a two-dimensional data set is generated from a series of one-dimensional experiments. If two sets of one-dimensional data are plotted against one another, so-called cross-peaks appear symmetrically above and below the diagonal line where the two data sets intersect. These indicate which NMR-active atoms are closely connected to one another. Cross-peaks result from a phenomenon called magnetisation transfer. This can occur across free space or through chemical bonds.

3.3.6 Electrophoresis

Electrophoresis involves resolving a mixture of proteins with respect to their molecular weights. Molecular weight measurement provides an additional check on the identity of a protein of interest, and indicates if it has formed abnormal aggregates or degradation products. The presence of contaminating proteins is also (in most cases) readily visible from electrophoresis.

The most commonly used method is called SDS-polyacrylamide gel electrophoresis (SDS-PAGE). Electrophoresis is similar to chromatography, except that a polyacrylamide gel is used as the matrix. An electric field is applied across this gel and microlitre quantities of protein are placed near the cathode end. The gel is at least 95% water (or, rather, buffer) and contains an anionic detergent called sodium dodecyl sulfate (SDS), which unfolds proteins and binds to them, uniformly coating them with negative charges. The negatively charged proteins travel towards the positive electrode (anode), situated at the far end of the gel matrix. The rate at which SDS-treated proteins can migrate through the gel is a function of their size (larger proteins will suffer more retardation by the gel). SDS-PAGE cannot generally be used for purification because it destroys proteins in the process (and only very small quantities can be used). Following electrophoresis, the gel may be stained, eg. with Coomassie Brilliant Blue, allowing visualisation of the separated proteins. After staining, different proteins will appear as distinct bands within the gel. It is common to run standard samples of known molecular weight in a separate lane in order to calibrate the gel. In this way, the weight of unknown proteins can be determined by comparing the distances travelled relative to the standards. SDS-PAGE cannot be used with smaller peptides, and often fails to separate proteins of very similar molecular weights.

Various refinements of the basic SDS-PAGE procedure have been developed. SDS eliminates some secondary and tertiary structures, but does preserve disulphide bridges. In reducing SDS-PAGE, proteins are briefly heated to near boiling in the presence of a reducing agent, such as dithiothreitol or 2-mercaptoethanol. This causes more severe denaturation by reducing disulphide linkages, thus overcoming additional forms of tertiary protein folding, and breaking up quaternary protein structure (oligomeric complexes). In many cases, for example when working with enzymes, an investigator will wish to retain some tertiary structure; when this is not desired, reducing SDS-PAGE is used. Isoelectric focusing, also known as electrofocusing, is a technique for separating different molecules by their electrical charge differences. It relies on the fact that the charge of a molecule changes with the pH of its surroundings and can also become neutral. In this technique, the molecules to be separated are placed in the middle of a gel containing a pH gradient. When an electrical current is applied across the gel, negatively charged molecules migrate through the

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pH gradient towards the anode while positively charged molecules move towards the cathode. A particle migrates through the pH gradient until it reaches a point where the pH equals its isoelectric point (pI). At this point the molecule no longer has a net electrical charge and does not travel any further.

The pH gradient is initially established by subjecting a solution of small molecules with varying pI values to electrophoresis. Gels with large pores (eg. polyacrylamide with a relatively high water content) are usually used in this process to eliminate any 'sieving' effects caused by differing migration rates for proteins of differing sizes. Isoelectric focusing can resolve proteins that differ in pI value by as little as 0.01 and is often the first step in two-dimensional gel electrophoresis (2D-PAGE), where proteins are separated first by their pI and then by molecular weight using SDS-PAGE.

The sensitivity of 2D-PAGE when used with complex mixtures is unparallelled, because even in proteins that contain several hundred amino acids, a change of a single amino acid can be detected. The 2D-PAGE result can be compared between biosimilar and pioneer proteins, and from batch to batch, to ensure identity and purity.

3.3.7 Western blotting

A western blot (or immunoblot) is an extension of gel electrophoresis, which can be run using either intact or denatured proteins. After electrophoretic separation, the proteins are transferred to a membrane (usually nitrocellulose or PVDF), which is placed in contact with the gel. The membrane is then probed with one or more specific antibodies, eg. monoclonal mouse antibodies, to identify the location(s) of the protein(s) of interest. Unbound antibody is washed from the membrane, which is then typically reacted with a secondary antibody (eg. anti-mouse) which binds to the primary antibody regardless of the specificity of the latter. The secondary antibody is normally labelled with a colourimetric or luminometric marker (eg. an enzyme), which allows it to be visualised. In the case of a marker enzyme, the results can be visualised with a substrate that becomes coloured, changes colour, or emits light when reacted with the enzyme.

3.3.8 Bioassays

A bioassay is an analytical procedure measuring a biological activity of a test substance via a specific response from a biological test system. Bioassays can use animals, *in vitro* cell lines, cell-based 'biochemical' assays (kinase receptor activity, reporter genes), binding assays (immunoassays, biosensors), and enzyme assays. The end result of a bioassay is a relative potency measure, expressed as units (or international units, IU) per unit mass of product. Potency is measured against international, national, or in-house standards, or a predicate batch. Bioassays are the only non-clinical tests that indicate that a product is biologically active. In equivalence studies, they reveal the extent to which changes in a protein have affected its activity. They are less useful in measuring other parameters (eg. pharmacokinetics) but critical in assessing immunogenicity. Only bioassays can confirm if a protein can elicit the production of antibodies that neutralise its biological effects. Bioassays also are critical for structure/function studies. Although physicochemical procedures can detect most modifications that might occur in a therapeutic protein, the impact of these changes can be assessed only when they are correlated with biological activity. Proteins with multiple biological activities may require

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multiple bioassays. When the mechanism of action is unknown or complex (eg. therapeutic vaccines), bioassays may be of limited value. Bioassays can also be limited by high degrees of variability, as with animal models. Bioassays are of particular value where they provide information on the stability of the test protein. They are also useful in assessing the importance of changes in glycosylation patterns. Bioassays are also critical in batch-to-batch quality control when no obvious change has occurred. Bioassay testing for consistency, comparability, and equivalence relies on a determination of parallelism, which (some authorities believe) is not always properly assessed.

Despite a growing range of physicochemical and bioassay information, variable effects in the clinic may be observed following a manufacturing change, but in the absence of demonstrable physicochemical and biological potency changes. Conversely, such clinical effects sometimes do not occur even when significant changes in these parameters can be demonstrated.

3.3.9 Other procedures

Immunoassays confirm purity by detecting protein contaminants from expression systems such as *E.coli*, *Saccharomyces cerevisiae*, or Chinese hamster ovary cells. A number of spectral techniques can provide information about the 3D structure of proteins. Fluorescence spectroscopy, circular dichroism, infrared spectroscopy and Raman spectroscopy all substantiate the presence of certain structural domains in a protein. Such procedures can be used to help develop a set of reference spectra to which all lots of a recombinant protein can be compared. If a biosimilar protein were structurally different from the original product, the various spectra would highlight those differences, even where minor.

3.4 Case studies

3.4.1 Introduction

Focusing on the two leading world markets, the EMEA has an approvals pathway for biosimilars while the FDA does not. In addition, the patent regimes in the two regions differ, so that a product such as erythropoietin may be off-patent in the EU while retaining a number of years of protection in the US. Furthermore, a particular patent claim may expire before the patent as a whole does. There are at least four product-specific EMEA guidelines available for companies developing biosimilar versions of biologicals: EPO, somatropin, G-CSF and insulin. There is also a separate guideline on immunogenicity testing. Immunogenicity cannot be predicted from animal studies or *in vitro* investigations. The FDA does occasionally approve "follow-on proteins"; if they are sufficiently similar to an existing approved product, a certain amount of basic science can be taken as read and the approvals process shortened. However, these products are not treated as therapeutically equivalent to the originator product and hence are not officially generics, unlike European biosimilars which can be used in place of an originator drug (and indeed may have to be, if cost is paramount). This issue is discussed more fully in the section on somatotropin below.

3.4.2 Erythropoietin

Erythropoietin is a glycoprotein hormone with large carbohydrate chains. In addition, it is heterogeneous, consisting of several different isoforms

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primarily differing in terms of glycosylation. It is expressed in cultured mammalian cells.

3.4.2.1 European position

At its June 21st, 2007 meeting the Committee for Medicinal Products for Human Use (CHMP) of the EMEA adopted positive opinions for three biosimilar erythropoietins – Binocrit (Epoetin alfa) from Sandoz, Epoetin alfa Hexal (Epoetin alfa) from Hexal (Novartis) and Abseamed (Epoetin alfa) from Medice Arzneimittel Puetter. These products are intended for the treatment of anaemia associated with chronic kidney disease and in oncology patients; and to reduce blood transfusion requirements in oncology patients and prior to elective orthopaedic surgery.

All three products have been shown to be similar to Amgen's Eprex/Erypo, the reference medicinal product already authorised in the EU, in the applied indications. The EMEA review began on March 29th, 2006 with an active review time of 205 days. All three products will be approved as 1,000IU/0.5mL; 2,000IU/1.0mL; 3,000IU/0.3mL; 4,000IU/0.4mL; 5,000IU/0.5mL; 6,000IU/0.6mL; 8,000IU/0.08mL and 10,000IU/1.0mL pre-filled syringes.

The EMEA published a guideline on biosimilar EPOs in April 2006. Immunogenicity, most notably the generation of neutralising antibodies, is of particular concern with EPO. The EMEA does not specify the number of people to be enrolled in clinical trials, saying only that comparative safety data from efficacy trials must be "sufficient to provide an adequate pre-marketing safety database". The exact antibody frequency of most epoetins is not known and also depends on the sensitivity of the assay. The frequency of around 1% cited by most companies is based on a highly sensitive assay. Without knowing the methodology used, it is difficult for the EMEA to give an exact estimate of the size of the immunogenicity database needed, so the guideline does not give a specific number. Comparative immunogenicity data are required over at least a 12 month period, and a validated, highly sensitive assay should be used to detect anti-epoetin antibodies. Trials intended to compare clinical efficacy with the reference epoetin should last at least six months. The applicant has a choice of study design, provided it can justify its approach. Clinical efficacy has to be "comparable" rather than "equivalent".

3.4.2.2 US position

Biosimilar epoetins are not currently an issue in the US because Amgen's patent number US5547933 (filed June 7th, 1995) remains in force until around 2015 (in Europe patent number EU148605 has expired).

3.4.2.3 Immunogenicity: pure red cell aplasia

Over the period 1998-2003, over 500 patients worldwide being treated with epoetins (92% of whom were receiving J&J's non-US Eprex/Erypo formulation) developed pure red cell aplasia. Most affected patients had chronic kidney disease and had received the drug subcutaneously. The reaction was attributed to an immune response, although in many cases detectable neutralising anti-EPO antibodies were not sought or not found. Patients on chemotherapy were thought to be protected by immunosuppression. Most patients responded to a combination of transfusions and immunosupression, and some were successfully re-treated

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with epoetins following recovery.

This problem was investigated by an international group of collaborators who reported their findings in the September 30th, 2004 issue of the *New England Journal of Medicine*. In the mid-1990s there was a significant shift in many countries from intravenous to subcutaneous administration for patients with chronic kidney disease. The subcutaneous mode of administration was thought to be both more cost-effective and less invasive.

As had been noted with other proteins, the subcutaneous administration of epoetin (particularly self-administration, with the attendant problems in the storage and handling of the product) had the potential to induce antibody formation. In 1998, the formulation of Eprex with human serum albumin that was marketed in Europe was changed in response to concerns that human serum albumin could transmit a variant of Creutzfeldt-Jakob disease. The reformulated Eprex contained different vehicles (polysorbate 80 and glycine).

In the US, Epogen and the second-generation epoetin product darbepoetin alfa (Amgen's Aranesp) have always included human serum albumin as a stabiliser, whereas in Europe and Canada, darbepoetin alfa is formulated with polysorbate 80 at a lower concentration than in the polysorbate Eprex formulation (0.005% *vs* 0.03%). Organic compounds leached by polysorbate 80 from the rubber plungers used in the prefilled syringes of Eprex may also have had a role in the product's immunogenicity. In mid-2003, the manufacturer of Eprex replaced the rubber plungers with Teflon-coated plungers. Another potential cause of increased immunogenicity is the silicone oil lubricant, which was introduced into the prefilled syringes of Eprex in 1994. In chronic kidney disease patients who do not have permanent vascular access, epoetin continues to be administered subcutaneously, and regulatory authorities now recommend a specific route of administration only when such patients receive Eprex in the formulation without human serum albumin.

3.4.2.4 Immunogenicity: product consistency issues

The red cell aplasia experience powerfully demonstrates how small manufacturing changes can have significant impacts on the pharmaceutical equivalence of a drug. In order to probe this issue further, Professor Huub Schellekens at the University of Utrecht in the Netherlands studied 11 biosimilar epoetin products sourced mainly from the Far East, and made by eight manufacturers. At that time there were no approved biosimilar products in the US or the EU. The products were examined for possible differences in erythropoietin content, potency and isoform distribution. Schellekens reported his findings in the March 2004 issue of the *European Journal of Hospital Pharmacy*.

Bioactivity was measured *in vitro* as a function of proliferation of B6SUtA cells, an erythropoietin-dependent cell line. Cell proliferation was measured indirectly with a tetrazolium dye. Results ranged from 80-125% of the claim. An *in vivo* bioassay of erythropoietin was performed, based on splenic 59-Fe incorporation by polycythemic mice (59-Fe is a gamma emitter). *In vivo* bioactivity ranged from 71-226% of the claim, with five samples failing to meet their specifications. Samples were subjected to polyacrylamide gel isoelectric focusing in a pH3-10 gradient with 6M urea as a denaturant. Gels were transferred to nitrocellulose membranes for Western Blot analysis. Unknown compounds were detected in three

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samples. Total protein content ranged from 80-120% of specifications, with five samples out of spec. Four major and two minor isoforms were identified in the epoetin alfa control. Two additional basic isoforms were identified in five samples, and three additional basic isoforms were identified in one sample. An additional acidic isoform was identified in four samples. Moreover, variation in the intensity of isoform bands in comparison to epoetin alfa was noted for five samples.

These results indicate poor quality control and highlight the need for regular monitoring of both analytical and clinical aspects of biosimilar products, including an assessment of the circumstances in which they are produced. Many biopharmaceuticals, including epoetin, are heterogeneous with respect to isoform distribution. As it is difficult to establish the contribution of different isoforms to the overall activity and toxicity of a protein drug, regulatory standards require consistency between production runs. With that in mind, Schellekens believes that the most alarming aspect of this comparison was the variation observed between different lots of the same product, which exposes major flaws in the control of the production process. Even if European or US biosimilar manufacturers achieve the highest standards, there is a risk that the high prices that biosimilars are likely to command (70-80% of originator prices) will draw in counterfeit products with these characteristics.

3.4.3 Somatotropin

Recombinant somatotropin is a relatively short (191 amino acid) non-glycosylated protein, the chemical composition of which is precisely known. It is expressed in *E.coli*.

3.4.3.1 European position

Two somatotropins, Sandoz's Omnitrope and Biopartners' Valtropin, which are biosimilars of Pfizer's Genotropin and Lilly's Humatrope respectively, were approved by the EMEA in 2006. Sandoz has also launched Omintrope in Australia, but only after submitting a full application to that country's Therapeutic Goods Administration. No abridged route for biosimilar products exists in Australian regulations. Biopartners is developing a sustained-release version of Valtropin, which is in Phase III trials and is expected to be submitted for EU approval in the second half of 2008. There are currently no marketed sustained-release hGH products.

3.4.3.2 US position

Sandoz has struggled to obtain approval for Omnitrope in other jurisdictions. In fact, in the US the company became engaged in a legal dispute with the FDA over the approval process. Sandoz first filed for approval of Omnitrope in December 2001, and resubmitted its application in July 2003, but the FDA did not issue a decision until May 2006, following a court order obtained by Sandoz requiring it to do so. US legislation on biosimilars and follow-on biological products is still being written and the FDA is still developing guidance for manufacturers. Genentech's rhGH patents (US4601980 granted in July 1986 and US4658021 granted in April 1987) expired around 2003. In the meantime the FDA had received citizen petitions from various industry sources, including Pfizer and Genentech, urging it to refuse Omnitrope on the basis that no application for a therapeutic protein product should rely on information contained in another approved application. The FDA blamed much of the delay in approving

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Omnitrope on these petitions, which it eventually rejected. It approved Omnitrope for the long-term treatment of paediatric patients, who have growth failure due to an inadequate secretion of endogenous growth hormone, and for long-term replacement therapy in adults with growth hormone deficiency of either childhood or adult-onset etiology.

However, the FDA does not accept that Omnitrope is interchangeable with any other recombinant protein products, as a true generic would be, and has designated it with a BX rating in the 'Approved Drug Products with Therapeutic Equivalence Evaluations' (the Orange Book). This code refers to "[d]rug products for which the data are insufficient to determine therapeutic equivalence". The FDA maintains that Omnitrope is merely a "follow-on protein product", ie. that it is sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product.

The FDA argues that it has approved other follow-on proteins on a similar basis, including GlucaGen (glucagon recombinant for injection), Hylenex (hyaluronidase recombinant human), Hydase and Amphadase (hyaluronidase), and Fortical (calcitonin salmon recombinant) nasal spray. The Agency accepts that it is possible to compare one rhGH preparation with another because the hormone is well characterised, bioassays and biomarkers exist, it has a long and well documented history of clinical use, its mechanism of action is known, and its toxicity profile is well understood.

The FDA insists that the approval of Omnitrope does not establish a pathway for the approval of follow-on products, nor does it mean that more complex and/or less well understood proteins approved as drugs could be approved as follow-on products. The Agency also points out that the majority of protein products are licensed as biological products under the Public Health Service Act, and not approved as drugs under the Food, Drug, and Cosmetic Act (as rhGH is). There is no abbreviated approval pathway for protein products licensed under the Public Health Service Act. Such a pathway would require new legislation.

Such legislation is in fact under active discussion. In April 2007, Barr Laboratories' CEO Bruce Downey told *Scrip* that he believed there was a growing consensus among US legislators and industry supporters that legislation creating a biosimilars approval pathway could be passed this year, either as an attachment to the Prescription Drug User Fee Act (PDUFA) reauthorisation, other legislation, or on its own. At around the same time, the FDA's deputy commissioner and chief medical officer, Dr Janet Woodcock, told a congressional panel of the US Senate that interchangeability of certain biosimilar products with their branded counterparts could be established through clinical testing of the immune response. Dr Woodcock suggested switching patients back and forth from one version of a biological to another, and monitoring their immune response in the process. It did not seem from her testimony that other issues raised by the microheterogeneity of protein therapeutics would be such an obstacle.

3.4.3.3 Immunogenicity issues

Further support for the key role of immunogenicity in the development of biosimilars comes from endocrinologist Dr Michael Ranke of the Tuebingen University Hospital for Paediatrics and Adolescent Medicine in Germany,

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who has reported the occurrence of anti-hGH antibodies in patients treated with biosimilar somatotropins. As far back as 1982, Dr Ranke conducted one of the first studies worldwide on recombinant growth hormone. He has also advised the German Working Group of Paediatric Endocrinology (APE) on new, simplified approval rules for biosimilars. He accepts that, compared with other protein hormones, growth hormone is chemically and structurally a relatively simple substance, whose biotechnological production is now a more or less routine procedure. The risk of contamination has vastly decreased since the early 1980s; by the third product generation in the late 1980s, the average number of foreign molecules per million molecules of growth hormone in recombinant preparations had been reduced from 1,000 to three. However, after treatment with growth hormone biosimilars that had recently been launched on the market, some patients started producing antibodies, although growth was not "sustainably" affected. Nevertheless, Dr Ranke notes that the reappearance, after 20 years, of anti-hGH antibodies "should give us pause for thought". Although he does not advocate testing biosimilars as if they were novel products, he is particularly critical of "today's approval of biosimilars for all indications, when only one has been screened".

3.4.4 Alpha interferon

Recombinant interferon alfa-2a is expressed in the bacterium *E.coli*. It is a non-glycosylated protein containing 165 amino acids, and its chemical composition is precisely known.

3.4.4.1 European position

In June 2006, the EMEA issued a negative opinion on Biopartners' interferon alfa-2a product Alpheon in hepatitis C because of quality, safety and efficacy concerns. The reference compound was Roche's Roferon-A. Biopartners had submitted Alpheon for the treatment of chronic hepatitis C in adults, despite the absence of an EMEA product guideline for alpha interferon biosimilars (which is expected at the end of 2007). It conducted a comparability exercise that included the results of a study comparing Alpheon's efficacy with that of Roferon-A in 455 patients. The study looked at how many patients responded after 12 weeks of a 48-week course, and six months after stopping treatment.

The CHMP said it had major concerns regarding the comparability of the two products because of differences including impurities. There were also insufficient data on the stability of the active substance in Alpheon and of the finished product, and the process used to make the finished product had not been adequately validated. While the number of patients responding to treatment with Alpheon in the clinical study was similar to that seen with Roferon-A, more patients had disease recurrence after stopping treatment with Alpheon than with Roferon-A. Alpheon also caused more side-effects. Moreover, in the CHMP's view the test used in the study to investigate Alpheon's ability to trigger an immune response had not been adequately validated.

3.4.4.2 US position

Roche's patent US4503035 (issued in March 1985), which covers Roferon-A, expired around 2003 and so this product is also liable to biosimilar competition in the US. However, we are as yet unaware of any pending applications.

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Table 3.1: Examples of post-translational modifications

1	acetylation
2	ADP-ribosylation (ADP = adenosine diphosphate)
3	alkylation
4	aminoacylation (tRNA-mediated)
5	biotinylation
6	C-terminal amidation
7	citrullination
8	deamidation
9	demethylation
10	dephosphorylation
11	disulfidation
12	farnesylation
13	flavin attachment
14	formylation
15	gamma-carboxylation
16	geranylgeranylation
17	glutamylation
18	glycosylation
19	glycylation
20	GPI (glycophosphatidylinositol) anchor formation
21	haem complex formation
22	hydroxylation
23	iodination
24	ISGylation (ISG = interferon-stimulated gene(s))
25	isoprenylation
26	lipoylation
27	myristoylation
28	nucleotidylation
29	oxidation
30	phosphatidylinositolylation
31	phosphopantetheinylation
32	phosphorylation
33	prenylation
34	proteolysis
35	pyroglutamylation
36	racemization (e.g. of prolines)
37	selenoylation
38	sulfation
39	SUMOylation (SUMO = Small Ubiquitin-related Modifier)
40	ubiquitination

Source: Biophoenix

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***Table 3.2: Analytical procedures useful for assessing the* equivalence of biotechnological products**

Analytical technology	Identity	Quantity	Purity	Structure	Heterogeneity	Activity	Stability
Amino acid analysis	X	X	X				
Amino acid sequencing (N- or C-terminal)	X			X			
Biochemical/colorimetry	X	X		X		X	X
Capillary zone electrophoresis	X	X	X		X		X
Carbohydrate mapping	X			X	X		
Cell based bioassays	X		X			X	X
Fluorescence-activated cell sorting						X	X
High performance liquid chromatography	X	X	X	X	X		X
Immunoassays	X	X	X	X		X	X
Isoelectric focusing	X		X		X		X
Mass spectrometry	X		X	X	X		X
Nuclear magnetic resonance	X	X		X			
Optical spectroscopy	X	X		X			
Peptide mapping	X			X	X		X
Polyacrylamide gel electrophoresis	X	X	X		X		X
Polymerase chain reaction	X	X	X				
Surface plasmon resonance	X					X	X
Ultracentrifugation (analytical)				X	X		X
Western blot	X		X	X			X

Source: USP/FDA

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CHAPTER 4
KEY BIOSIMILARS PLAYERS

4.1 Preface

Most biosimilar development work is currently being done by large generics or speciality pharmaceutical companies, which can afford both the costs of development and the risk of failure, and have the resources to market any approved products. These companies have been setting up subsidiaries or spin-offs focused on biosimilars. They have also been acquiring or linking up with smaller companies that have enabling technologies for biosimilar production.

The EU market is the initial target of most companies developing biosimilars. For example, several large generics companies active in biosimilar production are based in India. These firms have been acquiring European subsidiaries, or linking up with companies which have European sales teams in order to gain access to the EU markets.

This chapter profiles 15 selected companies which have, or are in the process of assembling, the components needed to compete in the (regulated) biosimilars market. They are based in India, Europe, the US, Canada and Israel.

4.2 India-based companies

4.2.1 Biocon

20th KM Hosur Road
Electronics City
Bangalore 560 100
India

Tel: +91 80 2808 2808
Fax: +91 80 2852 3423
Website: www.biocon.com
Ownership: Public
CEO: Kiran Mazumdar-Shaw
Employees: 3000

4.2.1.1 Company overview

Biocon is one of India's premier biotechnology companies. Biocon and its two subsidiary companies, Syngene International and Clinigene International form a fully integrated biotechnology enterprise, specialising in biopharmaceuticals, custom research, clinical research and enzymes. With successful initiatives in clinical development, bio-processing and global marketing, Biocon delivers products and solutions to partners and customers across the globe. Many of these products have FDA and EMEA approval.

Biocon has launched its own branded recombinant human insulin formation, Insugen, and India's first indigenously produced monoclonal antibody BIOMAb-EGFR.

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4.2.1.2 Biosimilar strategy

In July 2007, Biocon announced a definitive agreement to divest its enzymes division to Novozymes in order to strategically focus on its core biopharmaceuticals business, which includes APIs, biologicals and proprietary molecules both commercialised and under development.

Biocon says it is in a unique position to capitalise on the biosimilar market due to the investments it has made in developing expertise in characterisation and process validation. The company is confident that it has the technical skills and regulatory knowledge needed to get biosimilars such as insulin approved for the key US and EU markets.

4.2.1.3 Biosimilar pipeline

Insulin: Biocon markets recombinant human insulin in India under its own brand name Insugen and has registered the product in several export markets. The company has conducted European clinical trials with its biogeneric insulin. In addition, Biocon has supply arrangements with pharma majors and device companies to supply recombinant human insulin for use in their novel insulin formulations.

G-CSF: Biocon's biosimilar G-CSF has received regulatory approval from the Indian Drugs Controller General for the treatment of neutropaenia in cancer patients and the company intends to launch the product in India through its oncotherapeutics division. The biological activity of Biocon's G-CSF used in clinical trials was evaluated by the UK's National Institute of Biological Standards and Control (NIBSC), which provides independent testing of biological medicines. The NIBSC found that the potency of Biocon's drug met the necessary requirements of a biosimilar G-CSF.

4.2.1.4 Biosimilar collaborations

In July 2007, Biocon and US-based Abraxis Bioscience signed a licensing agreement giving Abraxis the right to develop biosimilar G-CSF in North America and the EU. Under the agreement, Biocon will receive an upfront fee and, following approval in the US and EU, royalties from Abraxis. Biocon will be responsible for manufacturing this product. The deal marks Abraxis's entry into the development of follow-on biologics. The company will develop the product first as a competitor for Amgen's Neupogen in the European market.

4.2.2 Dr Reddy's

Greenlands, Ameerpet
Hyderabad 500 016
India

Tel: +91 40 2373 1946
Fax: +91 40 2373 1955
Website: www.drreddys.com
Ownership: Public
CEO: GV Prasad
Employees: 9,100

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4.2.2.1 Company overview

Dr Reddy's Laboratories is a global Indian-based pharmaceutical company with proven research capabilities. Dr Reddy's produces finished dosage forms, APIs and biotechnology products which are marketed globally, with a focus on India, the US, Europe and Russia. The company conducts research in the areas of diabetes, cardiovascular, anti-infectives, inflammation and cancer.

The company's core API and branded formulations businesses are well established. The generics business started operations in 2001 and focuses primarily on the North American and EU markets. The company has built a robust pipeline of generic products, which is expected to drive growth in the medium and long term.

4.2.2.2 Biosimilar strategy

Dr Reddy's has indicated that it has a large number of biosimilar products under development, but is waiting for regulatory and marketing issues to be resolved in this area. The company is committed to developing its biologics business and has made substantial investments to develop world-class infrastructure and domain expertise. The Dr Reddy's Biologics Development Center has development and manufacturing suites for both *E.coli* and mammalian cell culture and caters to the highest development standards (cGMP, GLP and applicable bio-safety levels).

4.2.2.3 Biosimilar pipeline

Dr Reddy's biogeneric product pipeline comprises several recombinant proteins, both from mammalian cells as well as *E.coli*, that are in various phases of development.

Grafeel (G-CSF): Dr Reddy's is the first company in India to fully develop in-house a biosimilar, Grafeel (G-CSF). This product is used to treat cancer patients suffering from chemotherapy induced neutropaenia. The product has a leading position in the Indian market, and is also being marketed in Sri Lanka, the Ukraine and Brazil.

Reditux (rituximab): In May 2007, Dr Reddy's launched its cut-price rituximab (Reditux) in India. Reditux, a chimaeric murine/human anti-CD20 monoclonal antibody, is believed to be the world's first biosimilar mAb. The product is used in the treatment of Non-Hodgkin's Lymphoma. Reditux is priced at about Rs10,000 ($243) for a 100mg dose in a 10ml vial, around half the price of Roche's Mabthera. Roche's drug, which has been available in India for more than five years for the treatment of non-Hodgkin's lymphoma, was recently also approved for rheumatoid arthritis.

4.2.3 Reliance Life Sciences/Genemedix

Reliance Life Sciences
Dhirubhai Ambani Life Sciences Centre
R-282, TTC Industrial Area of MIDC
Thane-Belapur Road
Rabale Navi Mumbai 400 701
India

Tel: +91 22 6767 8000

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Fax: +91 22 6767 8099
Website: www.relbio.com
Ownership: Private
CEO: KV Subramaniam
Employees (Reliance Group): 25,000

Genemedix
Rosalind Franklin House
Fordham Road
Newmarket
CB8 7XN
UK

Tel: +44 (0)1638 663320
Fax: +44 (0)1638 663411
Website: www.genemedix.com
Ownership: Public
CEO: Julian Attfield
Employees: 47

4.2.3.1 Company overview

In February 2007, Reliance Life Sciences (RLS) acquired Genemedix, a UK-based biotechnology company with London and Singapore Stock Exchange listings. RLS is part of the Reliance Group, the largest private sector enterprise in India. The Genemedix acquisition was the first ever overseas acquisition of a listed biopharmaceutical company by an Indian firm.

Genemedix is a biopharmaceutical company that develops both novel and generic biologic drugs, often in partnership with the Shanghai Institute of Biochemistry. The company has also entered into joint ventures with other pharmaceutical companies across Asia, including Gland Pharma of India and Hovid of Malaysia. Genemedix had been operating under severe financial constraints for a number of years prior to its acquisition.

4.2.3.2 Biosimilar strategy

By acquiring Genemedix, Reliance has moved a step closer towards realising its aspirations of becoming a major bio-generics player.

Genemedix is currently developing drugs and forging partnerships to enter many of the major existing biologic markets in which key patents have expired or will soon expire. Delays in regulatory pathways have held the company back somewhat. In addition, a long period of corporate inactivity increased costs as did the building of a state-of-the-art manufacturing plant in Ireland in readiness for producing EPO as soon as it is approved. Genemedix is now planning to move its products into the developing world, where the regulatory barriers are much easier to negotiate, as well as accessing the western markets.

RLS claims to have its own portfolio of biosimilar products. It is currently constructing manufacturing facilities in India, which are anticipated to operate to full international standards and it has a large infrastructure of analytical testing and animal testing facilities. RLS is looking to introduce its products into the EU through Genemedix, and to leverage its own manufacturing capabilities by producing Genemedix's products, (which Genemedix is not currently able to make).

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4.2.3.3 Biosimilar pipeline

Due to financial constraints, Genemedix has recently had to rethink its biosimilar development programme, dropping its human insulin and IFN-alpha projects and putting its main focus on EPO and G-CSF.

EPO: Genemedix's lead product is a biosimilar EPO, which was once expected to reach the market by 2006, but is still in Phase III clinical trials. The company's EPO manufacturing plant in Ireland has GMP accreditation from the Irish Medicines Board and the company expects to file an application in Europe early in 2008.

G-CSF: The development of a biosimilar G-CSF is progressing at a slower rate. It is expected that the funds provided by the RLS acquisition will be sufficient to see the EPO and G-CSF programmes through to launch in the EU and US.

In addition, Genemedix has been selling Neustim, its GM-CSF product, in China since 2001. The company has a deal in place to sell the product in Russia and it is planning clinical trials in India.

4.2.3.4 Biosimilar collaborations

Under a collaboration signed in March 2003, US-based Antares Pharma's current and future injection devices will be used to support Genemedix's introduction of comparable biopharmaceuticals in certain territories.

4.2.4 Ranbaxy Laboratories

Plot 90, Sector 32
Gurgaon-122001 (Haryana)
India

Tel: +91 124 4135000
Fax: +91 124 4135001
Website: www.ranbaxy.com
Ownership: Public
CEO: Malvinder Mohan Singh
Employees: 11,343

4.2.4.1 Company overview

Ranbaxy Laboratories is an integrated, research-based, international pharmaceutical company producing a wide range of generic medicines. Ranbaxy's continued focus on R&D has resulted in several approvals in developed markets. The company's foray into novel drug delivery systems has led to proprietary platform technologies, resulting in a number of products under development. The company has customers in over 100 countries, ground operations in 44 countries and manufacturing operations in seven countries.

4.2.4.2 Biosimilar strategy

Until recently, Ranbaxy has stayed away from investing in biosimilars due to uncertainty over legislation. Even now, its approach does not involve sinking money into fixed assets like R&D labs and manufacturing. Instead, the company's strategy to enter the biosimilars segment will be through

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alliances or strategic investments in specialised companies for technologies and products. Ranbaxy has made a decision to aim first for the European market where biosimilar regulations are in place.

4.2.4.3 Biosimilar pipeline

Ranbaxy's first biosimilar product for the European market is G-CSF, which the company is developing in partnership with India's Zenotech Laboratories, a biotechnology-focused specialty generic injectables company. If successful, Ranbaxy's G-CSF might be the first Indian biosimilar to be launched in Europe.

Ranbaxy is also reportedly working on a biosimilar version of Genentech/Biogen Idec's Rituxan (rituximab), an anti-CD20 monoclonal antibody.

4.2.4.4 Biosimilar collaborations

In February 2007, Ranbaxy signed a global clinical development and marketing agreement for a biosimilar G-CSF product with Zenotech Laboratories. The collaboration will pool in Ranbaxy's significant regulatory and front-end infrastructure with Zenotech's expertise in the development and manufacture of biosimilar products. G-CSF will lead the way for the development of other biosimilar molecules within the Zenotech portfolio (of which there are currently ten). These products will be manufactured in Zenotech's FDA/EU approvable biologics facility located in Hyderabad.

4.3 Germany-based companies

4.3.1 Ratiopharm/Biogenerix

Ratiopharm
Graf Arco Strasse 3
Ulm 89070
Germany

Tel: +49 731 402 7712
Fax: +49 731 402 7716
Website: www.ratiopharm.com
Ownership: Private
CEO: Dr Claudio Albrecht
Employees: 5,373

Biogenerix
Janderstasse 3
High-Tech-Park Mannheim
D-68199 Mannheim
Germany

Tel: +49 621 8755610
fax: +49 621 8755633
Website: www.biogenerix.com
Ownership: Private
CEO: Elmar Schafer
Employees: 41

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4.3.1.1 Overview

Biogenerix is a subsidiary of Ratiopharm, an international generics producer and in its home country Germany, the top-selling and most commonly prescribed pharmaceutical brand.

Biogenerix specialises in the development of biopharmaceutical drugs with known modes of actions and established markets. With its internal resources and a large network of strategic partners and service providers, the company develops biopharmaceuticals for marketing and distribution by the Ratiopharm group and other global partners.

4.3.1.2 Biosimilar strategy

The Ratiopharm group recognised the importance of biogenerics early on and has been active in this field since the late 1990s. Biogenerix was set up in 2000 to develop a range of biosimilars and innovative follow-on biologics. In January 2007, Biogenerix indicated that it was accelerating the development of pegylated G-CSF for launch in Europe.

4.3.1.3 Biosimilar pipeline

GlycoPEG-G-CSF: In March 2007, Biogenerix and Neose Technology began the second German Phase I trial of GlycoPEG-GCSF in cancer patients who suffer from neutropaenia as a result of chemotherapy. The product will be compared with Amgen's Neulasta. Interim results from an ongoing Phase I study showed a dose-dependent response to GlycoPEG-G-CSF with no serious adverse events reported.

Biogenerix is also developing biogeneric EPO and IFN-beta products.

4.3.1.4 Biosimilar collaborations

In July 2003, Sicor (Teva Pharmaceutical Industries) signed a licence, development and marketing agreement with Biogenerix to jointly develop a recombinant protein pharmaceutical product, which would be manufactured and produced by Sicor and marketed in Europe by Ratiopharm following regulatory approval. Sicor entered into this collaboration partly in order to gain access to European markets through the Biogenerix clinical development programme and Ratiopharm's sales force.

In April 2004, Biogenerix entered into an agreement with Neose Technology to use Neose's proprietary GlycoAdvance and GlycoPEGylation technologies to develop a long-acting version of G-CSF. The two companies also agreed to co-develop an additional GlycoPEGylated protein.

4.3.2 Sandoz International (Novartis)

Industriestrasse 25
83607 Holzkirchen
Germany

Tel: +49 8024 476 2591
Fax: +49 8024 476 2599
Website: www.sandoz.com
Ownership: Public
CEO: Andreas Rummelt

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Employees: 21,000

4.3.2.1 Company overview

Sandoz International is the generics division of Novartis. It develops, manufactures and markets off-patent medicines, as well as pharmaceutical and biotechnological active ingredients. Sandoz has been bringing innovative technologies and delivery systems to the market for generic products, such as transdermal patches, inhalation products, sustained-release implants and multi-particulate drug delivery dosage forms.

In 2005, Sandoz expanded greatly with its acquisitions of Germany's Hexal and Eon Labs of the US. Hexal has expertise in patches and implants, advanced formulations, and biopharmaceutical formulations. Sandoz now has a portfolio of over 600 generics in more than 5,000 forms.

4.3.2.2 Biosimilar strategy

Sandoz has declared that biosimilars will be a pillar of its strategy in the future. Since 30% of innovative drugs currently under development are based on biotechnological processes, the company believes that the generic business model has to include biosimilars to provide savings for patients and healthcare systems. In the past few years Sandoz invested approximately $150 million in development and manufacturing facilities for biosimilars.

Sandoz conducted its own marketing for its first biosimilar product, Omnitrope, but the marketing of future biosimilars is likely to depend on their respective market situations.

4.3.2.3 Biosimilar pipeline

hGH: In February 2006, the EU approved Sandoz's Omnitrope. The product had been marketed in Australia since November 2005 and it is now available in Germany, Austria, the UK, the Netherlands, Denmark, Sweden and Italy where it is sold at a 25% discount to the price of Pfizer's Genotropin. In June 2006, Omnitrope was approved as a follow-on product by the FDA. It was launched in January 2007 at a discount of 30%.

EPO: In June 2007, the EMEA approved Sandoz's Binocrit (epoetin-alfa). It was shown to be similar to Amgen's Eprex/Erypo, the reference medicinal product already authorised in the EU.

Sandoz is also developing four biosimilars in collaboration with Momenta Pharmaceuticals.

4.3.2.4 Biosimilar collaborations

In July 2006, Sandoz entered into an exclusive collaboration with Momenta Pharmaceuticals to develop four follow-on and complex generic versions of previously approved recombinant biotechnology and complex drugs. As part of the collaboration, Sandoz made an initial payment of $75 million to Momenta for the purchase of approximately 4.7 million shares. The collaboration will include one late-stage compound from Momenta's pipeline and two late-stage compounds from Sandoz. The product candidates in the collaboration will all use Momenta's characterisation technology, which enables the detailed chemical sequencing and analysis of complex mixtures.

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4.3.3 Stada Arzneimittel/Bioceuticals Arzneimittel

Stada Arzneimittel
Stadastrasse 2-18
D-61118 Bad Vilbel
Germany

Tel: +49 6101 603 113
Fax: +49 6101 603 506
Website: www.stada.de
Ownership: Public
CEO: Wolfgang Jeblonski
Employees: 1,067

Bioceuticals Arzneimittel
Stadastrasse 2-18
D-61118 Bad Vilbel
Germany
Ownership: Spin-off

4.3.3.1 Company overview

Stada Arzneimittel is an international pharmaceutical company with a focus on generic, branded and specialty pharmaceutical products. Stada is one of the leading generics companies in the EU.

Bioceuticals Arzneimittel is a Stada spin-off company focused on the development of biosimilar products. The firm is financed predominantly via venture capital. Stada holds 15% of the shares in Bioceuticals and a call option to acquire the outstanding shares beginning in 2011.

In August 2008, Stada acquired Russia's generics specialist Makiz.

4.3.3.2 Biosimilar strategy

Stada entered the biosimilars field in 2000, although its foray into what was then uncharted territory encouraged it to decide on venture capital financing. Biosimilar development proved to be much more cost-intensive than originally proposed and Bioceuticals' IFN-beta1a project has been a casualty of rising costs. The company decided that marketing opportunities no longer justified the high expenditure needed to complete the project. Nevertheless, in 2006 Stada increased its own shareholding of Bioceuticals' stock.

In November 2006, Stada completed a comprehensive reorganisation of its biosimilars programme, which was undertaken in order to hedge against uncertainty and limit the company's potential liabilities. The company decided to continue development of the two most advanced biosimilar programmes, EPO and G-CSF.

4.3.3.3 Biosimilar pipeline

EPO: So far EPO-alpha and EPO-beta have been launched on the market; the EPO biosimilar being developed by Bioceuticals is EPO-zeta. This product was filed with the EMEA in June 2006, and the company is hopeful

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that it will receive approval to market the drug for dialysis patients by late 2007. Once approved, Stada's EPO biosimilar will be manufactured by Norbitec, (in which Bioceuticals is increasing its one third stake to two-thirds). EPO-zeta is also in clinical trials for use in cancer patients, and EU approval for this indication may follow its launch for the dialysis indication.

G-CSF: The next most advanced project is a G-CSF biosimilar to Amgen's Neupogen for which preclinical trials have now been completed. Clinical trials are expected to get underway in 2007.

4.3.3.4 Biosimilar collaborations

In November 2006 Stada, Bioceuticals and Hospira signed a development, manufacturing and distribution agreement focused on EPO. Once approved, the worldwide distribution rights for Epo-Zeta will be transferred to Hospira. In Germany, the product will be distributed following regulatory approval by both Hospira and Stada's subsidiary Cell Pharm.

4.4 Other EU-based companies

4.4.1 Bioton/Biopartners

Bioton
ul. Staroscinska 5
02-516 Warszawa
Poland

Tel: +48 (22) 721 4000
Fax: +48 (22) 721 1333
Website: www.bioton.pl
Ownership: Public
CEO: Adam Wilczega
Employees: 599

Biopartners
Baarermatte
6340 Baar
Switzerland

Tel: +41 (0) 41 766 2080
Fax: +41 (0) 41 766 2081
Website: www.biopartners.ch
Ownership: Private
CEO: Jean-Noel Treilles
Employees: 14

4.4.1.1 Company overview

Polish biotech Bioton manufactures recombinant human insulin and its pharmaceutical forms, along with preparations from the cephalosporin, aminoglycoside and macrolide groups. At the end of 2004, Bioton took its first step towards international expansion by acquiring 90.54% of the Australian generics manufacturer Scigen.

In March 2007, Bioton acquired Biopartners, a private Swiss biopharmaceuticals firm, including its German subsidiary. Biopartners is a developer of biosimilars and first-generation biopharmaceuticals.

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4.4.1.2 Biosimilar strategy

The next phases of Bioton's strategy will encompass development, implementation of the production process and introduction to the market of subsequent recombinant protein products. Through its acquisition of Biopartners, Bioton expects to gain access to additional biotechnological know-how in product development and registration processing.

4.4.1.3 Biosimilar pipeline

Bioton's own pipeline includes recombinant human insulin. Biopartners has initiated a number of biosimilar programmes.

Valtropin (hGH): In May 2006, the EMEA approved Biopartners' Valtropin (recombinant hGH), which is a biosimilar version of Lilly's Humatrope (somatropin). Valtropin was developed jointly with the South Korean company, LG Life Sciences. Biopartners has commercialisation rights in Europe, Japan and other parts of Asia, but it will not market the product itself. The company has signed up Cambridge Laboratories to market Valtropin in the UK, and Nycomed for Scandinavia, Russia and some other European markets. It is also in negotiations with other firms. A sustained-release version of Valtropin is expected to be submitted for EU approval in the second half of 2008. There are currently no marketed sustained-release hGH products.

IFN-alpha: Valtropin's approval was followed in June 2006 by a negative opinion from the CHMP for the company's biosimilar IFN-alpha, Alpheon. The CHMP stated that it had identified major quality concerns, as well as differences between Alpheon and the reference product, Roche's Roferon-A. Technical issues in the manufacturing process are being addressed by Biopartners and its contract manufacturer. The company believes that the stability and impurity issues have been clearly identified and are solvable, and will not represent an insurmountable barrier for the resubmission of the marketing application for the product.

Biopartners expects to start a development programme for EPO, licensed from LG Life Sciences, in the second half of 2007.

4.4.1.4 Biosimilar collaborations

Since April 2000, Biopartners and LG Life Sciences have entered into collaborative agreements to jointly develop, manufacture and commercialise a number of biopharmaceutical products, including hGH (daily and sustained-release formulations), EPO, and IFN-alpha.

4.4.2 DSM (DSM Biologicals)

Het Overloon 1
6411 TE Heerlen
The Netherlands

Tel: +31 (45) 578 8111
Fax: +31 (45) 571 9753
Website: www.dsm.com
Ownership: Public
CEO: Peter Elverding
Employees: 22,000

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4.4.2.1 Company overview

DSM is active worldwide in the supply of nutritional and pharmaceutical ingredients, performance materials and industrial chemicals. DSM has a decentralised organisational structure built around business groups that are empowered to carry out all business functions.

The company's pharma cluster comprises the DSM Pharmaceutical Products and DSM Anti-Infectives business groups.

DSM's strategy, named 'Vision 2010 – Building on Strengths', focuses on accelerating profitable and innovative growth of the company's specialties portfolio. As part of this strategy, DSM Pharmaceutical Products is currently restructuring the activities of its DSM Pharma Chemicals and DSM Biologics business units.

4.4.2.2 Biosimilar strategy

In 2004-2005 DSM Biologics formulated its Vision 2010 plan, outlined its goals and reviewed the state of the contract manufacturing market over the next five years. It concluded that there was substantial overcapacity in the volume of biotechnology contract manufacturing worldwide. Because of the insurgence of cost-competitive Indian and Chinese companies onto the market, the firm decided to close certain plants altogether and mothball others for use in the event of a future resurgence in demand for contract biotech production.

DSM confirmed that in the field of biopharmaceuticals, the development of cell line technology (the software) will potentially have more impact than the installment of new contract manufacturing capacity (the hardware). That is why two years ago, DSM had already started to focus on its alliance with Dutch biotech firm Crucell on the development of the human cell line production technology platform PER.C6. Crucell and DSM will put more emphasis on the development of this PER.C6 technology by building a strong portfolio of intellectual property, with the objective of licensing this cell line, including supporting fermentation technologies, to the biopharmaceutical industry.

4.4.2.3 Biosimilar pipeline

The PER.C6 cell line, for which DSM Biologics holds an exclusive licence from Crucell (with the right to sub-license), comes from a single, human retina-derived cell, which was purposely immortalised using recombinant DNA technology. As a result, PER.C6 cells can replicate indefinitely, allowing them to be cultured in single cell suspension under serum-free conditions in quantities appropriate for large-scale manufacturing. The company believes that the PER.C6 cell line is ideally suited for the development and large-scale manufacturing of a multitude of biopharmaceuticals, including antibodies, other therapeutic proteins, vaccines and gene therapy products. The PER.C6 cell line has been licensed to a wide range of organisations and biopharmaceutical companies engaged in the development of therapeutics.

4.4.2.4 Biosimilar collaborations

In July 2007, DSM Biologics and Crucell announced that they had further intensified their PER.C6 cell line collaboration, by executing an agreement to

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expand the existing commercial relationship to include new classes of proteins, including biosimilar protein products.

4.5 US-based companies

4.5.1 Barr Pharmaceuticals/Pliva

Barr Pharmaceuticals
223 Quaker Road
Pomona
NY 10970
USA

Tel: +1 845 362 1100
Fax: +1 845 362 2774
Website: www.barrlabs.com
Ownership: Public
CEO: Bruce L Downey
Employees: 1,900

Pliva
Ulica grada Vukovara 49
Zagreb 1000
Croatia

Tel: +385 1 612 0999
Fax: +385 1 611 1011
Website: www.pliva.hr
Ownership: Public
CEO: Zeljko Covic
Employees: 6,654

4.5.1.1 Company overview

In October 2006 Barr Pharmaceuticals acquired Pliva, a major Croatian producer of generic and biogeneric medicines. The acquisition has made US-based Barr one of the world's largest generic manufacturers, with an enhanced presence in Europe.

Barr operates in more than 30 countries worldwide and is engaged in the development, manufacture and marketing of generic and proprietary pharmaceuticals, biopharmaceuticals and APIs. Barr operates through its principal subsidiaries: Barr Laboratories, Duramed Pharmaceuticals (proprietary products subsidiary), and Pliva (and its subsidiaries). The Barr group of companies markets more than 115 generic and 25 proprietary products in the US and more than 1,200 products in other markets.

In the generic pharmaceuticals segment, the company currently manufactures and distributes approximately 150 different dosage forms and strengths of approximately 75 different generic pharmaceutical products.

4.5.1.2 Biosimilar strategy

For many years, Barr's strategy has been to develop generic versions of branded products that possess some combination of unique factors that it believes limit competition from other generics manufacturers. Such factors include difficult formulation, complex and costly manufacturing

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requirements or limited raw material availability. Challenging the patents covering certain brand products continues to be an integral part of its generics business. In the US, the company aims to be the first to initiate a patent challenge and to obtain 180 days of exclusivity for selling a generic version of the product.

Barr is investing heavily in the biosimilar/follow-on biologics market. The Pliva acquisition is expected to create a solid foundation for accelerating the development of its generic biopharmaceutical products in Europe and the US. Barr has actively lobbied the executive and legislative branches of the US government to create an abbreviated regulatory pathway for the approval of generic biologics. It believes it is well situated, in terms of its experience with complex IP issues, to address patent and other barriers to the introduction of biosimilars.

4.5.1.3 Biosimilar pipeline

Desmopressin: In July 2005, the FDA approved Barr's generic desmopressin acetate tablets, a biosimilar version of Ferring BV's DDAVP tablets. Ferring manufactures DDAVP for Sanofi-Aventis, which markets the product in the US. DDAVP Tablets are indicated as antidiuretic replacement therapy in the management of central diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. They are also indicated for the management of primary nocturnal enuresis. Barr launched its desmopressin product following a district court ruling that applicable DDAVP patent was unenforceable and therefore not infringed, and subsequently received 180 days of marketing exclusivity on its product. The company recorded revenues of over $90 million from sales of desmopressin.

G-CSF: Pliva's most advanced biosimilar product is G-CSF, which the company is developing in collaboration with Mayne Pharma (Hospira).

Barr is actively working on the development of two additional, undisclosed generic biopharmaceutical products.

4.5.1.4 Biosimilar collaborations

In 2005, Pliva signed a deal with Mayne Pharma (Hospira) for the commercialisation of biosimilars, including EPO. However, this was amended in early 2006, and EPO was removed from the agreement following publication of EMEA regulatory guidelines, which were more stringent than the companies had anticipated. In August 2006, Pliva finalised its agreement with Mayne for the joint development of a biosimilar G-CSF to be marketed in Europe, south-east Asia, the middle east and the far east.

4.5.2 Hospira/Mayne Pharma

Hospira
275 North Field Drive
Lake Forest
IL 60045
USA

Tel: +1 224 212 2267
Fax: +1 224 212 3210
Website: www.hospira.com

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Ownership: Public
CEO: Christopher B Begley
Employees: 13,000

Mayne Pharma
Level 21, 390 St Kilda Rd
Melbourne
Victoria 3004
Australia

Tel: +61 3 9868 0700
Fax: +61 3 9868 0299
Website: www.maynepharma.com
CEO: Thierry Soursac
Ownership: Public
Employees: 2,000

4.5.2.1 Company overview

Hospira, spun off from Abbott Laboratories in 2004, is a global specialty pharmaceutical and medication delivery company. Hospira's portfolio of products and services includes four major product lines: specialty injectable pharmaceuticals; medication delivery systems; injectable pharmaceutical custom manufacturing services; and other products, including critical care devices. Hospira's portfolio includes one of the industry's broadest lines of generic acute care and oncology injectables. The US is the largest market for Hospira's products.

In February 2007, Hospira acquired Mayne Pharma, a leading oncology-focused specialty pharmaceuticals company.

4.5.2.2 Biosimilar strategy

Hospira has the necessary resources to market biosimilars, which require a pan-European hospital sales force. The company is now assembling the necessary components to compete in this new market. It sees developing and providing access to biosimilars as a natural extension of its leadership position in generic injectable pharmaceuticals and an important part of its strategy of investing for growth.

4.5.2.3 Biosimilar pipeline

G-CSF: Prior to being acquired, Mayne entered into an agreement with Pliva to co-develop a biosimilar G-CSF product for the European, south-east Asian, middle eastern and Asia Pacific markets.

EPO: A biosimilar EPO product is being developed through a collaboration with Bioceuticals.

4.5.2.4 Biosimilar collaborations

See section 4.3.3.4. for details of the collaboration between Stada, Bioceuticals and Hospira.

See section 4.5.1.4. for details of Mayne's collaboration with Pliva (Barr Pharmaceuticals).

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4.5.3 Dynavax Technologies/Rhein Biotech

Dynavax Technologies
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Berkeley CA 94710-2753
USA

Tel: +1 510 848 5100
Fax: +1 510 848 1327
Website: www.dynavax.com
Ownership: Public
CEO: Dino Dina
Employees: 153

Rhein Biotech (Dynavax Europe)
Eichsfelder Str. 11
40595 Düsseldorf
Germany

Tel: +49 211 758 450
Fax: +49 211 758 45130
Website: www.dynavax.com/euoverview.htm
CEO: Zbigniew Janowicz
Employees: 45

4.5.3.1 Company overview

Dynavax Technologies discovers, develops and intends to commercialise innovative products to treat and prevent allergies, infectious diseases and chronic inflammatory diseases using proprietary approaches that alter immune system responses in specific ways. In April 2006, Dynavax acquired Rhein Biotech, which is now its European affiliate (Dynavax Europe).

Rhein Biotech offers a comprehensive suite of proprietary production and manufacturing capabilities from generation of a recombinant production organism using proprietary expression systems to process development, manufacturing of clinical samples, manufacturing of commercial products and technology transfer.

4.5.3.2 Biosimilar strategy

Dynavax Technologies has entered the area of biosimilars through its acquisition of Rhein Biotech, which has a number of patents and patent applications covering technology platforms for recombinant protein production technologies. Prior to its acquisition, Rhein Biotech had developed a leading technology platform for the production of recombinant products: *Hansenula polymorpha* yeast expression technology. *Hansenula* technology is used in a number of commercial biopharmaceutical and biotechnology applications and is acknowledged as the industry standard for protein production. The company has granted numerous research licences and commercial licences for the use of this technology.

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4.5.3.3 Biosimilar pipeline

Rhein Biotech is collaborating with Minapharm in the area of biosimilars (see below).

4.5.3.4 Biosimilar collaborations

In April 2007, Rhein Biotech formed a joint venture, Rhein-Minapharm-Biogenetics, with Egyptian generics manufacturer Minapharm. Minapharm has launched Thrombexx, a biosimilar version of Bayer's Refludan (lepirudin). Thrombexx was produced using Rhein Biotech's *Hansenula* yeast expression system. Minapharm also sells biosimilar versions of IFN-alfa2a and pegylated IFN-alfa2a.

4.6 Canada-based companies

4.6.1 Cangene

155 Innovation Drive
Winnipeg
Manitoba R3T 5Y3
Canada

Tel: +1 204 275 4200
Fax: +1 204 269 7003
Website: www.cangene.com
Ownership: Public
CEO: John Langstaff
Employees: 617

4.6.1.1 Company overview

Cangene is one of Canada's largest biopharmaceutical companies, using patented manufacturing processes to produce plasma-derived hyperimmune globulin products and recombinant therapeutic proteins. Cangene has three FDA and Health Canada-approved products and a fourth that has been approved in Canada only.

The Apotex Group gained 83% of Cangene's shares in 1995 when Rx Pharmaceuticals, its plasma processes subsidiary, acquired Cangene. Apotex is the largest Canadian-owned pharmaceutical company.

4.6.1.2 Biosimilar strategy

Cangene focuses on developing its own versions of established products using proprietary host systems. The company believes that due to its proprietary production techniques, its recombinant products are less likely to infringe on other companies' patents. The company believes that it is well placed to take advantage of the next big wave in the generic pharmaceutical industry. Cost-effective manufacturing is key in developing generic products; Cangene's proprietary Cangenius expression system simplifies protein recovery, and a new fermentation facility brings the full manufacturing process in-house.

4.6.1.3 Biosimilar pipeline

Cangene has chosen to go through the formal NDA process in the US for

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Accretropin and in Canada for Leucotropin.

Accretropin (hGH): Cangene has completed Phase III clinical trials on Accretropin, a biosimilar hGH product. These trials were designed to support regulatory submission in Canada, the US, Europe and other jurisdictions. These studies followed a comparative bioavailability study, which compared Cangene's hGH with an approved product.

Leucotropin (GM-CSF): Leucotropin, a biosimilar GM-CSF product, was successfully used to complete Phase III trials and found to be an effective and safe treatment in myeloid reconstitution in subjects with Hodgkin's and non-Hodgkin's lymphoma.

4.6.2 Microbix

115 Skyway Ave
Toronto, Ontario
M9W 4Z4
Canada

Tel: +1 416 234 1624
Fax: +1 416 234 1626
Website: www.microbix.com
Ownership: Public
CEO: William J Gastle
Employees: 36

4.6.2.1 Company overview

Microbix is a biotech company developing and commercialising biologics, vaccines and large-market, non-therapeutic biologic products. Microbix specialises in developing proprietary biological technologies and commercialising them through global partners. The company has IP in large-market biotherapeutic drugs, vaccine technologies and animal reproduction technologies.

4.6.2.2 Biosimilar strategy

Microbix's business strategy has been to develop its large-market products (such as urokinase) through profits generated from its platform virology business until external funds become available. The company recently established a business model that it is applying to follow-up products and technologies. It is partnering products earlier in their development cycle, the product is transferred to the partner for manufacturing and the partner finances all costs to the market. Because there are no costs associated with revenue from royalties and upfront payments, the revenue is profit.

4.6.2.3 Biosimilar pipeline

Urokinase: Microbix developed the first biosimilar version of Abbott Laboratories' Abbokinase, ThromboClear. The company originally planned to market ThromboClear as a follow-on product in the US, but it reviewed this strategy because of slowing sales for the brand-name drug after the manufacturer announced that it was no longer producing the product.

Microbix subsequently entered into negotiations with Angiogen for exclusive rights to manufacture ThromboClear for a proprietary use. Microbix believes

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the potential market for urokinase (for new indications) has increased signficantly above the current urokinase market, but these will not be approved through a generic regulatory mechanism.

An unnamed generic biotherapeutic drug is the subject of preliminary licensing discussions.

4.6.2.4 Biosimilar collaborations

In March 2006, Microbix concluded an agreement with Angiogen to collaborate in the development of Angiostatic Coctail cancer therapy that combines urokinase with a small molecule drug. Microbix is now the only source of urokinase, and Angiogen holds the US patent for the use of urokinase in oncology; the companies believe that this effectively shuts out the competition in what they expect to be a $3 billion annual market for this form of cancer treatment.

4.7 Other companies

4.7.1 Teva Pharmaceutical Industries/Sicor

Teva Pharmaceutical Industries
5 Basel St.
Petach Tikva 49131
Israel

Tel: +972 3 926 7267
Fax: +972 3 923 4050
Website: www.tevapharm.com
Ownership: Public
CEO: Shlomo Yanai
Employees: 26,700

Sicor
19 Hughes
Irvine
CA 92618
USA

Tel: +1 949 455 4700
Fax: +1 949 855 8210
Website: www.sicor.com
CEO: Marvin S Samson
Employees: 1,900

4.7.1.1 Company overview

Teva Pharmaceutical Industries, headquartered in Israel, develops, manufactures and markets generic and innovative human pharmaceuticals and APIs, as well as animal health pharmaceutical products. Close to 90% of Teva's sales are in North America and Europe.

In January 2004, Teva acquired the US company Sicor, which makes generics and APIs. Through the Sicor acquisition, Teva now has three plants in Mexico, China and Latvia that develop, manufacture, and market biosimilar materials.

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In January 2006, Teva completed its acquisition of Ivax, a manufacturer of branded and generic pharmaceuticals and veterinary products. The combined company, which will operate under the Teva name, will have a presence in over 60 countries and will employ approximately 26,000 people.

4.7.1.2 Biosimilar strategy

In 2005, Teva established a dedicated R&D group based in Israel and specialising in the development of mammalian cell culture products. Teva was awaiting clarification of the European regulatory pathway before taking a decision on its biogenerics strategy. The company also has plans to enter the American biogenerics market if the FDA creates an expedited process for the approval of follow-on biologics, and the company is working with the FDA and other organisations to address the safety issues such a process would present.

4.7.1.3 Biosimilar pipeline

IFN-alpha: Teva Pharmaceuticals' biosimilar IFN-alpha2b has been approved in Lithuania (for Sicor) and in another 17 countries.

G-CSF: Sicor has also gained approval in Lithuania for its biosimilar G-CSF product.

In 2005 Teva offered Tev-Tropin (recombinant hGH) in the US at a lower price than other somatropin products on the market. It is believed that Teva has filed for a follow-on version of insulin in the US.

4.7.1.4 Biosimilar collaborations

See section 4.3.1.4. for details of the collaboration between Sicor and Biogenerix.

In January 2005, Teva joined forces with the Israeli drug delivery firm, Transpharma Medical, to develop transdermal formulations of up to five compounds, including high molecular weight proteins. Teva stated that developing new versions of injectable protein therapeutics would help it make its mark in the emerging biogenerics field.

In October 2006, Teva and another Israeli company Procognia entered into a collaboration agreement for the development of two biopharmaceuticals. Under this deal, Procognia will supply Teva with services and access to its proprietary glycol-analysis technology on an exclusive basis. Teva believes that accessing the Procognia technology will provide it with a distinct competitive advantage, since glyco-analysis is a complex part of the production of biopharmaceuticals.

In November 2006, Teva and Protalix Biotherapeutics signed a collaboration and licensing agreement for the development of two proteins, using Protalix's plant cell culture platform. The undisclosed proteins, aimed at large markets, are not part of Protalix's current product development pipeline. Protalix's proprietary technology provides a scaleable cell system for industrial production of recombinant biopharmaceuticals.

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CHAPTER 5
MARKETS FOR BIOSIMILARS

5.1 Introduction

North America and Europe are currently the largest geographical markets for therapeutic proteins, while Latin America (in particular Brazil) is the most rapidly growing. The market for biosimilars has existed for years in Asia, Eastern Europe and Latin America: however, in North America and Europe, the market is a new one. In this chapter we assess the market potential for the different classes of biosimilars, taking into account factors such as the level of competition, equivalence and interchangeability issues, and probable changes in the regulatory climate.

5.2 Leading drug classes

Five groups of drugs accounted for more than 50% of all sales of branded protein drugs worldwide in 2006. Summary details for these appear in Table 5.1.

Table 5.1: Leading protein drug classes in 2006

Drug type	Sales ($ billion)	Percent
Erythropoietins	13.4	20.0
Insulins	7.7	11.5
Interferons	6.7	9.9
G-CSFs	4.8	7.1
Somatotropins	2.5	3.7
Others	32.1	47.8
Total	67.1	100.0

Source: Biophoenix

These drugs and their applications (chiefly oncology, autoimmune and inflammatory disease (AIID), metabolism, and infectious disease), comprise established markets. According to the Tufts Center for the Study of Drug Development, biological drugs (including members of these five groups) have accounted for approximately 25-35% of FDA new drug approvals since the turn of the millennium, and that proportion is expected to remain constant in the near future.

5.3 Major players

The major types of corporate player in these markets are: (a) multinational innovator companies, (b) drug delivery and device companies, and (c) 'next-generation' innovators. The multinational innovators, which actually develop, launch and market these products include companies such as Amgen, Lilly and Roche. Some leading examples are listed in Table 5.5 below. Drug delivery and device companies work in collaboration with the multinationals to develop improved extended-release and/or non-injection formulations. An example is Nektar Therapeutics, which developed Pfizer's Exubera inhalable insulin. The next-generation innovators are smaller, specialist biotech companies, frequently working in collaboration with established innovators. Ultimately many of the successful companies will be acquired by their larger partners, although a few will become major players in their own right as Amgen has done. To these we must now add new

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biosimilars companies such as Biopartners and Sandoz, together with longer established biosimilars companies from the unregulated markets, predominantly in the Far East, such as LG Life Sciences and Shantha Biotechnics. The more prominent of these were profiled in Chapter 4.

5.4 Market outlook

While biosimilar revenues are currently small, this is mainly because there have only been a few approvals, and these have been recent and geographically limited. In 2006, the European Generic Medicines Association (EGA) said it expected the market for biosimilars to reach $7-8 billion within five years of the first marketing authorisation, which represents 11% of today's protein therapeutics market. According to a 2006 report by McKinsey & Company, the US market for generic drugs was worth approximately $19 billion in 2004 ($45 billion worldwide), and over half of the prescriptions written in the US were generic. Given that IMS Health valued the global pharma market as $559 billion in 2004, generics represented 8% of it.

5.5 Pricing of biosimilars

Biosimilars are expected to be priced around 25% cheaper than innovator products. Sandoz, for example, said in 2006 that it would sell Omnitrope at a 25% discount to the reference hGH product, Pfizer's Genotropin. This is a rather smaller discount compared with the figures usually seen with conventional generics, which according to the US Generic Pharmaceutical Association are normally in the 30-80% discount range.

The average retail price of a conventional generic prescription drug in the US was $29.82 in 2004, while the average retail price of a branded prescription drug was $101.71 (according to data from the US National Association of Chain Drug Stores). The smaller discounts for biosimilars reflect the higher development costs of biological drugs relative to small molecule products, as well as more expenditure on sales and marketing.

For example, Avastin, Genentech's colon cancer treatment, costs over $50,000 per patient per year (or $550 per 100mg vial wholesale, ie. $5.50/mg). The same company's Lucentis for wet macular degeneration (which is a related product), costs $23,400 per treated eye per year.

5.6 Profitability of biosimilars

As noted in the preceding section, the scope for price-cutting in the biosimilars market is limited by high development and sales/marketing costs. By the same token, high product prices might also mean healthy profits.

However, Nomura Securities has estimated that it costs €15-40 million ($21-55 million) to bring a biosimilar product to market, assuming that biomarker endpoints can be used in clinical trials (and considerably more if clinical endpoints must be used). There is also the cost of securing the necessary production capacity; Sandoz has spent more than €100 million ($140 million) on this alone. On top of this comes the cost of sales and marketing. Most biosimilars will be sold to hospital specialists (eg. EPO sold to oncologists) rather than primary healthcare practitioners. Nomura suggests that a European field sales force of some 150 people plus the associated infrastructure would cost about €30 million ($40 million) per year to

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operate. Economies of scale would be possible if the company already had a sales force (many conventional generics companies do not) and/or if the product range included several biosimilars that could be sold to the same end-users.

Given these development and marketing costs, Nomura has attempted to calculate the sales of a biosimilar product needed to provide a reasonable ROI. Assuming a gross margin of 75% and development costs of €30 million, peak sales (given a 10-year product life) would have to be at least €70 million per year if a sales force had to be set up and at least €40 million per year if one was already in place. Nomura believes it may be difficult to achieve sales at this level. Taking EPO and interferon alpha as examples, second-generation sustained-release innovator products have captured large market shares. Amgen's Aranesp has about 33% of the EPO market, and Roche's Mircera is likely to capture more (it is currently in registration). The market is also becoming rather crowded. There are already four innovator players: Amgen (Aranesp), J&J (Eprex), Roche (Neo-Recormon), and Shire (Dynepo), together (in Europe) with three biosimilars. PEGylated interferons have captured the bulk of the rather smaller, and even more crowded, interferon alpha market. Biosimilars will also not be helped by fears of immunogenicity.

This means that the companies most likely to succeed in the developing biosimilars marketplace will be those with ready access to the necessary product development and sales/marketing infrastructure. These could include established pharmaceutical companies with innovator and biosimilar divisions such as Novartis/Sandoz. Other examples could include strategic alliances between European or US generics specialists and established biosimilar manufacturers from unregulated markets such as the far east.

5.7 Substitutability and interchangeability

A key issue is whether a biosimilar can be substituted for a branded original, as with small molecule generics. The position taken by the FDA is unambiguous; the Agency says that follow-on proteins are NOT equivalent to the originals. The EMEA takes a similar view, stating in its April 2007 'Biosimilars Q&A' that "[s]ince biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional". This is important because, for example, substitutability would allow those operating a healthcare cost-containment regime to automatically substitute a biosimilar for the reference drug, perhaps even in the case of established (and not just new) patients. This would in turn mean that a biosimilar manufacturer might not even need a large hospital sales force; a small number of people experienced in negotiating with third-party insurers, hospital pharmacists, and similar individuals could be all that is needed, with correspondingly lower prices and increased profits.

The term substitutability refers to the ability of **pharmacists** to **dispense** a biosimilar rather than the reference drug in response to a prescription. Substitutability is the responsibility of a country's healthcare authority and is normally governed by legislation, following consultation with scientific and medical experts. Although the term interchangeability, which is not referenced in EU or US legislation, is often used as a synonym, it actually refers to the ability of **doctors** to **prescribe** a biosimilar in place of the reference product. This is a scientific and clinical issue, but seems a

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somewhat weaker concept since doctors' clinical freedom would in theory allow them to do so anyway.

Closely linked to these concepts is the question of whether biosimilars should have the same INN (international non-proprietary name) as the reference drug. Generics firms say they should, because a comparability study has been concluded with the originator product. Innovator firms say that biosimilars, unlike standard chemical generics, are not identical to the reference drug and so should have a different INN. This issue remains unresolved, although the progress of biosimilars will clearly be impeded if they all must have different INNs. The current consensus is that the WHO has not (yet) changed the INN system, so companies should claim the same INN as the reference drug. The regulator could raise this question with the WHO if it did not agree. In theory, products with different INNs could be biosimilar and substitutable, but this would require a case by case evaluation. Some might argue that such an evaluation should have been part of the approvals process, and INNs assigned accordingly.

The main technical barriers to substitutability and interchangeability arise from the difficulty in fully characterising biological pharmaceuticals. The greatest worry is that exposure to an unnecessarily wide range of subtly different molecular variants might trigger an immune response in the patient. This could seriously impair the management of his or her condition, because the resulting antibodies could interfere not just with the particular preparation that triggered them, but with all related drugs (eg. all epoetins). Worse still, endogenous production of the protein might be affected, as happened with Eprex-associated red cell aplasia, where there was a total cessation of red blood cell production. Related to this are concerns over stability, potency, plasma half-life, and so on. However, it would appear that these concerns could all be addressed with current technology using appropriate clinical and/or laboratory studies. For example, immunogenicity could be assessed by switching patient volunteers between biosimilar and reference epoetins and measuring antibody production.

In February 2007, the French parliament adopted a new law on medicines, which included recognition of the unique nature of biosimilars and a prohibition on automatic substitution between biological medicines. The Swedish and the Norwegian medicines agencies issued official statements with a similar message.

At the time of writing, the latest news from the US is that (in June 2007) the US Senate health committee has passed the Biologics Price Competition and Innovation Act (S 1695). This draft bill would give innovator companies 12 years of marketing protection for new biologicals and allow the FDA to approve biosimilars that are substitutable, ie. they can be substituted for reference products at the pharmacy. The first such biosimilar that is approved for a given reference product would receive one year of market exclusivity. Biosimilar applicants would have to provide one or more clinical studies to demonstrate that there are no clinically meaningful differences from the reference product, although the FDA could waive this requirement. A biosimilar could not be approved until 12 years after the date on which the reference product was first licensed. The draft bill could take several years to become law as it still needs to get approved by Congress, and even then could be vetoed. The EU framework offers a 10-year period for innovative biologicals, with the opportunity for an additional year for new indications.

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5.8 World pharmaceutical market overview

The global pharmaceutical was worth $643 billion in 2006 (Table 5.2). If it continues to increase at its present compound annual growth rate (CAGR) of around 6% per annum (at constant exchange rates, ie. after allowing for currency fluctuations), and excluding inflation, it will be worth over $850 billion in 2011. The largest segments are cardiovascular and CNS, which make up about 40% of the world total. The category in third place, GI tract/metabolism, is worth about $91 billion.

Table 5.2: World pharma market by therapeutic category, 2006-2011

Indication	2006 ($ billion)	%	CAGR	2011 ($ billion)	%
Cardiovascular	126.0	19.6	5.4	163.9	19.3
Central Nervous System	121.5	18.9	7.5	174.4	20.5
GI Tract & Metabolism	91.5	14.2	6.6	126.0	14.8
Respiratory Tract	56.9	8.8	3.3	66.9	7.9
Infectious disease	48.7	7.6	-0.5	47.5	5.6
Musculo-Skeletal	36.8	5.7	3.7	44.2	5.2
Cancer & Immunology	36.7	5.7	13.5	69.2	8.1
GU Tract & Sex Hormones	34.2	5.3	5.6	44.9	5.3
Hematology	25.0	3.9	7.3	35.5	4.2
Dermatology	17.6	2.7	1.4	18.9	2.2
Sensory Organs	13.4	2.1	6.5	18.4	2.2
Endocrinology	10.4	1.6	2.7	11.8	1.4
Parasitology	1.0	0.2	3.6	1.2	0.1
Other	23.2	3.7	3.7	27.8	3.3
World total	643.0	100.0	5.8	850.7	100.0
(Generics = $51.44 billion in 2006)					

Source: Calculated from IMS data

Of particular interest from the standpoint of biopharmaceuticals, are the infectious disease, musculo-skeletal, and cancer/immunology segments. These are all middle-ranking segments, worth around $40-50 billion each. Cancer/immunology is the most dynamic, growing at almost 14% per annum. The least dynamic is infectious diseases, with a growth rate close to zero in recent years. IMS, whose data we relied upon in preparing this table, uses the ATC (Anatomical Type Classification) drug classification system developed by the European Pharmaceutical Marketing Research Association (EphMRA). Under this scheme, anti-inflammatory products are classified under the affected organ system, so most fall under musculo-skeletal, a category worth in total around 6% of the world market ($37 billion) and growing at around 3.7% per annum.

Table 5.3 provides a breakdown of the global market by region in 2006, with forecasts (based largely on extrapolation of current growth rates) to 2011. The total market value is, of course, the same as shown in Table 5.2. North America and Europe are the largest markets, with shares of 45% and 28% respectively, while Latin America is the most rapidly growing. The Japanese and European markets are the slowest growing. Many of the slower-growing national markets are currently subject to tight fiscal controls on healthcare expenditures (for example Japan, Italy and the UK). These countries could provide ready markets for biosimilars.

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Table 5.3: World pharma market by region, 2006-2011

Indication	2006 ($ billion)	%	CAGR	2011 ($ billion)	%
North America	289.9	45.1	8.0	426.0	50.1
Europe (Top 5)	181.8	28.3	4.0	221.2	26.0
Japan	56.7	8.8	0.0	56.7	6.7
Latin America (Top 3)	27.5	4.3	12.0	48.5	5.7
Australasia/Africa	52.0	8.1	5.0	66.4	7.8
Rest of World	35.1	5.5	-1.8	32.1	3.8
World total	643.0	100.0	5.8	850.7	100.0
(Generics = $51.44 billion in 2006)					

Source: Calculated from IMS data

5.9 World market for protein biopharmaceuticals

Table 5.4 contains an analysis of currently marketed protein biopharmaceuticals by application. The table includes forecasts for 2011, based mainly on extrapolation of current growth trends. The overall CAGR for these agents is rather higher than for pharmaceuticals as a whole (9.8% *vs* 5.8%). The market is now worth about $67 billion, or 10% of total pharma sales, and we expect it to rise to $118 billion, or 12% of pharma sales, in 2011. Monoclonal antibodies currently make up 27% of the biopharmaceuticals market, but this figure will rise to 36% in 2011 because sales are increasing more rapidly (14.9% *vs* 7.5% CAGR). Oncology is the dominant application, accounting for one-third of sales overall (and over 50% of all mAbs, data not shown). Indeed, in value terms, protein drugs now account for about two-thirds of the worldwide oncology market ($23 billion of $34 billion). AIID is the most rapidly growing segment.

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***Table 5.4: Biopharmaceuticals market by application in 2006 and* 2011**

Rank	Application	2006 ($ million)	Percent	2011 ($ million)	Percent	CAGR Percent
01	Oncology	23,201	34.6	40,969	34.8	9.9
02	Autoimmune and Inflammatory Disorders (AIID)	10,076	15.0	22,803	19.4	14.6
03	Diabetes and Endocrinology	9,312	13.9	16,902	14.4	10.4
04	Hematology	7,024	10.5	10,868	9.2	7.5
05	Central Nervous System	4,974	7.4	5,663	4.8	2.2
06	Infectious Disease	4,776	7.1	7,764	6.6	8.4
07	Women's Health	1,594	2.4	2,100	1.8	4.7
08	Cardiovascular	948	1.4	1,451	1.2	7.4
--	Other	5,223	7.8	9,103	7.7	9.7
01	Other proteins	48,865	72.8	75,540	64.2	7.5
02	mAbs	18,264	27.2	42,083	35.8	14.9
--	Total	67,129	100.0	117,623	100.0	9.8

Source: Biophoenix/Datamonitor

In Table 5.5 we analyse the biopharmaceuticals market in 2006 by manufacturer, and include forecasts for 2011. Forecasts are once again based on an extrapolation of the sales of existing products, together with estimated sales for agents currently in clinical trials but likely to be launched during the forecast period. Amgen and Roche have the biggest shares overall, with 40% of the total market between them.

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***Table 5.5: Biopharmaceuticals market by company in 2006 and* 2011**

Rank	Name	2006 ($ million)	Percent	2011 ($ million)	Percent	CAGR Percent
01	Amgen	13,807	20.6	26,385	22.4	11.4
02	Roche	12,992	19.4	23,977	20.4	10.8
03	Johnson & Johnson	6,053	9.0	5,476	4.7	-1.7
04	Novo Nordisk	4,553	6.8	6,795	5.8	6.9
05	Lilly	3,530	5.3	6,010	5.1	9.3
06	Schering-Plough	2,561	3.8	3,712	3.2	6.4
07	Wyeth	2,408	3.6	4,394	3.7	10.5
08	Biogen Idec	2,393	3.6	3,710	3.2	7.6
09	Serono	2,375	3.5	2,607	2.2	1.6
10	Sanofi-Aventis	2,144	3.2	3,090	2.6	6.3
11	Abbott	1,917	2.9	4,548	3.9	15.5
12	Genzyme	1,604	2.4	3,071	2.6	11.4
13	Bayer	1,530	2.3	2,247	1.9	6.6
14	Chugai	1,332	2.0	1,893	1.6	6.0
15	Schering AG	1,210	1.8	1,373	1.2	2.1
16	Allergan	884	1.3	1,174	1.0	4.8
17	Novartis	882	1.3	1,579	1.3	10.2
18	Medimune	842	1.3	1,411	1.2	9.0
19	Pfizer	841	1.3	2,717	2.3	21.6
20	Bristol-Myers Squibb	602	0.9	3,989	3.4	37.1
--	Others	2,669	4.0	7,465	6.3	18.7
--	Total	67,129	100.0	117,623	100.0	9.8

Source: Biophoenix/Datamonitor

It is not yet possible to provide comparable information to that shown in Tables 5.4 and 5.5 for biosimilars because the only regulated market in which they are available is Europe and no product has yet achieved 12 months' worth of audited sales.

5.10 Approved biosimilar products

The first biogeneric protein approved in both the EU and the US (and Australia) is Sandoz's Omnitrope, a generic equivalent of Pfizer's Genotropin, ie. recombinant human growth hormone.

5.10.1 US

In the US, follow-on biologics (FOBs) are drugs which have undergone a shortened approvals procedure because the agent is sufficiently similar to an already approved reference product that various scientific and technical issues can be taken for granted. FOBs are not therapeutically equivalent to (substitutable for) the reference product. Moreover, the FDA is only prepared to consider for expedited approval drugs filed under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA). The FDA says it has no statutory authority to address the rather larger number of potential follow-on biologics governed by the Public Health Service Act (PHS), which

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was intended to represent the major pathway for biologic approvals. The necessary legislation (the Biologics Price Competition and Innovation Act (S 1695)) has been passed, but is presently at the draft stage and may not be fully enacted for several years.

The first FOB approved in the US was hyaluronidase, which is used to increase the absorption and dispersion of other injected drugs. Most hyaluronidase products are natural proteins, purified from mammalian testicles. Their amino acid sequences vary according to species, tissue and other factors. The FDA initially approved follow-on versions of mammalian testicular hyaluronidase (ovine and bovine) and has more recently approved a human recombinant hyaluronidase follow-on product, Halozyme Therapeutics' Hylenex, marketed by Baxter Healthcare.

In July 2005, Barr Pharmaceuticals launched a follow-on version of Ferring Pharmaceuticals' peptide DDAVP (desmopressin), after a successful patent challenge (Ferring's patent was due to expire in 2008).

The FDA has also approved the follow-on recombinant somatropin, Sandoz's Omnitrope. Sandoz's NDA submitted to the FDA did not include Phase II dose-finding studies and contained less toxicology. The NDA relied on demonstration of similarity to an approved product rather than clinical data for one of its indications. Another example is Zymogenetics' GlucaGen (recombinant glucagon), which it now manufactures for Novo Nordisk. Glucagen is a follow-on version of Lilly's Glucagon R. In August 2005, the FDA approved Unigene's Fortical (recombinant salmon calcitonin) as a follow-on to Novartis's Miacalcin (which is synthetic salmon calcitonin), even though Miacalcin's patents will not expire till 2015.

Sales of these recently launched niche follow-on proteins are mostly too small to analyse meaningfully. Unigene's Fortical is sold in the US through Upsher-Smith Laboratories, whose sales receipts in 2005 and 2006 were around $6.5 million. This could represent $13 million per year at wholesaler prices. Glucagen sales would be of the same order. More typically, Barr's revenues from US sales of DDAVP in the 2006 fiscal year were around $160,000; thus wholesaler receipts could have been in the order of $350,000. Halozyme's Hylenex has yet to generate significant sales or royalty income.

In 2003, the FDA also approved a biologic (Biogen's Avonex, recombinant interferon-beta) on the basis of clinical data from another manufacturer, Bioferon (a German company in which Biogen held a 50% share), which had manufactured earlier batches of the product. Although this is an interesting precedent, Avonex is not by any reasonable definition a biosimilar. There are of course many instances where one company manufactures FDA-approved drugs for another. These manufacturers may change from time to time, or (subject to legal constraints) they may decide to supply more than one vendor. If a manufacturer's product is approvable when sold by one vendor, it should presumably be acceptable if sold by another.

5.10.2 Europe

The EMEA published a set of final guidelines on similar biological medicinal products which came into effect on June 1st, 2006. The guidelines gave guidance on quality, non-clinical and clinical issues. There are four product-specific annexes for insulin, somatropin (hGH), erythropoietin and G-CSF,

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which give guidance on specific non-clinical and clinical issues. A "concept paper" for interferon alpha is also available. For EPO, the guidance recommends a comparative single-dose pharmacokinetic and pharmacodynamic study. At least two adequately powered, randomised, double-blind clinical trials should be conducted. Safety should be demonstrated with at least 12 months of comparative immunogenicity data. In addition, the EMEA provides scientific advice on the development of biosimilars.

In February 2006, the EU approved Sandoz's Omnitrope (human growth hormone). In May that year, Biopartners' Valtropin was approved. Omnitrope is a biosimilar of Pfizer's Genotropin, while Valtropin is a biosimilar of Lilly's Humatrope. In June 2007, three biosimilar recombinant human erythropoietin (epoetin-alfa) products received approval recommendations in the EU: Sandoz's Binocrit, Hexal Biotech's Epoetin alfa Hexal, and Medice Arzneimittel Puetter's Abseamed. In each case, the reference product is J&J's Eprex/Erypo.

5.11 Forecasts by product

For each product group (eg. erythropoietin) please refer to the table indicated in Chapter 2, which provides detailed product listings, including next-generation products, competing branded products, biosimilars (where applicable), products with engineered enhancements (such as increased plasma half-life) and products formulated for improved or non-injectable delivery. Note that Tables 2.1-2.5 contain additional information on launched products, eg. expression systems, while Tables 2.6-2.10 include patent-related information.

Our forecasts for total protein sales appear in Table 5.6 and our forecasts for the corresponding biosimilars appear in Table 5.7. We consider the top five protein therapeutics categories open to biosimilar competition, worth over 50% of the total protein market in 2006. We anticipate that a biosimilars approvals pathway allowing for interchangeability between a biosimilar and its reference product will be set up in the US by 2009. We expect that total sales of therapeutic proteins will rise from $67 billion in 2006 to $117 billion in 2011, representing a CAGR of 9.8%. This is noticeably better than the average constant-exchange CAGR for the pharma industry as a whole (currently 5.8%).

The fastest-growing proteins are the monoclonal antibodies (average CAGR of almost 15%), which we cannot consider here as they are not yet open to (legitimate) biosimilar competition. We forecast that total sales of biosimilars will rise from $30 million in 2006 to $3.2 billion in 2011, which represents a market penetration of 2.7% across the board. This low figure is partly due to the fact that certain important product groups, most notably the epoetins, cannot be sold in the important US market during the forecast period owing to patent restrictions. It is not meaningful to quote CAGRs for biosimilars because of zero or low baseline sales figures. Apart from a few niche proteins and peptides in the "Other" category (see below), there is currently no available sales history for any approved biosimilar.

5.11.1 Erythropoietin

Epoetins are recombinant human erythropoietins that have the same amino acid sequence as endogenous EPO (Table 2.16). However, the three currently commercially available types of epoetin (alpha, beta and omega)

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contain more sialylated, acidic carbohydrate residues. Second-generation epoetins have further carbohydrate or other side-chain modifications. The current EPO market of over $13 billion is dominated by Amgen and Roche.

Patents for epoetin alpha are owned by Amgen and Kirin, which market epoetin alpha under the brand names Epogen and ESPO respectively. Epoetin alpha is also marketed by Amgen's licensee Johnson & Johnson as Procrit in the US and as Eprex in other territories. Epoetin alpha is indicated for the treatment of anaemia associated with chronic renal failure, in zidovudine-treated AIDS patients, in cancer patients on chemotherapy, and in patients scheduled to undergo elective surgery who would otherwise require blood transfusion. The European patent for epoetin alpha expired in 2004, but the US patents provide some continuing protection until 2013. The US composition-of-matter patent for EPO also expired at the end of 2004. However, Amgen was able to extend its patent life by patenting the technique required to produce EPO in mammalian cells; these process patents are enforceable in the US through 2013. Worldwide sales of epoetin alpha were $6.5 billion in 2006.

Patents for epoetin beta are owned by Roche and Chugai, and were acquired from the Genetics Institute. These companies market the product in non-US territories under the brand names Neo-Recormon and Epogin, respectively. The indications for epoetin beta and epoetin alpha are similar. The European patent expired in 2006. Sales of epoetin beta in 2006 were around $2.5 billion.

Epoetin omega is marketed as Epomax by Baxter Healthcare, which sells it in a limited range of countries outside the US. Baxter acquired it from Elanex Pharmaceuticals. Epoetins alpha and beta are produced in Chinese hamster ovary (CHO) cells, whereas epoetin omega is produced in baby hamster kidney (BHK) cells.

Epoetin delta (Dynepo) was developed by Transkaryotic Therapies (Shire Pharmaceuticals) and Sanofi-Aventis in Europe and has obtained European marketing authorisation. Shire is planning a European launch in 2007. It was produced in large quantities in a human cell line using TKT's gene activation technology, which is based on the activation of the native EPO gene by gene targeting. Indications are similar to other epoetins.

Second-generation epoetins have a longer duration of action, and hence require less frequent doses. This has been achieved through glycol-engineering. Amgen and Kirin are in the lead with darbepoetin alfa (Aranesp), which was approved in 2001. Its half life is more than three times greater than that of Epogen, and it can be given just once weekly. In 2006 it achieved sales of $4.7 billion (an increase of 25% over 2005), largely at the expense of epoetin beta. Sales of Epogen and Procrit/Eprex decreased 6-7% over the same period. Roche's PEGylated second-generation EPO (Continuous Erythropoiesis ReceptorActivator, CERA) was recently filed in the US and in the EU for renal anaemia, and could be launched in 2007, but immediately attracted a US patent infringement suit from Amgen. The import of CERA into the US also became the subject of an investigation by the US International Trade Commission (ITC) in response to Amgen's lawsuit. Another important factor driving the EPO market is that the doses used have been increasing, and are given to a wider range of patients.

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The European market is wide open for first-generation EPO biosimilars, and about 10 companies are believed to be working on them. In addition to Sandoz, HexalBiotech and Medice Arzneimittel Puetter (sourced from Rentschler), other companies reportedly include Stada, Bioceuticals and DSM Biologics. Genemedix (which is being acquired by India's Reliance Life Sciences) is expecting to file an application for EPO in Europe early in 2008. Biogenerix is developing a biogeneric EPO. Biopartners (Bioton) expects to start a development programme for EPO, licensed from LG Life Sciences. Beckpharma's EPO has been approved and produced in Cuba for 8-9 years. The company is planning to bring it to the EU market.

The recent EMEA guidelines have prompted some consolidation among EPO biogeneric developers because of the higher than expected investment required. Also revenues from the European EPO sector could be rather limited, as it is considered to represent only 20-25% of the global EPO market. In 2005, Pliva (Barr Pharmaceuticals) signed a deal with Mayne Pharma for the commercialisation of biosimilars. However, EPO was removed from the agreement in 2006 following publication of the EMEA regulatory guidelines, which were more stringent than the companies had anticipated.

There are a number of recombinant epoetin alpha products on the market outside the US and Europe. The companies involved include Dong-A, LG Life Sciences, Dragon Pharmaceutical, Elanex Pharmaceuticals Shantha Biotechnics and Wyeth. These products mainly serve the EPO needs of emerging countries, but Indian companies in particular are working on the manufacture of biogeneric EPO to European or FDA standards. As the local low price markets are rather small, these companies are aiming at Western markets in their long term business strategy.

Our forecasts for total EPO sales appear in Table 5.6 and our forecasts for EPO biosimilars appear in Table 5.7. Overall, EPO represents about 20% of the protein therapeutics market. We expect that second-generation epoetins will maintain an above average CAGR of almost 11%, after allowing for additional growth by displacement of first-generation epoetins. The US market does not look promising over the forecast period because of patent restrictions. Also, widespread physician dispensing in Japan creates a bias against generics in that country. Physicians have an incentive to prescribe branded products because these attract higher reimbursement levels and have higher profit margins. We expect 10% penetration of Europe and the other regulated markets, or 5% overall, leading to sales of $1.2 billion in 2011.

5.11.2 Insulin

Recombinant insulin was first produced by Genentech scientists in 1978. Today there are almost 200 branded insulin products available worldwide representing an estimated production of 4,600kg per year. The insulin market is dominated by three major players: Novo Nordisk, Lilly and Sanofi-Aventis (Table 2.15). Worldwide sales of insulin and insulin analogues in 2006 approached $8 billion. Insulin is therefore one of the most important biopharmaceutical product classes both medically and by market size. Worldwide demand for insulin is also steadily increasing. According to the WHO, about 171 million people suffer from diabetes mellitus, and this figure is expected to double by 2030. Patents for most first generation insulin products have already expired. Lilly's Humulin and Novo Nordisk's Novolin are both now off-patent. Humulin is expressed in bacteria, while Novolin is

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expressed in yeast.

As exogenous natural insulin cannot replicate endogenous hormone secretion, the insulin molecule has been engineered into analogues with altered amino acid sequences. Several such analogues are commercially available today, with either an accelerated or prolonged duration of action. Of course, these are mostly still patent protected.

Fast-acting insulin analogues were obtained by altering single amino acid residues in order to block aggregation. Insulin Lispro (Lilly), insulin aspart (Novo Nordisk) and insulin glulisine (Sanofi-Aventis) are commercially available examples. Long-acting analogues underwent amino acid substitutions to make the isolectric point more basic. After subcutaneous injection, these molecules aggregate at neutral tissue pH values, slowing their absorption into the circulation. Engineered long-acting insulin analogues support a once-daily dosage regime and are an alternative to conventional insulins; insulin glargine (Sanofi-Aventis) and insulin detemir (Novo Nordisk) are examples.

Biogeneric recombinant insulin is already available in unregulated markets and manufactured in countries such as Poland and India. Although the EMEA provided a regulatory path for the development and registration of biosimilar insulin, this protein does not appear to be a target for European biogenerics companies. The focus in Europe and the US appears to be on needle-free delivery instead. The FDA's recent approval of Pfizer's Exubera inhaled insulin, using technology from Nektar Therapeutics, illustrates this trend. Major manufacturers, such as Novo Nordisk, now believe that the new generation of insulins are so clearly superior and there is such a change in doctor and patient attitude toward them that they will simply not go back to using unmodified human insulins. Hence the only future for such products is within an advanced needle-free delivery system. Lilly recently discontinued its intermediate-acting Humulin formulations (Humulin L and Humulin U), citing declining sales and the creation of better insulin therapies over the past few decades.

Indian biogenerics companies are, however, still in the business of manufacturing and developing conventional insulin analogues. Like their European and US counterparts, Indian companies such as Biocon are also using biogeneric insulin to develop forms of needle-free delivery, eg. oral or transdermal insulin. It is anticipated that as new delivery technologies (in particular pulmonary) replace traditional injection methods, they will require a greater supply of insulin due to the increased dosing requirement of inhaled products. Sembiosys Genetics is one company addressing this issue by developing transgenic (plant-produced) insulin.

Our forecasts for total insulin sales appear in Table 5.6 and our forecasts for insulin biosimilars appear in Table 5.7. Overall, insulin represents about 11% of the protein therapeutics market. We expect insulin sales growth to slightly underperform that of the protein therapeutics market as a whole, ie. around 7% per year. The introduction of second-generation products is largely displacing first-generation insulins, which are beginning to seem increasingly undesirable. Although, first-generation recombinant insulins are off-patent in most countries, we expect just 3% penetration of the regulated markets by biosimilar first generation insulins, leading to sales of $350 million in 2011.

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5.11.3 Interferons

The most commercially important interferons are the alpha and beta groups. Human alpha interferons are a family of naturally occurring signalling proteins. At least 23 proteins of 165-amino acid length and 19-20 kDa molecular weight are recognised. Their therapeutic use stems from their anti-viral, immunomodulatory and anti-proliferative effects. Interferon alpha was first approved for combating malignancies. Anti-viral applications such as chronic hepatitis B and C now make up the bulk of sales. Recombinant interferon alpha products have almost completely replaced purified human interferon alpha products (Table 2.14).

The two biggest players are Schering-Plough with interferon alpha-2b and Roche with interferon alpha-2a. The patents for interferon alpha have expired in the US and expire in the EU in 2007. Both companies have introduced long-acting PEGylated versions of interferon essentially as replacements for their first generation products. Total sales of branded interferon alpha products in 2006 were $2.7 billion. Roche's Pegasys accounts for about 50% of the market, and Schering-Plough's Pegintron has a further 35%. Interferon alpha is used alone or in combination with ribavirin for the treatment of chronic hepatitis C (Pegintron and Pegasys) and chronic hepatitis B (Pegasys).

In 2006, the EMEA issued a negative opinion on Biopartners' interferon alpha-2a product Alpheon in hepatitis C because of quality, safety and efficacy concerns. Teva Pharmaceuticals' biosimilar interferon alpha-2b is approved in Lithuania and in a number of other countries. While there are numerous first generation alpha-interferon products manufactured and sold in the unregulated markets, the number of first-generation biosimilar developments in the US and Europe is rather limited because the standard of care is now the pegylated interferons. A number of alternatives to PEGylation are being explored in order to extend the duration of action of interferon alpha, but these are (or will be) mainstream products, and not biosimilars.

There are two types of marketed interferon beta. Interferon beta-1a is produced in mammalian cells, and its amino acid sequence and glycosylation pattern are identical to those of endogenous human IFN-beta. In contrast, interferon beta-1b is produced in *E.coli* using an altered coding sequence that produces a serine-for-cysteine substitution at position 17. The N-terminal methionine is also missing, and the glycosylation of the natural product is lacking. Interferon beta-1b, in a standard antiviral assay, has only approximately one-tenth of the biological activity of interferon beta-1a and is also more immunogenic.

The market for interferon beta products, mainly used in the treatment of multiple sclerosis (Table 2.20), is nearly twice the size as that for interferon alpha. The three major players -- Biogen Idec (40%), Serono (now Merck Serono; 33%) and Schering AG (now Bayer Schering Pharma AG; 27%) -- achieved total sales of $4.0 billion in 2006. Although interferon beta patents are currently expiring, biosimilars have made little progress. As discussed earlier, biogenerics companies such as Sandoz, Stada and Biopartners have prioritised other products such as hGH and EPO. This is despite the fact that, so far, there are no second-generation (eg. PEGylated) interferon beta products on the market, although there are several in development. Interferon beta suppliers are currently increasing their sales by extending indications, eg. to include very early-stage multiple sclerosis.

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Some IFN-beta products on the market have been approved for indications other than multiple sclerosis. The originating companies include Rentschler (brain inflammation), Mochida (HBV infection), Sclavo and Toray (cancer), and Yeda (keratoconjunctivitis). Many recombinant IFN-beta products continue to be developed for multiple sclerosis. Developers include Rentschler, Bolder Biotechnology, Keryos, Sidus and Vakzine. Some are engineered products, such as Vakzine's Soluferon (a second-generation IFN-beta product with enhanced bioavailability) and Biogen's inhalable IFN-beta-Fc fusion protein. Merck KGaA and Nektar Therapeutics are collaborating on the development of an inhalable PEGylated formulation of Rebif for CNS pain.

Our forecasts for total interferon alpha and beta sales appear in Table 5.6 and our forecasts for EPO biosimilars appear in Table 5.7. Overall, interferons represent about 10% of the protein therapeutics market. We expect CAGR figures around the pharma industry average (4% for beta; 8% for alpha), which is below average for other protein therapeutics. Although the patent situation does not look too unfavourable for interferon biosimilars, this segment is apparently not being intensively targeted. We expect an average 3% penetration of the regulated markets (4% for beta; 2% for alpha), leading to sales of $288 million in 2011.

5.11.4 Granulocyte colony stimulating factor

Granulocyte colony-stimulating factor (G-CSF) stimulates the production of infection-fighting neutrophils (granulocytes). G-CSF is a glycoprotein that exists in two forms; one 174 amino acids long and the other comprising 180 amino acids. The more abundant and active 174 amino acid form has been used in the development of recombinant products.

There are two leading recombinant G-CSF products, both from Amgen: Neupogen and Neulasta (a PEGylated, long-lasting version of Neupogen) (Table 2.19). The market was worth $4.8 billion overall in 2006. Amgen has an 88% share (mostly with Neulasta), Roche has 7% with Neutrogin, Kirin has 4% with its own version of Neupogen, and Kyowa Hakko Kogyo makes up the remainder with Naltoplastim. Recombinant G-CSF is used primarily for the treatment of chemotherapy-induced neutropaenia, or infection in such patients. Key patents covering Neulasta expired in Europe in 2006, and will expire in the US in late 2013.

A number of recombinant G-CSF products are on the market in countries outside the US and the EU. Manufacturers of such drugs include Dong-A, Dragon Pharmaceutical, Hangzhou, Roche/Sanofi-Aventis, and Kyowa Hakko. In Europe, Keryos, which has a recombinant G-CSF product (BK-0023) in Phase II trials, recently asserted that preclinical studies in neutropaenia and anaemia to assess pharmacokinetics, pharmacodynamics and toxicology in comparison with Amgen's Neupogen, demonstrated that the concept of a biosimilar drug, as set out in EMEA guidelines, could be applied to BK-0023.

Most of the products in development, many of them biosimilars, are long-acting, PEGylated forms of recombinant G-CSF. Developers include: Kirin Brewery/Amgen, Maxygen, Neose Technologies, Keryos, Green Cross and Bolder Biotechnology (cys-PEGylated). Hanmi has a long-acting conjugate product in development. Sygnis Pharma is developing a recombinant G-CSF product for the treatment of ischemic stroke.

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In July 2007, Biocon and Abraxis Bioscience signed a licensing agreement that gives Abraxis the right to develop a biosimilar of G-CSF in North America and the EU. Abraxis will develop the product first as a competitor to Neupogen in the European market.

G-CSF is the most advanced biogeneric product under development by Pliva Barr Pharmaceuticals) in collaboration with Mayne Pharma. Biogenerix indicated in January 2007 that it was to focus on developing a pegylated G-CSF as quickly as possible for launch in Europe. Dr Reddy's is the first Indian company to develop a biogeneric, Grafeel (G-CSF), in-house in India. The product enjoys a leading position in the Indian market and is presently being marketed in India, Sri Lanka, the Ukraine and Brazil.

In February 2007, India's Ranbaxy Laboratories announced that it was set to venture into biosimilar development, with G-CSF as its first generic biologic (in collaboration with Zenotech). The company has made a strategic decision to aim first for the European market where biosimilar regulations are in place.

Our forecasts for total G-CSF sales appear in Table 5.6 and our forecasts for G-CSF biosimilars appear in Table 5.7. Overall, G-CSFs represent about 7% of the protein therapeutics market. We expect that second-generation G-CSFs will maintain an above average CAGR of about 10%, after allowing for additional growth by displacement of first-generation agents. As with epoetins, the US and Japanese markets do not look promising over the forecast period. We expect 10% penetration in Europe and the other regulated markets, or 5% overall, leading to sales of $422 million in 2011.

5.11.5 Somatotropins

Somatotropin is human growth hormone (hGH), and the recombinant form contains the same 191 amino acid sequence as pituitary hGH. Most commercially available somatotropins are produced in bacterial cells (*E.coli*), except for one, Serono's Saizen, which is produced in mouse C127 cells (Table 2.2). The natural product is not glycosylated. Before the availability of recombinant somatotropin, the hormone was derived from human cadavers, but this practice was discontinued once the risk of prion (eg. Creutzfeldt-Jakob disease) contamination was discovered.

FDA approved indications for the various somatotropin preparations include the long-term treatment of short stature due to growth hormone deficiency in children and adults, the treatment of short stature in Turner syndrome, idiopathic short stature, short bowel syndrome, and AIDS wasting (Table 2.28). Sales of branded somatotropin products were $2.5 billion in 2006, of which the top five comprised 98%, and grew 6.8% over the previous year. These are Pfizer's Genotropin (34%), Novo Nordisk's Norditropin (19%), Lilly's Humatrope (18%), Genentech's Nutropin (15%), and Serono's Saizen (12%). Of these, the fastest-growing is Norditropin, and only Humatrope is in decline. In 2005, Ferring began US marketing of a somatotropin sourced from Biotechnology General (BTG), via Gate Pharmaceuticals (a division of Teva). Although this went through a normal approvals procedure, it is sold at a discount and appears effectively to be a reduced price biosimilar.

Patents on somatotropin in the US and Europe have expired and do not represent an obstacle to the commercialisation of biosimilar hGH (although Norditropin's patent protection is set to continue until 2015). Novartis's generic subsidiary Sandoz, which now has bacterial and mammalian

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bioreactor facilities in Austria, has received regulatory approval for its biogeneric somatotropin, Omnitrope, in Australia, the EU and the US. The FDA stated that "despite their differences, Omnitrope and Genotropin are highly similar in their clinical effects". In May 2006, Biopartners' Valtropin was also approved in the EU. It was licensed in from LG Life Sciences of Korea, which had also filed an NDA with the FDA in 2005. This is an example of a key player in one of the unregulated markets, which has shown itself able to manufacture a product to GMP standards. Omnitrope was launched in Australia at an initial discount of 10%, but Sandoz indicated that a 25% discount would be available in Western markets.

The EMEA's regulatory requirements for somatotropin are less stringent than for EPO. There should be a single-dose cross-over pharmacokinetic study with subcutaneous administration. Clinical efficacy should be demonstrated in at least one (EPO needs two) adequately powered, randomised, double-blinded comparative clinical trial in treatment-naive children with growth hormone deficiency. The applicant must also provide 12 months of comparative immunogenicity data.

So far, no 'second-generation' (eg. slow release or enhanced potency) somatotropin has been released. There are however now a number of delivery formats in development, such as pens, disposable injectors, and needle-free injectors. LG Life Sciences and Biopartners have a slow release formulation of biogeneric somatotropin awaiting launch in Europe and the US. A number of second-generation somatotropins are in development, in many instances by biosimilars manufacturers, including PEGylated derivatives, fusion proteins, versions with engineered potency and/or stability enhancements, together with pulmonary, oral, intranasal and transdermal formulations. Examples appear in Table 2.28.

Our forecasts for total hGH sales appear in Table 5.6 and our forecasts for hGH biosimilars appear in Table 5.7. Overall, hGH represents just 4% of the protein therapeutics market. We expect CAGR figures on a par with the pharma industry average. The patent position seems quite favourable, and hGH is being targeted intensively by biosimilars manufacturers, despite its small market size. We expect 10% penetration of Europe and the other regulated markets, leading to sales of $330 million in 2011.

5.11.6 Other proteins and peptides

Sales for 2006 of $30 million listed under 'Others' in Table 5.7 reflect sales of existing follow-on proteins approved by the FDA; mainly calcitonin and glucagon, but also including other niche products such as hyaluronidase and DDAVP. We expect a number of proteins and peptides to appear in this category over the coming years, and we have allocated a total of $600 million to cover these in 2011, equivalent to a market penetration of 1% of the 'Others' category in Table 5.6.

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Table 5.6: Biopharmaceuticals market by protein in 2006 and 2011

Protein	2006 ($ million)	Percent	2011 ($ million)	Percent	CAGR Percent
Erythropoietin	13,400	20.0	24,929	21.2	10.9
Insulin	7,719	11.5	11,591	9.9	7.0
Interferons B	4,005	6.0	5,071	4.3	4.0
Interferons A	2,670	4.0	4,240	3.6	8.0
G-CSFs	4,764	7.1	8,440	7.2	10.0
Somatotropin	2,472	3.7	3,315	2.8	5.0
Others	32,098	47.8	60,037	51.0	11.0
Total world	67,129	100.0	117,623	100.0	9.8

Source: Biophoenix/Datamonitor

Table 5.7: Biosimilars market by protein in 2006 and 2011

Protein	2006 ($ million)	Percent	2011 ($ million)	Percent	% market penetration
Erythropoietin	0	0.0	1,247	38.6	5.0
G-CSFs	0	0.0	422	13.0	5.0
Insulin	0	0.0	348	10.7	3.0
Somatotropin	0	0.0	331	10.2	10.0
Interferons B	0	0.0	203	6.3	4.0
Interferons A	0	0.0	85	2.6	2.0
Others	30	100.0	600	18.6	1.0
Total World	30	100.0	3,236	100.0	2.8

Source: Biophoenix

5.12 Forecasts by Region

The market for protein therapeutics by region, together with our forecasts to 2011, are shown in Table 5.8. These forecasts are derived mainly by extrapolation of existing trends, as indicated previously. North America (mainly the US) has almost 40% of the market and Europe has 30%. The fastest growth rates are outside these two regions, a trend that is consistent with the pharmaceutical market in general. Our forecasts for biosimilars appear in Table 5.9. With the exception of a few niche products described earlier, there are no sales data for 2006. In 2011, Europe will be in the lead with nearly 45% of the market, and the distribution of sales will be somewhat different because, owing to patent constraints and prescribing practices respectively, we expect no EPO or G-CSF sales in the US and depressed sales of biogenerics in Japan. EPO represents the largest market opportunity for biosimilars, and G-CSF is also a sizeable opportunity. As previously indicated, we anticipate that a biosimilars approvals pathway allowing for interchangeability between a biosimilar and its reference product will be set up in the US by 2009.

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Table 5.8: Biopharmaceuticals market by region in 2006 and 2011

Region/country	2006 ($ million)	Percent	2011 ($ million)	Percent	CAGR Percent
North America	29,628	44.1	44,803	38.1	7.1
Europe	18,901	28.2	34,389	29.2	10.5
Japan	6,724	10.0	8,686	7.4	4.4
Latin America	2,676	4.0	10,366	8.8	25.3
Pacific Rim, Africa	5,174	7.7	11,557	9.8	14.3
Rest of World	4,026	6.0	7,822	6.7	11.7
Total World	67,129	100.0	117,623	100.0	9.8

Source: Biophoenix/Datamonitor

Table 5.9: Biosimilars market by region in 2006 and 2011

Region/Country	2006 ($ million)	Percent	2011 ($ million)	Percent
Europe	0	0.0	1,442	44.6
North America	30	100.0	627	19.4
Pacific Rim, Africa	0	0.0	433	13.4
Latin America	0	0.0	288	8.9
Japan	0	0.0	133	4.1
Rest of World	0	0.0	313	9.7
Total World	30	100.0	3,236	100.0

Source: Biophoenix

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CHAPTER 6
TRENDS AND OPPORTUNITIES

6.1 Biosimilars market gaining momentum

Europe has already cleared the path to biosimilar approval, and the US is set to follow suit shortly. In June 2007, the US Senate health committee passed landmark legislation creating an approval pathway for biosimilars. The Biologics Price Competition and Innovation Act would allow the FDA to approve biosimilars that are interchangeable with reference products. The first interchangeable biosimilar that is approved for a given reference product would receive one year of market exclusivity. The European Generic Medicines Association believes that the biosimilars market will be driven by interchangeability. Despite delays and avoidance by the FDA, as illustrated by biosimilar guidelines in the EU, it is anticipated that regulatory frameworks for biogenerics will be consensually-acceptable and relatively predictable.

The US is the world's most dynamic generics market. However, it is also one of the toughest, with strong competition exerting considerable pressure on margins. In Europe, Germany has a particularly well developed generics market. Generics companies based in the country are well positioned for success in the biosimilars market, since the German market is characterised by high prices, high usage of biopharmaceuticals, high growth and widespread acceptance of generics.

In recent years there has been an increase in the number of major players in the generics industry that are based outside the US and EU; several large companies are based in India, for example. Asian governments are trying hard to implement strict quality control standards such as GMP and to push for FDA approved manufacturing plants to ensure quality in line with international standards. Many India-based companies claim to have equivalent technological capabilities to US firms, although at a clear cost advantage. India has the largest number of FDA-approved GMP facilities outside the US. Many Indian scientists return to the country having trained in Europe and the US, so there now exists a capacity and capability to develop biosimilar products. All the biotechnology products produced by Indian companies are generic in nature. With India becoming TRIPS-compliant, Indian companies are targeting western biogenerics markets and linking up with local companies.

6.2 Competing through superior delivery

The majority of protein therapeutic sales currently come from immediate release formulations, with subcutaneous injection the most popular route of delivery.

Novel drug delivery could offer a biosimilar product a competitive edge over competing products in a number of ways. For example, use of technologies that result in a more stable plasma drug concentration could improve the safety profile of the drug. The potential for immunogenicity might be reduced by avoiding subcutaneous delivery and immediate release formulations; it is now known that intramuscular delivery is less likely to provoke immunogenicity while intravenous delivery is the least immunogenic. Immunogenicity also increases with more frequent dosing; this may be reduced through the use of depot systems. Drug carriers

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include biodegradable microparticles, natural and synthetic polymers, microcapsules and liposomes.

Meanwhile, PEGylation has been shown to enhance bioavailability, optimise pharmacokinetics, reduce toxicity, and improve solubility and stability. Enzon licensed this technology to Nektar Therapeutics and several refinements and proprietary approaches have recently been developed. Annual worldwide sales of PEGylated drugs are estimated to total about $6 billion.

Several PEGylated biopharmaceuticals have gained approval over the past few years, including Schering-Plough's PEGIntron (IFN-alpha). PEGylated interferons typically only need to be administered weekly (as opposed to three times per week for non-PEGylated products) and maintain more constant levels of interferon in the blood. In fact, the superior performance of these products has led the US National Institutes of Health (NIH) to declare PEG-interferon to be the standard of treatment for hepatitis C. Several companies that had been working on generic versions of Schering-Plough's Intron have discontinued development because most patients are now prescribed PEGIntron.

Another highly successful PEGylated protein on the market is Amgen's Neulasta, a second generation version of the company's Neupogen product (G-CSF). Neulasta has a longer half-life and increased bioavailability over Neupogen, allowing for significantly reduced dosing frequency to once per chemotherapy cycle. Biogenerix and Neose Technology are developing GlycoPEG-GCSF, a biosimilar of Amgen's Neulasta (Neulasta is non-glycosylated), using Neose's GlycoAdvance and GlycoPEGylation technologies.

Other half-life extension technologies include conjugation of polysialic acid, approaches exploiting human serum albumin's long circulation half-life, and, in the case of peptides, introduction of non-natural D-amino acids or peptide cyclisation.

Recent advances, particularly particle engineering and formulation methods to control particle size, consistency and stability are expanding the applications for pulmonary delivery to proteins and peptides. For example, Momenta Pharmaceuticals, which recently formed a collaboration with Sandoz for the development of biosimilars, is focusing on the pulmonary delivery of therapeutic proteins, where bioavailability has been problematic, with a specific focus on hGH, insulin, EPO and IFN-beta.

Nasal delivery is attractive because of its convenience and the large surface area for absorption generated by the nasal microvilli, but currently this approach still generally results in low bioavailability. The next frontier is oral delivery of therapeutic peptides, but this has always presented a significant challenge. Nevertheless, several proprietary technologies are under investigation.

6.3 Diversifying biosimilar pipelines

The companies active in the biosimilars sector are all targeting the same high-volume sales products, which are now off-patent in Europe, namely hGH, EPO, G-CSF and IFN-alpha. These products represent well established biotherapeutic categories, where there are several launched branded products and various products in development (Tables 2.11-2.13). Targeting

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these categories minimises the risks involved with introducing new products, allowing safety and efficacy trials to be run with fewer patients. However, there are many more potential targets for biosimilar development in areas which have so far attracted fewer developers in the western markets. In India and some other Asian countries, several companies have indicated that they have substantial pipelines of biosimilar products.

Chapter 2 (Tables 2.1-2.5) identified 14 peptide and 59 protein biotherapeutics launched on the US market, which achieved global sales of at least $20 million in 2006; around half of the protein products enjoyed 2006 sales in excess of $500 million. These products represent plausible target products for biosimilar development.

6.4 Tackling immunogenicity

Most therapeutic proteins and some peptides show some kind of immunogenicity. Immunogenicity can both cause severe immune reactions and reduce the efficacy of a therapeutic. No standard method for preclinical screening of protein therapeutics for immunogenicity currently exists. The fact that none of the available preclinical assays is sufficiently predictive for the immunogenicity of innovative biotherapeutics in man also has a direct bearing on assessing the immunocomparability of biosimilars. Comparability or non-comparability of biologicals as to their immunogenic potential can only be determined in appropriately designed clinical studies.

Mandatory immunogenicity evaluations are particularly important for biosimilars because they are likely to have different manufacturing processes, formulations and containers/closures than their innovator predecessors.

Notably, slight changes in the manufacturing processes can have a significant impact on safety and/or efficacy. For example, in 2002, Johnson & Johnson made a change to the excipients in the finished Eprex product, which caused antibody-mediated pure red cell aplasia in some patients. It was established that during the latter part of the shelf-life of the new product, an impurity leached into the product from the closure stopper in some of the containers of Eprex; this post-production impurity likely served as an adjuvant in triggering the severe immunogenic response.

Next-generation protein therapeutics (and possibly biosimilars) may be engineered to avoid immunogenicity. A number of laboratories are developing *in silico* interventions coupled with *in vitro* confirmatory assays. For example, *in silico* methods can be used to identify and avoid functional T-cell epitopes. Algonomics is using this approach, combined with predictive animal models to rationally design proteins with reduced immunogenic potential without loss of function. Xencor's ImmunoPDA technology offers a fully comprehensive approach to addressing the immunogenicity problem and involves redesigning and re-engineering therapeutic proteins by using computational methods to identify and replace antigenic epitopes.

6.5 Expanding the range of cell production systems

Compared with bacterial production methods, mammalian cell culture is technically complex, slow and expensive, yet these cell lines continue to command an effective monopoly in terms of producing large recombinant therapeutic glycoproteins.

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Several currently available protein-based therapeutics, including Cerezyme, Epogen, Leukine and Thyrogen possess glycosylation patterns distinct from their *in vivo* counterparts. There is no evidence that the changes in glycoslyation of these proteins materially compromises or changes efficacy, potency or safety. However, glycoform variability can be problematic if different product glycoforms have differential therapeutic properties, as is the case for EPO, tissue plasminogen activator, monoclonal antibodies, and some hormones and cytokines.

The manufacture of therapeutic proteins with a reproducible and consistent glycoform profile remains a considerable challenge to the biopharmaceutical industry. Mammalian cell-derived glycoproteins are generally subject to heterogeneity of the glycans, which vary in exact detail of glycosylation, and glycocomponent profile can be influenced by such things as cell culture conditions. The nature of glycoforms produced may impact glycoprotein folding, stability, trafficking and immunogenicity as well as its primary functional activity.

Mammalian cell culture conditions may be manipulated to influence productivity, for example, by altering temperature, growth rate and media composition. Variation in upstream processing has been shown to influence the glycoform profile of several therapeutic proteins. High production levels may be associated with poor product quality. Essential media nutrients may compromise product quality by, for example, promoting the non-enzymatic addition of glucose. Downstream processing can also potentially compromise product integrity by, for example, selectively purifying or enriching a particular glycoform.

Proteins whose quality, safety and efficacy profile remains acceptable in the absence of a normally occurring post-translational modification can be produced in *E.coli*. A number of recombinant protein therapeutics completely lack glycosylation, even though the *in vivo* counterparts are glycosylated. Proleukin, Betaseron, Neupogen, Neumega and Kineret, in part because of their production in a prokaryotic cell, lack glycosylation. Safety and efficacy has been proven for all of these drugs, and thus in certain instances the complete lack of glycoslyation of a protein does not appear to affect safety or efficacy of a protein therapeutic.

Novartis has created bacteria which can produce glycoproteins with customised glycosylation, by engineering them to take up N-acetylglucosamine (GlcNAc) or N-acetylgalactosamine (GalNAc) derivatives of amino acids. The sugars are incorporated co-translationally, rather than being added to the protein after it comes out of the ribosome, as happens naturally or in conventional bacterial bioengineering.

Other cell production systems capable of carrying out glycosylation include yeast and plant cells. Compared with mammalian cell lines, these cells typically grow to higher cell densities in shorter fermentation cycles and in less expensive and more chemically-defined media, and have a lower risk of transmitting mammalian pathogens. Although yeast expression systems can produce large amounts of glycosylated protein at a fairly low cost, they add sugar side chains of high mannose content. Plants can synthesise humanlike complex N-glycans, but they cannot make galactose. Glycoproteins produced by plant cells lack sialic acid that characterises human glycoproteins; they also contain specific xylose and fucose residues that tend to be immunogenic in humans.

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In many ways, glycoengineered yeast represents a particularly attractive alternative to mammalian cells for producing therapeutic glycoproteins, and has long been used for the production of both recombinant and native industrial enzymes. Recently Glycofi, which was acquired by Merck & Co in 2006, successfully re-engineered the yeast *Pichia pastoris* to replicate the full repertoire of human glycosylation reactions. Humanising glycosylation in yeast required the knock-out of four yeast genes and the introduction of over 14 heterologous genes. The re-engineered lines secrete human glycoproteins with fully complex, terminally sialyated N-glycans and were initially used to create antibodies with consistent glycosylation patterns. The company has also successfully performed the most difficult reengineering step, the addition of the sugar sialic acid, which may allow the yeast strain to be used for the production of virtually any glycoprotein.

Plants may be engineered to eliminate potentially immunogenic fucose and xylose sugars from their glycoproteins. They can also be genetically engineered to express galactosyltransferase, which adds galactose to glycoproteins. Several groups have been trying to introduce a sialic acid pathway into plants, with limited success so far.

6.6 Exploring transgenic production systems

Transgenic milk production offers a cost-effective system for the manufacturing of large amounts of complex therapeutic proteins. There are a number of proteins that, due to a combination of complex structure and large therapeutic dosing, have until now eluded recombinant production using traditional bacterial and cell culture bioreactors. For example, the commercial recombinant production of antithrombin and alpha1-antitrypsin has not yet been achieved; the only source is human plasma because of the high dose needed.

The targeting of a therapeutic protein to the milk of a transgenic animal is achieved by introducing a transgene encoding the protein fused to milk-specific regulatory elements into the germline of the chosen production species. Following germline integration, mammary gland-specific transgenes are predictably inherited by the offspring of the founder animal. Technologies that permit the clinical-grade purification of therapeutic proteins from the milk of transgenic dairy animals have also been developed.

Glycosylation patterns characteristic of proteins produced in transgenic milk of higher mammals differ somewhat from those of native human proteins. The presence of N-glycolylneuraminic acid, for example, could potentially trigger immunological and other complications in man. In addition, the therapeutic product has an almost tenfold lower plasma half-life.

Several companies have generated transgenic animal herds that yield large amounts of therapeutic proteins. The first therapeutic protein produced in an animal bioreactor -- GTC Biotherapeutics' ATryn, a recombinant form of human antithrombin expressed in transgenic dairy goats -- was approved in 2006 by the EMEA. The human antithrombin purified from milk has been shown to be structurally indistinguishable from human plasma-derived antithrombin with the exception of some glycosylation differences; these do not, however, impact the major biological activity of the protein.

Progress is also being made in creating transgenic chickens to enable the manufacture of therapeutic proteins in eggs. In 2005, Origen Therapeutics

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scientists first reported the production of monoclonal antibodies in chicken eggs. Origen plans to breed flocks of birds depositing therapeutic proteins in their eggs.

Both recombinant and transgenic human monoclonal antibodies are currently in development. Abgenix, which was acquired by Amgen in 2006, was the first company to use a transgenic mouse, XenoMouse, for therapeutic monoclonal antibody production. Medarex markets its transgenic HumAb-Mouse. In these transgenic mice, murine germ-line antibody genes have been replaced with human ones. When challenged by a foreign protein, transgenic mice produce fully human, functional antibodies.

6.7 Developing cell-free protein synthesis

Production of recombinant proteins can also be achieved *in vitro* using extracts derived from cells. Cell-free systems can direct most, if not all, of the metabolic resources of the cell towards the exclusive production of one protein. Moreover, the lack of a cell wall and membrane components *in vitro* is advantageous since it allows for control of the synthesis environment. The redox potential, pH or ionic strength can be altered with greater flexibility than *in vivo* since cellular growth or viability is not a concern. Furthermore, direct recovery of purified, properly folded protein products can be easily achieved.

Current cell-free protein synthesis systems can synthesise proteins with high speed and accuracy, but produce only a low yield because of short reaction times and system instability over time. The large-scale implementation of cell-free systems has also been limited by high reagent costs. Nevertheless, over the past decade, the productivity of cell-free systems has improved, suggesting that cell-free technologies may allow large scale production of protein pharmaceuticals in the not-too-distant future. Patents are currently being sought for new methods of optimising cell-free protein synthesis; examples of recently published US patents (both granted patents and patent applications) are provided in Table 6.1.

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***Table 6.1: Recently published cell-free protein synthesis patents* and applications**

No	Pat or App No	Title / abstract	Inventor(s) / Assignee(s)	Filed Date / Pub Date
001	US App No 20070154983	Methods of in vitro protein synthesis Improved methods are provided in vitro synthesis of biological molecules, providing for improved yields, lowered costs and enhanced utility. Improved yield and lowered cost is obtained by the use of a phosphate free energy source in the presence of exogenous phosphate, and optionally in the absence of exogenous nucleoside triphosphates.	Calhoun, Kara; Jewett, Michael Christopher; Swartz, James Robert The Board of Trustees of the Leland Stanford Junior University	2004-11-18 2007-07-05
002	US Pat No 7235382	Preparation containing cell extracts for cell-free protein synthesis and means for synthesising protein using the preparation Disclosed are a preparation containing cell extracts for cell-free protein synthesis, prepared by excluding from a living organism a system, participating to inhibiting of self protein synthesis reaction, an apparatus for cell-free protein synthesis reaction equipped with a reaction tank for cell-free protein synthesis, and a kit for use therefor; the preparation can be stored at room temperature and prepared as a preparation in a state where biological functions of the cell extracts are maintained, and further, disclosed is methods for cell-free protein synthesis comprising providing cell extracts from which an inhibitor for self protein synthesis reaction is substantially excluded, having introduced therein treatment selected from supplement, storage, exchange or discharge with respect to an element selected from at least mRNA serving as a template for synthesis reaction, an energy reproduction system enzyme, a substrate, and an energy source.	Endo, Yaeta; Nishikawa, Shigemichi CellFree Sciences Co., Ltd. (Kanagawa, JP)	2005-03-25 2007-06-26
003	US App No 20070141661	Cell extract for high-functioned cell-free protein synthesis and method of preparing the extract The subjects of the present invention are to prepare a highly functionalized cell extract for cell-free protein synthesis and to specify and eliminate inhibitors and unstable substances present in conventional and various cell extracts for cell-free protein synthesis. Also provided is a method for preparing the cell extract for use in a cell-free protein synthesis means, wherein ATP-mediated phosphorylation pathway of sugar present in the cell extract is controlled. In particular, the control is introducing at least one selected from the following: 1) removing monosaccharides, 2) removing phosphorylated sugars, 3) controlling production of monosaccharides from polysaccharides, and 4) controlling production of phosphorylated sugars from monosaccharides.	Endo, Yaeta; Ogasawara, Tomio Not available.	2004-12-17 2007-06-21

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No	Pat or App No	Title / abstract	Inventor(s) / Assignee(s)	Filed Date / Pub Date
004	US App No 20070134755	Method of producing cell extract for cell-free protein synthesis A cell extract for cell-free protein synthesis is produced by removing substances, which bind to an affinity support to be used in purification or interaction analysis, from a cell extract having protein synthetic activity. Then, a target protein is synthesized by using the cell extract for cell-free protein synthesis. The synthesized target protein can be purified by using the affinity support and used in interaction analysis.	Yoshiyama, Yoshiko; Koga, Hirohisa Not available.	2005-03-02 2007-06-14
005	US App No 20070128688	Method for cell-free protein synthesis using complementary oligonucleotide The present invention provides a practical cell-free protein synthesis method capable of easily synthesizing a large amount of protein at low cost. A method for cell-free protein synthesis performed in a reaction solution containing mRNA and a living cell-derived extract solution, the reaction solution containing an oligonucleotide complementary to a sequence present in a 3' terminal region of the mRNA.	Shikata, Masamitsu; Kobayashi, Shinichiro Shimadzu Corporation	2006-11-27 2007-06-07
006	US App No 20070004001	Total amino acid stabilization during cell-free protein synthesis Compositions and methods are provided for the enhanced in vitro synthesis of protein molecules, by optimizing the metabolism of amino acids present in the reaction mix, preferably all amino acids in the reaction mixture. By performing synthesis with extracts from genetically modified microbial strains that are deficient in multiple amino acid metabolizing enzymes reduces the enzymatic activities responsible for catalyzing these reactions and improves the overall yield of synthesis.	Calhoun, Kara Anne; Swartz, James Robert Not available.	2006-06-05 2007-01-04
007	US App No 20060264612	Optimised protein synthesis The invention concerns a method for the optimized production of proteins in an in vitro or in vivo expression system and reagents suitable therefor.	Watzele, Manfred; Buchberger, Bernd; Paulus, Michael Not available.	2003-12-09 2006-11-23
008	EP1685240	Improved methods of in vitro protein synthesis Improved methods are provided in vitro synthesis of biological molecules, providing for improved yields, lowered costs, and enhanced utility. Improved yield and lowered cost is obtained by the use of a phosphate free energy source in the presence of exogenous phosphate, and optionally in the absence of exogenous nucleoside triphosphates.	Calhoun, Kara; Jewett, Michael Christopher; Swartz, James Robert Univ Leland Stanford Junior (US)	2004-11-18 2006-08-02

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No	Pat or App No	Title / abstract	Inventor(s) / Assignee(s)	Filed Date / Pub Date
009	US App No 20060141559	Extract from cultured mammalian cell, process for preparation thereof and method of cell-free protein synthesis using the extract A method for preparing a cultured mammalian cell extract liquid, comprising at least the step of rapidly freezing a cultured mammalian cell suspended in a solution for extraction; a cultured mammalian cell extract liquid prepared by the process; and a method for cell-free protein synthesis using the extract liquid. Preferably, the method for cell-free protein synthesis comprises the step of prior to conducting of synthetic reaction, effecting incubation of a reaction liquid for cell-free protein synthesis in a state of containing components other than exogenous mRNA for a specified period of time.	Suzuki, Takashi; Ezure, Toru; Ito, Masaaki; Higashide, Shoken; Endo, Koki Not available.	2004-06-09 2006-06-29
010	US App No 20060134735	Process for producing extract for cell-free protein synthesis and cell extract produced thereby It is intended to provide a process for producing an extract for cell-free protein synthesis whereby the productivity of a protein and the production efficiency can be improved. Cells are cultured under suppressed growth conditions. In the stationary phase of the culture, the cells are collected and then disrupted. The above-described cells are preferably bacterial cells, in particular, Escherichia coli cells. In the suppressed growth conditions as described above, the culture temperature is preferably from 20 to 32.degree. C., more preferably 26.degree. C. or higher and lower than 30.degree. C.	Matsuda, Natsuko; Kigawa, Takanori; Chumpolkulwong, Namtip; Takemoto, Chie; Shirouzu, Mikako; Tanaka, Akiko; Yokoyama, Shigeyuki Riken	2005-11-21 2006-06-22
011	US App No 20060121560	DNA fragment to promote translation reaction and method for cell-free protein synthesis system using the same The present invention provides a DNA fragment allowing easy cloning of a desired gene and capable of further improving translation efficiency, a protein expression vector and a template DNA having the DNA fragment, a mRNA obtained from the template DNA, a reaction solution for cell-free protein synthesis system containing the template DNA or the mRNA, a method for cell-free protein synthesis system using the template DNA, and, kit for cell-free protein synthesis system including the expression vector. A DNA fragment having the base sequence represented by any of SEQ ID No. 1 to 11 to use for promoting translation reaction, a protein expression vector and a template DNA having the DNA fragment, a mRNA obtained from the template DNA, a reaction solution for cell-free protein synthesis system containing the template DNA or the mRNA, a method for cell-free protein synthesis system using the template DNA, and, kit for cell-free protein synthesis system including the expression vector.	Suzuki, Takashi; Ito, Masaaki; Ezure, Toru; Shikata, Masamitsu; Kobayashi, Shinichiro Shimadzu Corporation	2005-12-07 2006-06-08

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No	Pat or App No	Title / abstract	Inventor(s) / Assignee(s)	Filed Date / Pub Date
012	US Pat No 7048915	Composition for cell-free protein synthesis The present invention provides a composition for cell-free protein synthesis, which is superior in storage stability in a freeze-dried state, more particularly a freeze-dryable or freeze-dried composition for cell-free protein synthesis, which contains a cell extract for cell-free protein synthesis and inositol, and a freeze-dryable or freeze-dried composition for cell-free protein synthesis containing a cell extract for cell-free protein synthesis, and a deliquescent material in a proportion of not more than 0.01 part by weight per part by weight of a protein in the composition; and a composition for cell-free protein synthesis superior in storage stability in a frozen state, more particularly a freezable or frozen composition for cell-free protein synthesis, containing a cell extract for cell-free protein synthesis and polyhydric alcohol.	Kuroita, Toshihiro; Kawakami, Bunsei; Kawamura, Yoshihisa; Nishikawa, Shigemichi; Endo, Yaeta CellFree Sciences Co., Ltd. (Kanagawa, JP)	2002-04-18 2006-05-23
013	US Pat No 7045593	Process for synthesizing protein using cell-free protein synthesis system A method for producing a protein using a cell-free protein synthesis system comprising a detergent so that the protein can be synthesized without aggregation, is provided. The protein is a protein comprising a hydrophobic region in at least a portion thereof, for example, a membrane protein or its fragment (portion). And the detergent is a mild detergent which would not denature the protein, for example, a nonionic or amphoteric ionic detergent.	Tajima, Kaori; Kigawa, Takanori; Shirouzu, Mikako; Yabuki, Takashi; Ishihara, Goushi; Yokoyama, Shigeyuki Riken (Saitama, JP)	2002-04-26 2006-05-16
014	EP1655375	Process for producing extract for cell-free protein synthesis and cell extract produced thereby It is intended to provide a process for producing an extract for cell-free protein synthesis whereby the productivity of a protein and the production efficiency can be improved. Cells are cultured under suppressed growth conditions. In the stationary phase of the culture, the cells are collected and then disrupted. The above-described cells are preferably bacterial cells, in particular, Escherichia coli cells. In the suppressed growth conditions as described above, the culture temperature is preferably from 20 to 32 DEG C, more preferably 26 DEG C or higher and lower than 30 DEG C.	Matsuda, Natsuko; Kigawa, Takanori; Chumpolkulwong, Namtip; Takemoto, Chie; Shirouzu, Mikako; Tanaka, Akiko; Yokoyama, Shigeyuki Riken (JP)	2004-05-21 2006-05-10
015	US App No 20060084146	Method for cell-free protein synthesis using extract solution derived from insect cell The present invention provides a simple cell-free protein synthesis method capable of affording synthesis of a protein in a high amount in a short time at a low cost. A method for cell-free protein synthesis using an extract derived from an insect cell, the method comprising removing a component which can pass through a semipermeable membrane through the semipermeable membrane while maintaining synthesis reaction, thereby to continuously synthesize a protein. Preferably, an mRNA is additionally supplied while said synthesis reaction is maintained. Further, said insect cell is preferably an established culture cell derived from Trichoplusia ni ovum cell.	Shikata, Masamitsu; Hanafusa, Nobuhiro; Kobayashi, Shinichiro Shimadzu Corporation	2005-10-12 2006-04-20

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No	Pat or App No	Title / abstract	Inventor(s) / Assignee(s)	Filed Date / Pub Date
016	EP1634947	Extract from cultured mammalian cell, process for preparation thereof and method of cell-free protein synthesis using the extract A method for preparing a cultured mammalian cell extract liquid, comprising at least the step of rapidly freezing a cultured mammalian cell suspended in a solution for extraction; a cultured mammalian cell extract liquid prepared by the process; and a method for cell-free protein synthesis using the extract liquid. Preferably, the method for cell-free protein synthesis comprises the step of prior to conducting of synthetic reaction, effecting incubation of a reaction liquid for cell-free protein synthesis in a state of containing components other than exogenous mRNA for a specified period of time.	Suzuki, Takashi; Ezure, Toru; Ito, Masaaki; Higashide, Shoken; Endo, Koki Shimadzu Corp (JP)	2004-06-09 2006-03-15
017	US App No 20050186655	Preparation containing cell extracts for cell-free protein synthesis and means for synthesizing protein using the preparation Disclosed are a preparation containing cell extracts for cell-free protein synthesis, prepared by excluding from a living organism a system, participating to inhibiting of self protein synthesis reaction, an apparatus for cell-free protein synthesis reaction equipped with a reaction tank for cell-free protein synthesis, and a kit for use therefor; the preparation can be stored at room temperature and prepared as a preparation in a state where biological functions of the cell extracts are maintained and further, disclosed is means for cell-free protein synthesis comprising cell extracts from which an inhibitor for self protein synthesis reaction is substantially excluded, having introduced therein treatment selected from supplement, storage, exchange or discharge with respect to an element selected from at least mRNA serving as a template for synthesis reaction, an energy reproduction system enzyme, a substrate, and an energy source.	Endo, Yaeta; Nishikawa, Shigemichi Not available.	2005-03-25 2005-08-25
018	US App No 20050032086	Methods of RNA and protein synthesis The present invention relates to methods for RNA and/or protein synthesis using in vitro or in vivo expression systems. More specifically, the present invention provides a method for RNA and/or protein synthesis characterized in that the concentration of alpha subunit of RNA polymerase, but not of other subunits, is increased in the cellular or cell-free system, comparing to its natural concentration existing in the cellular or cell-free system.	Sakanyan, Vehary; Snapyan, Marina; Ghochikyan, Anahit; Lecocq, Francoise-Michele Not available.	2004-01-27 2005-02-10

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