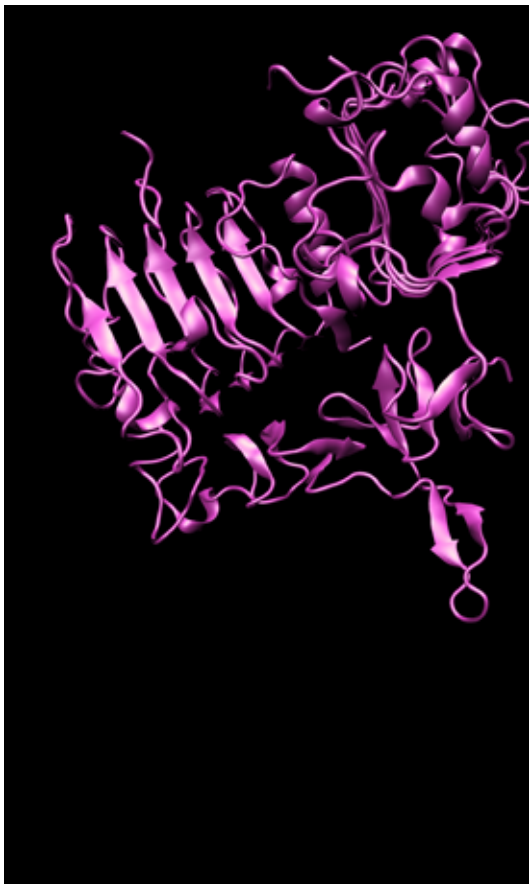
Biological therapies: how can we afford them?

Demand for biological drugs is putting pressure on health budgets. **Christopher Kelly** and **Fraz Mir** examine why they are so expensive and what can be done to increase access



The success of biopharmaceuticals is producing a growing problem for public healthcare services worldwide. Newer biological therapies offer fresh hope for the treatment of many serious diseases but are much more expensive than conventional drugs. Clinicians are increasingly finding themselves torn between offering new treatments to patients and respecting the financial restrictions imposed by healthcare authorities on the basis of cost effectiveness.

In the UK, the NHS has been under pressure after the National Institute for Health and Clinical Excellence (NICE) initially recommended against funding drugs such as trastuzumab for breast cancer, erlotinib for non-small cell lung cancer, and ranibizumab for age related wet macular degeneration.[1] Widespread emotive media coverage of such cases heightens public expectation that the health service will fund all drugs in all situations, regardless of cost. However, unless biological therapies can be made more affordable, Western healthcare systems face a financial crisis, exacerbated by the pressures of cuts in public spending, to survive in the current financial climate. We examine the reasons for the high costs and the possibilities for reducing them.

Revolutionary drug treatment

Biological therapies are generally derived from living material (human, animal, or micro-organism) and have a highly complex chemical structure. Many fundamental differences exist between biological drugs and traditional "small molecule" drugs (table 1).[2]

The US Food and Drug Administration considers biological therapies to include "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings."[3] Over 150 biological drugs are currently available in the United States[4] with many more in the pipeline, providing treatment for common diseases through to rare genetic conditions (table 2).

Although many biological products have been used for decades (such as insulins, somatostatin, erythropoietin, and interferon[2]), newer and more expensive treatments (notably monoclonal antibodies) are becoming available for a rapidly growing range of diseases. The newer biological therapies are among the most expensive drugs available. Many factors contribute, including the complex manufacturing processes, high costs of research and development, the huge perceived value of such drugs to patients (such as avoiding blindness in wet macular degeneration), and the fact that

Table 1 | Comparison of classic pharmacological and clinical characteristics of traditional and biological drugs[2]

Traditional	Biologicals
Pharmacological properties	
Multiple effects	Specific
Short acting	Long acting
Non-immunogenic	Immunogenic
Species independent	Species dependent
Small molecules	Large molecules
Stable	(Heat) sensitive
Clinical therapeutics	
Oral administration	Parenteral
General practice	Hospital
Metabolised	Degrade
Interactions	No classic interactions
Toxicity	Exaggerated pharmacology

Table 2 | Worldwide sales of the major classes of biological drugs[5]

Drug class	2007 sales (£bn)	% revenue growth from 2006	Examples
Major cancer antibodies	7.5	48	Rituximab, trastuzumab, bevacizumab
Tumour necrosis factor antibodies	6.18	26	Etanercept, infliximab, adalimumab
Erythropoietins	5.63	–1	Darbepoetin alfa, epoetin alfa
Insulin and insulin analogues	5.33	25	Insulin lispro, insulin detemir, insulin glargine, isophane insulin
Recombinant coagulation factors	2.57	14	Factors VIIa (recombinant), VIII, and IX
Interferon beta	2.55	22	Avonex, Rebif, Betaferon
Granulocyte colony stimulating factor	2.30	10	Pegfilgrastim, lenograstim, filgrastim
Human growth hormone (somatropin)	1.32	12	Genotropin, Norditropin, Humatrope, Nutropin, Serostim
Interferon alfa	1.30	21	Pegasys, Pegintron, IntronA
Enzyme replacement	1.09	34	Imiglucerase, agalsidase beta

DR. TIM EVANS/SPL

BARRY BATCHELOR/PA

Above left: Molecular model of trastuzumab (blue and yellow), a monoclonal antibody that binds to the HER2/neu receptor (pink) on breast cancer cells, causing them to die during their reproductive cycle. Campaigning by patients' groups (above right) has put pressure on Western governments to fund such biological therapies

there is less competition in the marketplace to drive down prices.[6] In-hospital costs of administering the largely parentally administered drugs, subsequent additional travel costs of patients to receive treatment, and costs of monitoring and managing adverse events (such as infections) also contribute to the overall expenditure.[7]

Meeting demand

Demand for these therapies is enormous, as both patients and doctors seek to improve health outcomes in difficult to treat diseases. Pressure is now growing to use biologicals earlier in disease progression rather than reserving their use for disease that is refractory to cheaper traditional therapies.[8]

Clinicians are prescribing biological therapies at increasing rates. Average US annual sales growth in revenue for biologicals was 20% between 2001 and 2006, compared with overall drug market growth of only 6-8%.[9] Worldwide sales of major cancer antibodies increased by 48% from 2006 to 2007.[5] Capitalising on these new opportunities, drug companies have shifted research and development resources to focus on lucrative biological drugs, and over 500 biological therapies are currently in clinical development.[10]

However, the rapid uptake of such treatments costing up to £70 000 a year[11] for each patient is unsustainable in a public healthcare system. Without substantial increases in healthcare funding, money will have to be reallocated from other areas. In the UK, NICE attempts to control costs by setting a maximum incremental cost effectiveness ratio of £30 000 per quality adjusted life year added (QALY).[1] Even so, campaigning by patients' groups and subsequent political embarrassment has led to the approval of drugs that exceed this notional limit, including trastuzumab and imatinib.[1] New guidelines to standardise access to end of life drugs were introduced in January 2009, although their impact is expected to be limited.[12]

The introduction of cheaper generic or, more accurately, "biosimilar" versions of biological drugs could potentially greatly reduce costs and increase access to treatment

Generic "biosimilar" drugs

The introduction of cheaper generic or, more accurately, "biosimilar" versions of biological drugs could potentially greatly reduce costs and increase access to treatment. Inexpensive generic versions of conventional drugs (such as omeprazole and simvastatin) have been hugely beneficial worldwide. Generic versions are much cheaper than the original branded products, although the active molecules are identical with equivalent physiological and pharmacological properties.

Potential cost reductions with biosimilars are estimated at 18-50%.[13-15] Profit margins are smaller than for conventional drugs, leaving less room for discounting. One report estimates that etanercept for rheumatoid arthritis has a gross margin of about 67%, compared with over 90% for a typical small molecule drug.[16]

However, even at relatively modest discounts, biosimilars could still produce large savings worldwide. A recent industry report suggests that savings across the top 12 categories of biological therapies could be $67bn-$108bn over the first 10 years and $236bn-$378bn over 20 years in the US alone.[15] Furthermore, these estimates are likely to understate savings by failing to take account of many factors likely to reduce

the price of biosimilars and further expand their use.

Producers of biosimilars tend to use manufacturing facilities in developing countries, significantly reducing costs. Once competition from cheaper biosimilars is introduced, evidence from traditional generic drugs suggests that prices of branded drugs will reduce in response. Unsurprisingly, this tends to result in an increase in patients using the cheaper drugs, as cost effectiveness improves and healthcare services become able to fund the treatments.[15] In addition, studies underestimate the number of drugs that will lose patent protection once a regulatory pathway is created in the US. The patents of about a fifth of generic drugs certified during 1998-2002 are alleged to be invalid.[17]

Patent protection on most top selling biological products is still valid for at least another five years, limiting the speed and extent to which real financial benefits can be gained

Many hurdles

Several important hurdles[18] are faced by potential generic manufacturers of biological therapies, leading regulators in the US and Europe to conclude that it may never be possible to create a true generic biological drug. Terms such as biosimilars or follow-on biologicals are therefore preferred to describe products that potentially qualify for abbreviated regulatory pathways.

Physical limitations provide a fundamental hurdle. Whereas traditional drugs are generally manufactured using a well defined series of synthetic chemical reactions, biological drugs are usually produced from a proprietary bank of living cells (mammalian, bacterial, or yeast). Even the smallest variability in production conditions can lead to important differences in the final product's efficacy or safety profile,[19] and this may be difficult to detect.[20] Even scaling-up production capacity of an established drug can produce structural differences in the final product that are unacceptable to regulatory authorities, as in the case of the new bulk manufacturing processes for Genzyme's Myozyme.[21]

Furthermore, the cell lines are the protected intellectual property of the originating drug company and are therefore not available to potential generic competitors. Thus reproducing the successful business model used by traditional generic manufacturers may prove difficult. Traditional generic drugs are economical to produce because of the lack of research and development costs, low cost manufacturing processes, and swift regulatory approval. Development of a small molecule generic typically costs £1m-£2.5m,[16] whereas a biosimilar drug costs about £120m.[15] Commercial viability of biosimilars depends on reasonable development costs, but these increase exponentially if clinical trials are required to prove equivalence.

Interchangeability, whereby a branded drug can be automatically substituted for its biosimilar counterpart, is also fundamental to ensure sufficient sales. Such interchangeability is contentious. In the UK a recent review panel called for an "urgent ban" on pharmacist substitution of biosimilars until effective safeguards were in place.[22]

Industry regulators need to encourage competition

Although the primary goal of regulators is to ensure public safety and confidence, it is vital to encourage market competition and access for generic manufacturers. The benefits of competition are not generally obtained until four or five sellers enter a market,[6] and shortened approval processes for biosimilars are required worldwide to help achieve this.

In the United States, generic versions of traditional drugs can be approved for market using trial data from the branded drug. This does not apply to biological drugs. The Biologics Price Competition and Innovation Act of 2007 is a first step, requiring a generic company to conduct at least one clinical trial to show equivalence, although even this requirement could be waived. President Obama's first budget in February 2009 announced proposals to set up a faster pathway for biosimilar drugs,[23] and new legislation is being discussed.[24] However, it may take until 2011 for the FDA to implement any new policies.[25] A critical issue is the period of data exclusivity for innovator companies before generic manufacturers can use the original data to support their own abbreviated approval. This represents a key form of intellectual property for drug companies and is expected to have a major role in determining the speed with which generic manufacturers can bring biosimilars to market.

In the European Union, the *Guideline on Similar Biological Medicinal Products* asserts that because of the complexity of biological products, the traditional generic approval process is scientifically inappropriate and comparability studies are required to show equivalent quality, safety, and efficacy for any new biosimilar.[26] The first biosimilar authorisation under the legislation was granted in April 2006 for Omnitrope (somatotropin). Just a few weeks later, Omnitrope was launched in Austria and Germany 20% cheaper than the innovator drug, Pfizer's Genotropin.[27] Other products have not been so successful. For example, Alpheon, a biosimilar interferon alfa, was rejected because of "impurities identified" between the biosimilar and original drug, a "lack of data on the stability" of the drug, and because the manufacturing process had not been "adequately validated."[28]

New model for pricing drugs

The UK Office of Fair Trading[29] recently concluded that the current Pharmaceutical Price Regulatory Scheme does not provide adequate value for money from the NHS drug budget. It recommended replacing the existing profit and price controls with a "value-based approach," basing a drug's price on its cost effectiveness, as measured in QALYs.[30] If the health benefits expected from a new drug do not exceed the health benefits forgone as other NHS treatments are displaced, then the price could be negotiated lower.[31] Such a model has already been successfully introduced in Australia, Canada, and Sweden.[30]

This reform could give the NHS increased flexibility to respond to new drugs. At present, if a drug does not meet cost effectiveness targets, the only two options are to refuse funding completely or define a subgroup of patients in whom it is cost effective.[30] Value based pricing would allow manufacturers to offer different prices for each specific use of a drug depending on cost effectiveness.[31] This may facilitate access to expensive biological therapies for more patients.

Clinicians can help improve cost effectiveness

Clinical research can contribute to improving the cost effectiveness of new biological treatments. Optimal duration of therapy and doses remain to be accurately established for most molecularly targeted agents.[7] For example, the standard duration of treatment with trastuzumab in HER2+ breast cancer is one year, but shorter treatment periods are being explored in randomised trials.[7]

Research into identifying predictive factors may also be crucial to improve cost effectiveness. By treating only patients who have specific characteristics that are known to result in a positive response to a particular drug (so called enriched populations), wastage can be reduced and valuable resources conserved.

Promising future

Biosimilars are becoming an increasing reality. Biosimilar human growth hormone, erythropoietin, and granulocyte colony stimulating factor are now available in Europe. Efforts need to be focused on introducing careful legislation to facilitate competition. Issues such as lack of trust in biosimilar drugs by prescribers and patients, plus the absence of interchangeability for biosimilar drugs in many markets is holding back growth in Europe.[32] Policies are needed to improve confidence in equivalence without compromising patient safety.

However, patent protection on most top selling biological products is still valid for at least another five years, limiting the speed and extent to which real financial benefits can be gained. A concerted effort is required to ensure that legislation is in place to create a favourable environment for development of biosimilar products once patents expire.

Christopher J Kelly medical student, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge CB2 0QQ
Fraz A Mir consultant physician, Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital
Correspondence to: F A Mir fam31@cam.ac.uk

Accepted: 30 June 2009

Contributors and sources: CJK worked as a drug equity research analyst at UBS Investment Bank in London before starting medical training. FAM is a member of the Clinical Pharmacology Unit, Cambridge. Both authors contributed equally to writing the article. FAM is guarantor.

Competing interests: FAM has been reimbursed by several drug companies for attending conferences, speaking, and organising educational meetings.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Steinbrook R. Saying no isn't NICE—the travails of Britain's National Institute for Health and Clinical Excellence. *N Engl J Med* 2008;359:1977-81.
2 Muller M. Biological therapies: concepts and challenges. *Wiener Klinische Wochenschrift* 2006;118:508-12.
3 US Food and Drug Administration. *Frequently asked questions about therapeutic biological products*. www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm.
4 Judlowe S, Murphy B. *Proposed legislation for follow-on biologic pharmaceuticals in the US*. 2008. www.buildingipvalue.com/05_NA/135_138.htm.
5 La Merie Business Intelligence. *Top 20 biologics 2007*. www.pipelinereview.com/content/view/18533/353/.
6 Frank RG. Regulation of follow-on biologics. *N Engl J Med* 2007;357:841-3.
7 Sleijfer S, Verweij J. The price of success: cost-effectiveness of molecularly targeted agents. *Clin Pharmacol Ther* 2009;85:136-8.
8 Drug slows early stage arthritis. *BBC News* 2009 Jun 16. http://news.bbc.co.uk/1/hi/health/8102351.stm.
9 Aggarwal S. What's fueling the biotech engine? *Nature Biotech* 2007;25:1097-104.
10 Grabowski H, Cockburn I, Long G. The market for follow-on biologics: how will it evolve? *Health Affairs* 2006;25:1291-301.
11 Sikora K. Paying for cancer care—a new dilemma. *J R Soc Med* 2007;100:166-9.
12 Raftery J. NICE and the challenge of cancer drugs. *BMJ* 2009;338:b67.
13 Datamonitor. *Biogenerics 2005: a new level of complexity*. www.researchandmarkets.com/reports/312417/.
14 Tuck Biogenerics Panel. *Capital markets perspectives*. 2008. http://mba.tuck.dartmouth.edu/cib/PDFs/Butz.pdf.
15 Shapiro R. *Generic biological treatments and the associated cost savings*. 2008. www.sonecon.com/docs/studies/0208_GenericBiologicsStudy.pdf.
16 *Introduction to the pharmaceutical and biotech industries*. London: UBS Investment Bank Equity Research, 2005.
17 Berndt E, Mortimer R, Parece A. *Do authorized generic drugs deter paragraph IV certifications? Recent evidence*. 2007. www.analysisgroup.com/uploadedFiles/Publishing/Articles/PhRMA_Authorized_Generic_Entry.pdf.
18 Yakatan S, Mintz C. Does a biogenerics industry really exist? *BioExecutive Int* 2005;1:2-6.
19 Covic A, Kuhlmann M. Biosimilars: Recent developments. *Int Urol Nephrol* 2007;39:261-6.
20 Royston J. Glycosylation of recombinant antibody therapeutics. *Biotechnol Progr* 2008;21:11-6.
21 Mitchell Crow J. FDA takes tough line on biologic drug. *Chemistry World* 2008 Apr 24. www.rsc.org/chemistryworld/News/2008/April/24040802.asp.
22 Biosimilars "are not the same as generics," MPs told. *Pharma Times* 2008 Apr 10 www.pharmatimes.com/ClinicalNews/article.aspx?id=13237.
23 Mundy A. Generic-drug makers hail Obama budget proposal. *Wall Street Journal* 2009 Feb 25. http://online.wsj.com/article/SB123561281773277865.html.
24 Federal Trade Commission. *Emerging health care issues*. 2009. www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.
25 Shenouda M, Patel R, Elliott J, Smith K, Parekh K. *Political update with Ethan Siegal*. UBS Investment Bank Equity Research, 2008.
26 European Medicines Agency. *Guideline on similar biological medicinal products*. 2005. http://www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf.
27 Wright E. Generic and biosimilar medicinal products in the European Union. *Chemistry Today* 2007;25(2):4-6.
28 European Medicines Agency. *Questions and answers on recommendation for refusal of marketing application for alpheon*. 2006. www.emea.europa.eu/humandocs/PDFs/EPAR/alpheon/H-585-RQ&A-en.pdf.
29 Office of Fair Trading. *Pharmaceutical price regulation scheme*. 2007. www.oft.gov.uk/shared_oft/reports/comp_policy/oft885.pdf.
30 Webb DJ, Walker A. Value-based pricing of drugs in the UK. *Lancet* 2007;369:1415-6.
31 Claxton K, Briggs A, Buxton MJ, Culyer AJ, McCabe C, Walker S, et al. Value based pricing for NHS drugs: an opportunity not to be missed? *BMJ* 2008;336:251-4.
32 European biosimilars' market performance mirrors US legislative progress: slow but steady. *Biopharma Today* 2009 May 19. www.biopharmatoday.com/2009/05/european-biosimilars-market-performance-mirrors-us-legislative-progress-slow-but-steady-.html.

Cite this as: *BMJ* 2009;339:b3276

ANSWERS TO ENDGAMES, p 701. For long answers use advanced search at bmj.com and enter question details

PICTURE QUIZ

An itchy ear that became painful

1 The diagnosis is acute diffuse otitis externa with cellulitis of the pinna.
2 *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the two most likely causative agents.
3 Patients with acute diffuse otitis externa with cellulitis should be treated with oral flucloxacillin, antimicrobial eardrops (such as hydrocortisone and gentamicin drops), and oral analgesics.
4 Referral to secondary care is advised when swelling or debris in the ear canal prevents the admission of eardrops.

STATISTICAL QUESTION

Relative risk reduction and absolute risk reduction

a

CASE REPORT

Persistent diarrhoea in a young woman

1 Irritable bowel syndrome with predominance of diarrhoea.
2 The Rome III criteria encourage clinicians to make a positive diagnosis of irritable bowel syndrome on the basis of validated symptom criteria rather than make a diagnosis of exclusion. Tests recommended by National Institute for Health and Clinical Excellence (NICE) guidelines are a full blood count, erythrocyte sedimentation rate or plasma viscosity, C reactive protein, and antibody tests for coeliac disease (endomysial antibodies or anti-tissue transglutaminase).
3 The presence of alarm signs warrants further evaluation. Such signs include rectal bleeding, short history of symptoms, documented weight loss, nocturnal symptoms, male sex, family history of colon cancer, recent use of antibiotics, and age greater than 50 years.
4 Treatment relies on a strong doctor-patient relationship and pharmacotherapy aimed at symptom control. New drugs include lubiprostone, a selective C_2 chloride channel activator, for the treatment of irritable bowel syndrome with constipation, and alosetron, a $5HT_3$ antagonist, for the treatment of irritable bowel syndrome with diarrhoea.