MAGIC BULLETS WITH A HEFTY PRICE TAG

Sales of monoclonal antibodies are projected to reach more than $160bn in the US alone over the next few years, so is it any wonder that drug companies fiercely protect their profits? **Allen Shaughnessy** considers why these drugs are so eyewateringly expensive

The drug industry just doesn't feel the love these days. Mistrust abounds among the general public as well as within the medical industry. It's no surprise, then, that eyebrows raise and fingers point when a company withdraws an effective drug from the market shortly after proof is published of its benefit in a completely new treatment arena. What is it up to?

Alemtuzumab is a monoclonal antibody marketed to treat chronic lymphocytic leukaemia. It has also been used, off-label, for multiple sclerosis, and last month two phase III studies were published showing its efficacy and superiority over interferon beta-1a.[1] The US Food and Drug Administration and the European Medicines Agency are considering approval for this indication.

By now many patients with multiple sclerosis should be taking the drug, even though it hasn't yet been sanctioned for this use by regulatory agencies. But Genzyme, a Sanofi company, withdrew it from the market two months before these studies were published. Some predict that once it is approved for multiple sclerosis alemtuzumab will be re-released under a new brand name (and at a much lower dose than that used for leukaemia), this time at a much higher cost.[2]

From a business perspective, this move makes sense. The cost of Campath, the brand name for the leukaemia version, was about $60 000 (£37 000; $46 000) a year. Lowering the dose to that used to treat multiple sclerosis would have reduced the price to $6000 a year.

This would have been a bargain basement price for immunomodulator treatment of multiple sclerosis. Natalizumab, another monoclonal antibody used for multiple sclerosis, is about $55 000 a year.[2]

While it might be a boon for patients and their healthcare payers, it does not make fiscal sense to produce a medicine that has been shown to be superior to existing treatments at a lower cost than the current price point. Corporations, including drug companies, are fiduciaries of shareholders and have a legal requirement to maximise the return on their investment.

Perhaps the manufacturer is taking its cue from Genentech, a subsidiary of Roche Pharmaceuticals, which sells bevacizumab for colon and other cancers and ranibizumab to treat patients with age related macular degeneration.

Although ranibizumab has theoretical advantages, and bevacizumab is not licensed for macular generation, clinicians around the world use bevacizumab rather than ranibizumab for the eye disorder because it is much cheaper. The cost differential was so striking that one primary care trust authorised the off-label use of bevacizumab rather than pay for the higher priced option, reversing its stance only after the company offered price concessions.[3]

Yet it seems inherently unfair to take a product, lower the dose, and inflate the cost several orders of magnitude. The uniqueness of monoclonal antibodies and the complexity of their development and production are touted as reasons why these products are so expensive. But is it really justified?

Monoclonal antibodies: new way to treat disease

In the late 1800s Paul Ehrlich, the German scientist and physician, imagined the development of a "magic bullet" that would selectively target a disease causing organism. Monoclonal antibodies could be the quintessence of his dream since it is possible to produce one that binds uniquely to almost any substance.

Sometimes monoclonal antibodies are used to stimulate the immune system to recognise the cell as foreign. In other situations they can block specific cell receptors required for tumour growth. They can even be used as radioimmunotherapy, delivering radiation to specific cell targets.

The first commercially marketed monoclonal antibody was muromonab-CD3, released in 1986 and used to suppress T cells to prevent rejection of organ transplants. Currently over 20 monoclonal antibodies are used as medical treatments for conditions ranging from cancer to autoimmune diseases to extremely rare inherited disorders. Monoclonal antibodies are also used for diagnostic testing—for example, home pregnancy tests use this technology.[4]

Even though the antibodies are highly targeted, they can often be used for different disorders that share the same pathology. For example, bevacizumab exerts its effect in patients with colorectal cancer by blocking the ability of vascular endothelial growth factor A to stimulate angiogenesis, which is required to support tumour growth. When injected into the eye, this same mechanism prevents the abnormal growth of blood vessels that results in age related macular degeneration and diabetic retinopathy.

Monoclonal antibodies are specifically produced from a single, cloned B lymphocyte cell line (hence "monoclonal"). To start the process, a mouse or rabbit is injected with an antigen that will stimulate B cells to produce an antibody specific to that antigen (each B cell produces an antibody to a single antigen). These B cells are collected from the spleen of the mouse and mixed with myeloma cells, which grow continuously. This mixture is chemically manipulated to fuse the B cells with the myeloma cells, forming "hybridomas." Antigen screening is used to select the hybridomas that produce the right antibody, and these can then be cultured indefinitely in large bioreactors.

Multiple sclerosis occurs when T and B lymphocytes mistakenly attack the myelinated axons in the central nervous system, destroying the myelin and axon to varying degrees. Alemtuzumab targets T and B lymphocytes while

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Monoclonal antibodies in numbers

$30bn: the combined revenue from the top 12 biological products in the United States in 2010

453%: expected increase in US sales of the above top 12 from 2010 to 2014. It will bring annual revenues to $166bn, comprising about 30% of the branded prescription drug market

$200 000: average cost of treating a patient for a year with one of the top nine biologicals in the US

$409 500: average cost per year for the average patient on the most expensive drug in the world, eculizumab, used to treat paroxysmal nocturnal haemoglobinuria

$2: average raw material cost per gram of product produced

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sparing other immune system elements. The antibody binds to the CD52 protein found on the surface of mature lymphocytes but not the stem cells that produce them. After treatment, these CD52 lymphocytes, now tagged with the antibody, are destroyed by the immune system. Depletion of these lymphocytes is pronounced and long lasting, with a median recovery time to normal levels of 35 months.

How good is the evidence?

Two recently published phase III studies have shown that alemtuzumab is effective in patients with relapsing-remitting multiple sclerosis. The studies, called Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS I and II),[5 6] enrolled previously untreated patients with low disability levels (CARE-MS I) and patients with a history of disease activity despite immunomodulator treatment (CARE-MS II). Alemtuzumab was more effective than interferon beta-1a in preventing relapses over the two years of study, producing a 54.9% improvement in previously untreated patients and 49.4% improvement in patients who had had treatment. In patients with more advanced disease, alemtuzumab also decreased the number of patients experiencing sustained accumulation of disability (hazard ratio 0.58, 95% confidence interval 0.38 to 0.87).

Treatment is not without risk. Immunosuppression related infections occur with alemtuzumab. In the CARE-MS I study, infections occurred in two thirds of alemtuzumab treated patients compared with 45% of patients treated with interferon. Herpes infection was also common (16-18%) despite antiviral prophylaxis in the CARE-MS I study.

Almost all patients receiving alemtuzumab experienced infusion related reactions despite pretreatment with high dose methylprednisolone. Other adverse effects reported in the studies were immune thrombocytopenia (1% in CARE-MS I) and thyroid disorders.

Why so expensive?

The top 12 biological products in the United States brought in combined revenue in 2010 of $30bn. By 2014, sales are expected to increase to $166bn, comprising about 30% of the branded prescription drug market.[7]

The average cost for the top nine biologicals is more than $200 000 a year in the US.[8] The most expensive drug in the world is eculizumab, used to treat the extremely rare paroxysmal nocturnal haemoglobinuria, which affects about 5000 patients in the US and 1000 in the UK, costing a whopping $409 500 a year for the average patient.

Monoclonal antibodies are so expensive in part because of the cost and complexity of manufacture, the need for relatively high doses, and the price point set by early innovative treatments. Although raw material costs are low—$2 per gram of product produced[9]—the process itself is extremely expensive. A typical production run takes 10-14 days and may produce only 5-25 kg of antibody. The process involves 10 distinct steps, from initial culture of the cells through three separations to isolate the antibody.[9] Royalties, research and development, and marketing costs add to the overall price. However, as the scale of production has increased over the past decade, production costs have decreased by two thirds.[9]

Governments in the US and UK have taken different approaches to dealing with the high cost. Since it is almost impossible to make the exact replica of a monoclonal antibody in a different processing plant, US lawmakers passed legislation in 2010 to promote competition in biological drugs by allowing "biosimilar" products to be marketed after the patent period. This ruling allows for production of generic monoclonal antibodies.[10] Given the cost and complexity of developing and manufacturing these drugs, though, the price reductions are expected to be in the range of 20-30% rather than the 80% reduction that occurs when generic versions of typical medicines are marketed.[11]

End result versus perceived value?

If I need to keep track of time, I can buy a watch on a street corner in downtown Boston for $15 or a branded "tourbillon chronometer" for several thousand dollars (or much more). Both tell the time as accurately as I need, neither will turn my wrist green, and, at a casual glance, both look like a typical watch. Yet my perception of the pricey watch is that its components and assembly are much more costly than those of the cheaper one. If I were to find out that both had essentially the same internal movements, I would be much less likely to fancy the expensive timepiece.

Had alemtuzumab not been previously available for the treatment of cancer at a lower price, there would have been no expectation regarding its cost, other than it would be in the range of existing multiple sclerosis treatments.

How do we decide what a product is worth? It is a human perversity that we are willing to pay a lot for something—until we know the cost of production. Then, we resent paying more, despite the fact that the product still is useful to us.

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Surplus of cash or deficit of ideas?

What are they?

Personal budgets were first introduced for social care in 1997 and are used by over 125 000 people in England.[1] Local councils give users a means tested sum of money to spend on care of their choice, as an alternative to existing social care packages. The Department of Health now wants to use personal budgets in healthcare, initially for people who need long term NHS community care.

In social care, the sum of money goes directly to users to spend as they wish. Although direct payment may be offered to some users of NHS personal budgets, for others the primary care trusts or clinical commissioning groups will hold the budget and approve or reject users' plans for the money.

Why is this in the news?

Lord Darzi's 2008 review, *High Quality Care For All*, first mentioned personal health budgets "to give individual patients greater control over the services they receive."[2] Since 2009, they have been piloted in 64 primary care trusts for people with long term conditions and for preventive measures, maternity care, and end of life care. A three year study of the pilot schemes was published on 30 November, and on the same day Norman Lamb, the care minister, announced that the Department of Health would spend £1.5m (€1.8m; $2.4m) on rolling out the scheme to another 56 000 people.[3]

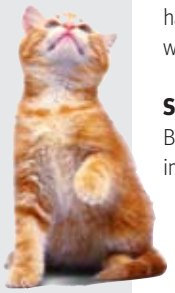
What "services" can be received?

The bad news is that the budget cannot be used instead of general practice or emergency services, or to fund part of a treatment that a patient is paying for privately. Also, it cannot be used for alcohol, tobacco, gambling, debt repayment, or any illegal activities. Otherwise, the definition of service depends on the primary care trust panel and could include[4] a football season ticket or personal trainer (see box for full list).

Have you confused the question with your Christmas wish list?

No, really, they were all approved by panels during the pilot studies. Actually, driving lessons were probably approved by a steering group. Flippancy aside, the three most common uses for the budget were for paid carers, physical exercise, and alternative therapists.

- Neurolinguistic sessions
- Laptop computer
- Acupuncture
- Gym membership
- Personal trainer
- A cat
- Reiki
- Manicure
- Theatre trip for two
- Mobile phone
- Football season ticket
- Driving lessons



Who else has tried them?

The Dutch have had personal budgets since 1997 for long term care but they exclude medical and alternative therapies. Most budget holders there are satisfied with the scheme, and there is a waiting list of people wanting to use it. However, costs in people with personal budgets seemed to rise much faster than in people with conventional care.[5] A literature review of studies in the United States, Canada, the Netherlands, Germany, and England by the Health Foundation found no evidence that personal budgets increased value for money or led to better health outcomes.[6] Budget holders did seem to feel more empowered and confident, though.

Do they help people get better?

Independent researchers carried out an evaluation after one year in 2235 recruits in 20 primary care trusts.[3] They compared people holding personal health budgets with people getting conventional care. Mortality seemed to be a third higher in the budget holders. Reassuringly this was not because personal health budgets are lethal but because budget holders tended to be in poorer health at baseline. The budgets did not make any difference to proxies for clinical outcomes, such as glycated haemoglobin concentration in people with diabetes.

So do they help with anything?

Budget holders had a "significant improvement" in subjective wellbeing and happiness compared with those getting conventional care.[3] Oddly enough, those whose budget was over £1000 a year were even more satisfied, but the results were significant only at the lesser used 90% confidence interval.

Won't this cost more money?

With even less than 90% confidence, the Department of Health thinks that "if half of the people eligible for NHS Continuing Healthcare chose to take the offer of a budget, this could imply a potential saving of around £90m."[7]

The evaluation report suggests this could be true only if the correct half of people take up the budget, if they do not use any existing services, if there are no set-up costs, and if we accept that 90% confidence interval.

An interim evaluation found that setting up personal health budgets cost each primary care trust an average of £93 280 in the first year.[8] Nationally, set-up costs would total £14m—or 300 000 acupuncture sessions. Ongoing costs are predicted to be substantially less though.

What did the users think?

Interviews showed that users who had had budgets for nine months still did not understand some minor details[4]:

"I didn't actually see anybody that worked for the, whoever gives the personal health budget out. I never saw anybody from any department anywhere. I don't even know whether it's a government fund or what. No idea," said one user.

Another person didn't realise the budget was personal: "I'm a bit scared really, 'cos somebody else who could be in a position where they need summat and I'm taking money away from it and it could put them at a loss."

Others "felt that they had run out of ideas and struggled to think of alternatives that they really wanted to spend the budget on (at the extreme, one woman had had 11 requests refused)."

Allocating a budget could even deplete bank accounts: "The budget was paying for driving lessons but the participant did not have a provisional licence and ended up paying for this themselves. In doing so, however, they had become overdrawn at the bank."

Surely there were some positive comments?

The majority of users preferred personal health budgets, and the unconventional purchases had been beneficial. One wheelchair user had bought a laptop to "improve speech and language" and also found "unforeseen social interaction benefits" because he could now see friends and family using Skype. Another, with a football season ticket, found it did him "a world of good" compared with "taking pills prescribed by the GP."

Some users even thought they were using NHS services less often, such as one man who used his budget to access a gym. He said as a result there were "Reductions in attending doctors . . . hospital visits and medication. All have gone down . . . The way I've looked at it . . . I've cut my . . . doctors' attendances by something like 80%."

So an Apple (Macbook) a day keeps the doctor away?

Indeed.

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- Feature: Lifebox: Make it zero (*BMJ* 2012;345:e8241)
- BMJ blog: Sophie Reshamwalla: Lifebox—is that the pulse oximeter charity?
- Digital map of where Lifebox oximeters have been distributed: http://bit.ly/UWqzWE

The difference a donation makes

Atul Gawande, writer, and surgeon at Brigham and Women's Hospital in Boston, US, is also chair of Lifebox, chosen as the *BMJ*'s Christmas charity. Jane Feinmann asked him just what a *BMJ* reader donation means

There are 20 national and international anaesthesia societies and associations backing the Lifebox campaign. Why are anaesthetists so passionate about these devices?
Pulse oximetry has enormous symbolic as well as practical value for anaesthetists in the West. The technology is a key component in the revolution in anaesthesia care over the last generation that has brought down the death rate from anaesthesia by over 95%. Anaesthetists were pioneers in bringing concepts of patient safety into medicine, and the oximeter is emblematic of these improvements. These advances, not just in technology but also in ideas, have not made their way into low income countries or even, in many cases, into middle income countries, where most anaesthetists are not doctors but medical officers with more limited training and much lower professional status and do not have the voice to make changes. The enthusiasm for Lifebox is because it is working to bring about the technological and cultural advances in safety that have not so far occurred in over 70 000 operating theatres in the world today.

What was the effect of the introduction of pulse oximetry in high income countries?
Before pulse oximeters were introduced, 1 in 5000 general anaesthetics resulted in the patient dying, with hundreds of deaths, often of perfectly healthy people, every year. Surgeons commonly told the patient: "Don't worry about the surgery; it is the anaesthesia that is the risky part of the operation." That was no longer true by the late '80s. By then, pulse oximetry, together with better monitoring of the patient generally, had brought mortality from anaesthesia down to 1 in 100 000 operations.

Will the effect of Lifebox be as dramatic in low income countries?
It is already happening. If all we were doing was parachuting in a bunch of pulse oximeters, we wouldn't have such a tremendous impact, but we work with local

"As part of the distribution of equipment we organise training in pulse oximetry, safe surgery, and emergency obstetrics"
Atul Gawande

anaesthesia societies and ministries of health to identify the need for pulse oximeters and then help deliver these where they will be appropriately used. As part of the distribution of equipment we organise training in the use of pulse oximetry, safe surgery, and emergency obstetrics. Six months later, we've shown, the devices are still in use and the knowledge received during training has been retained.

Poor countries struggle to afford basic healthcare. Shouldn't *BMJ* readers be funding immunisation rather than a luxury such as pulse oximetry?
Several studies show that the cost effectiveness of emergency surgery, notably after road traffic incidents or in obstetrics, is as high or higher than that of vaccines in low income countries. Bear in mind that road traffic incidents are now one of the top five killers in the developing world, with cardiac disease replacing respiratory disease and malnutrition as the number one cause of death in Asia and Latin America. With a Lifebox oximeter costing about 10% of the normal price of a theatre monitor, making surgery safer costs pennies per patient at an incredibly high risk moment of people's lives.

At £160, the Lifebox pulse oximeter is considerably more expensive than the FDA approved and CE marked "high quality" devices that sell online for £20 or so. Why is this?
Those inexpensive devices are "spot" pulse oximeters. They're not designed for continuous monitoring; nor do they have a pulse tone or an audible alarm that sounds when the heart rate or oxygen levels deteriorate. As well as meeting the minimum specifications for the provision of safe oximetry in the operating theatre, Lifebox oximeters can withstand extreme heat and cold, the battery is functional for at least 12 hours, and they can be dropped from table height without breaking. There is a serious problem with medical equipment in low resource countries that breaks down soon after arrival—the Lifebox oximeter is optimally designed for the needs of that environment.

What was the effect of last year's *BMJ* donation?
It was a really extraordinary injection of funds—more than £33 000, allowing us to distribute oximeters in Bangladesh, Cambodia, Cameroon, Nepal, Nicaragua, Papua New Guinea, Sierra Leone, and Uganda. It funded 210 pulse oximeters directly and put training into these places. In 2012, we went from providing training and oximeters in one country, Uganda, to doing the same in 10 countries by the close of this year. There was an indirect result that the *BMJ* campaign bought us—credibility with other non-governmental organisations. We have partnered several groups that have allowed us to take the programme to multiple other places, ranging from Honduras and El Salvador to Eritrea and Ethiopia. Our whole organisation could not be more grateful.

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To donate to Lifebox go to www.lifebox.org/donations or use the coupon on p 11.

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