

bmj.com

► Feature: Will industry influence derail UN summit? (*BMJ* 2011;343:d5328)

bmj.com/blogs

► The final declaration for the UN summit on NCDs

doc2doc Discuss this feature on BMJ Group's diabetes forum <http://bit.ly/iJA8uP>

THE PRICKLY PROBLEM OF ACCESS TO INSULIN

Insulin remains unaffordable in many countries even though it is no longer protected by patents. **Deborah Cohen** examines why

For some parents in parts of Africa, having a child die from diabetes is a relief. They no longer have to foot the bill for insulin, which means they can pay to send their other children to school. It's a story that Jean-Claude Mbanya, professor of medicine and endocrinology at the University of Yaoundé, Cameroon, and president of the International Diabetes Federation, hears during his clinics—and one that is probably not specific to diabetes. But nearly a century after the discovery of insulin, the price remains alarmingly high.

Much has changed since insulin's discovery in the 1920s, when scientists Frederick Banting and Charles Best isolated it from the pancreas of dogs. It was a feat that persuaded its discoverers to license the process free of charge to approved manufacturers—insulin was seen as a gift to humankind rather than an opportunity for commercial profit.¹

But millions of people in poorer countries are unable to claim this gift—manufacturers charge for it, and it comes with too high a price attached.

In most high income countries the state or health insurance company pays the bill. But people in low and middle income countries have to pay out of their own pockets. The effect of a diagnosis of diabetes on household spending in many parts of the world is dramatic. A study in Malawi found that one month's supply of insulin

(purchased from a combination of public and private vendors) cost almost 20 days' wages.²

For people with type 1 diabetes, unavailability is immediately life threatening. The life expectancy of a child with newly diagnosed type 1 diabetes in much of sub-Saharan Africa varies between 7 months and 7 years, depending on the country.³

But insulin is increasingly used in type 2 diabetes—and it's this type of diabetes that is rapidly increasing in low and middle income countries. National figures collated by the International Diabetes Federation show diabetes now affects 3.3% of 20 to 79 year olds in Mali, 7.1% in India, and 10.6% in Jamaica.⁴

“Soon, four out of every five people with diabetes will live in developing countries. And the men and women most affected are of working age—the breadwinners of their families,” Professor Mbanya says.

World governments are attending a UN high level meeting in New York this month to agree action on non-communicable diseases. Diabetes is just one of the chronic illnesses to be considered at this event—others are cardiovascular disease, respiratory illness, and cancer.

Two weeks before the meeting a hard fought political declaration was eventually agreed. The hardest bargaining was done over trade flexibilities to measures governing intellectual property (known as trade-related aspects of intellectual property rights or TRIPS).⁵

Unlike the case in HIV/AIDS, however, intellectual property is not the main issue standing in the way of cost effective, evidence based diabetes care in low and middle income countries. A range of other factors is in play. The medicines that the World Health Organization deems essential for treating diabetes, such as metformin, sulphonylureas, and human insulin, are off patent.⁶ Newer



Frederick Banting and Charles Best isolated insulin from the pancreas of dogs

analogue insulins—which companies are keen to promote and which have contributed to the rise in the unit cost of insulin in the UK⁷—are still patented but are not recommended as first line treatment in type 2 diabetes by WHO⁶ or the UK's National Institute for Health and Clinical Excellence.⁸

Cost effective prevention, treatment, and care are key components of the final UN declaration that world governments will commit to when they meet in New York this month. They will also pledge to provide sustainable access to medicines and technologies “including through the development and use of evidence-based guidelines for the treatment of non-communicable diseases” and via “efficient procurement and distribution of medicines.” As well as implementing viable financing options, governments will say they will promote the use of affordable medicines,

This month the United Nations will stage its first summit looking at the world epidemic of non-communicable diseases—in particular, cardiovascular disease, cancer, diabetes, and chronic obstructive pulmonary disease (*BMJ* 2011;342:d3823). This article is part of the *BMJ*'s pre-summit coverage, looking at the risk factors linking these diseases.

including generics, which are generally between 1.3 and 3.5 times cheaper than originator (branded) products.⁹

But for diabetes there are obstacles to achieving these aims. Although there are some generic human insulins, substantive competition—in the form of a global generic market—has not occurred. Three major Western companies—Eli Lilly, Novo Nordisk, and Sanofi Aventis—have captured the diabetes market in the low to middle income countries such as the Philippines and Kyrgyzstan. Even Lars Rebien Soerensen, chief executive of Novo Nordisk, this month agreed that most low and middle income countries pay too much for the medicines. His explanation was that they order relatively small amounts and few manufacturers bid for the tenders.¹⁰

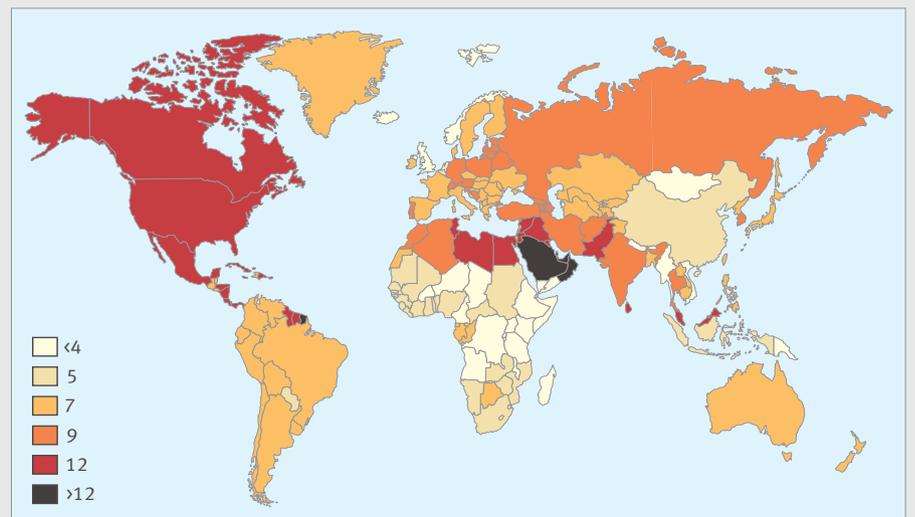
Even in countries that have a vibrant generic industry, such as India, competition to the main three insulin manufacturers has failed to take off.

Amit Sengupta, a general physician in Delhi and a member of the People's Health Movement, a global alliance of health activists, explains: "Most medicines used in India are generic—approximately 90% of the market is generic. But with insulin this isn't the case. The three main branded companies [Eli Lilly, Sanofi Aventis, and Novo Nordisk] occupy 90% of insulin market." He attributes the failure of generic manufacturers to compete in the insulin market to marketing and funding of medical education.

"Prescribers believe that generic insulin is substandard. They feel that there needs to be tighter control of insulin as the range for making a mistake is smaller. Insulin produced by 'big pharma' in foreign countries is seen as better," he added.

Cognisant of the appeal of branded drugs, one major Indian generic producer, Biocon has teamed up with Pfizer to commercialise generic versions of insulin and insulin analogue products. The result will be "branded generics."¹¹

Percentage of people with diabetes (20-79 years), 2010⁴



Source: IDF Diabetes Atlas

The regulators

But if governments are to sign up to a commitment to good quality generics, they need to ensure consumer confidence in the drugs. Countries with scarce resources often rely on regulators in developed countries to assess the quality of generic medicines when they come on to the market. Because insulin is a protein and considered "biological," the pathway for market approval differs from that for other generic drugs. But until recently the European Medicines Agency had no specific guidance for manufacturers of generic insulin or "biosimilars."

And the US Food and Drugs Administration is still finalising its guidance. In 2007, a debate over generic insulin erupted in the US. Concerned that the lack of a generic market meant insulin costs were spiralling, members of the public and state governors urged Congress to pass legislation requiring the FDA to issue guidance for generic insulin manufacturers—this was despite

objections from Eli Lilly and Novo Nordisk.

A petition from the state governors highlighted that the EMA had produced guidance in 2006.¹² However, according to EMA, no generic insulin has yet been approved in Europe, and there have been only three applications from one generic insulin company, Marvel LifeSciences. The applications were later withdrawn following concerns about the evidence submitted.¹³

Prequalification

But concerns over the quality of generics put resource poor countries without established regulatory agencies in a bind, since they have no means to address these concerns.

Back in 2001, faced with an escalating AIDS epidemic, unaffordable branded antiretrovirals and a market influx of generic medicines of unknown quality, aid agencies and poor countries turned to WHO for advice. The generic antiretrovirals were unable to get regulatory approval from the FDA, EMA, or other national regulatory bodies because the original drugs were still under patent—and companies at the time capitalised on fears about quality.

WHO stepped in to act as a regulator, drawing in expertise from its contacts in national agencies under what they called the "prequalification scheme." The result has been affordable quality controlled generic antiretrovirals in low income countries. Other medicines have gone through this scheme too. But the priority so far has been infectious diseases—such as tuberculosis, malaria, and influenza. Insulin has not yet been evaluated.

David Beran, project coordinator for the International Insulin Foundation (www.access2insulin.org), who has undertaken standardised health systems assessments in six low income countries, says that wherever he travels, prequalification comes up. "Countries may have generic policies,

ANALOGUES VERSUS HUMAN INSULIN

Some insulins are more affordable than others. According to WHO, in the run-up to the UN summit, questions have been raised by low and middle income countries about the role of insulin analogues compared with human insulin.⁶

Not everyone agrees which should be used. A 2011 WHO analysis suggests that analogues are not cost effective compared with human insulin and the cost per quality adjusted life year (QALY) varies dramatically.

"Given the lack of clear benefits for analogue insulins for glycaemic

control as well as the inconsistent and clinically debatable benefits for occurrence of hypoglycaemia, along with concerns about trial quality, the current evidence does not indicate a strong advantage for analogue insulins compared to regular human insulin for both type 1 and 2 diabetes," it says.⁶

Some countries, such as Germany, have refused to reimburse the cost of analogues.

But the IDF's recommendations, last updated in 2005 by Professor Philip Home from Newcastle University, suggest trial analogues are better. They say that when



starting insulin use a basal insulin once daily such as "insulin detemir, insulin glargine [analogue insulins] or NPH insulin [human]," arguing that the risk of hypoglycaemia is higher with human insulin.²⁵

Tanzania Diabetes Association diabetes centre sponsored by Novo Nordisk. The inauguration was performed by Lars Rebieen Soerensen, (right)



Lars Rebieen Soerensen, chief executive of Novo Nordisk, manufacturers of insulin



Jean-Claude Mbanya, president of the IDF and professor of medicine, Cameroon



Sir Michael Hirst, president-elect of the IDF and chairman of Pagoda PR company



Kaushik Ramaiya, a consultant physician and the general secretary of the Tanzania Diabetes Association

but they don't know what they're getting if generic companies offer insulin," he says.

For insulin to get on to the prequalification list the evaluation has to be financed. But WHO is under huge financial pressure. Sources have suggested that there were discussions about funding but it has proved to be a sticking point.

"People think of type 1 diabetes when you talk about insulin and they will think, 'Why do we need to deal with this? It's not as big a problem as some of the other diseases.' For the likes of many infectious diseases, the Global Fund will guarantee purchases of drugs and so there is an incentive to get things prequalified," Dr Beran says.

Novo Nordisk's chief executive has his own view on what WHO should do. "If WHO, and the global community, is concerned about the poorest countries' access to insulin, why don't they buy it on behalf of the poorest countries?" Mr Soerensen said in September. "We'd be tickled pink."¹⁰

Increasing use of insulin

As cheap insulin is difficult to access in many parts of the world, there are questions over whether it is the best first line treatment. Until recently, type 2 diabetes was largely treated with oral glucose lowering drugs rather than insulin. Cheap sulphonylureas and metformin are readily available and, according to one global price indicator guide, cost between \$0.1 (£0.06; €0.07) and \$0.62 a month without taxes and duties. This compares with \$4.20 for insulin.¹⁴

Oral glucose lowering drugs don't have the

same quality assurance difficulties as insulin. Nor do they need the expensive needles, syringes, and glucose testing strips. A study in five low and middle income countries found that in some places syringes were the most costly part of diabetes care for patients.¹⁵

Nevertheless, there is an industry supported push to intensify use of insulin to treat type 2 diabetes in sub-Saharan Africa. For example, Novo Nordisk's sponsored recommendations to the Diabetes Leadership Forum in Africa in 2010 said that: "Intensifying treatment [in type 2 diabetes] improves the quality of life as patients can expect more than one extra year of life without complications and insulin treatment was found to reduce complications associated with diabetes."¹⁶

However, four recent meta-analyses of intensified glucose control conclude that the macrovascular and microvascular benefits of intensifying treatment in type 2 diabetes are still up for debate.¹⁷⁻²⁰ And many people's diabetes will be controlled with oral drugs. Despite the uncertainty, a recent survey by Novo Nordisk in India found that almost all respondents agreed that insulin use reduced diabetic complications and was a better treatment than oral medications.²¹

The Novo Nordisk website for Indian doctors counsels them to alert patients newly diagnosed with diabetes to expect to use insulin. "The need for insulin is an almost inevitable result of the progressive nature of type 2 diabetes," it says, adding: "To help overcome the reluctance to start insulin, it is important that patients understand

the natural course of diabetes. If they understand the way that the disease progresses, they will realise that oral agents alone will not be enough to control blood sugar."

Professor Mbanya, however, says other factors need to be taken into account. "If patients have to pay for their own treatment, you need to think about the cost. If they can't afford insulin and they have type 2 diabetes, then don't start them on it," he says.

Conflicts of interest

But if insulin is being used to treat the burgeoning diabetes epidemic, there should be more incentive to guarantee affordable access.

Unlike the strident HIV lobby calling for access to essential medicines, the push for affordable insulin has been muted. The main representative of people with diabetes on the global stage is the International Diabetes Federation (IDF), which some critics suggest may be restrained by its supporters.

Although the federation does much good in improving diabetes services globally, it receives funding directly from the major drug companies, through sponsorship of its conferences and support for its projects. Its 2010 annual report says that its "global partners" are Novo Nordisk, Eli Lilly, and Sanofi Aventis and lists other companies that contribute. There are no specific details about amounts.²²

The companies do support the IDF's good work. In many low income countries, its member

associations provide insulin, drugs, and technologies free of charge or at subsidised prices. But one critic has commented that this puts drug companies at the dual advantage of looking good for marketing purposes and placing them in good stead for purchases if money does become available.

"In such contexts the care and diabetes education provided by our associations is the only diabetes service available. IDF's Life for a Child Programme provides insulin and other diabetes supplies free of charge to vulnerable children with type 1 diabetes," a spokesperson for the IDF says. The programme supports 7000 children with diabetes until they reach 23 years old.²³

"We want to ensure that the safest and most proven medicines are purchased at the lowest possible prices and improve drug distribution systems to ensure continuity in the availability of essential diabetes medicines," she added. And in line with the political declaration, this is a more reliable and sustainable way of tackling the problem than drug donations.

But not everyone is convinced they have taken a tough enough line. "For IDF one issue is conflict of interest. They get funding from several different drug companies and this is an issue for access to medicines. So are there competing agendas? They have yet to come out strongly about access to insulin. Is it a case of 'You don't bite the hand that feeds you?'" Dr Beran says.

And one conflict of interest within the IDF that may be difficult to reconcile is that its president elect, Michael Hirst, is chairman of

public relations company Pagoda PR,²⁴ which represents Novo Nordisk and Roche Diagnostics.²⁵

Role of analogues

Access to affordable medicines may also be hampered by the need for companies to maintain their market share of patented drugs. When the use of generic insulin was mooted in the US back in 2007, Novo Nordisk's president, Martin Soeters, said that, although he expected to see inexpensive generic human insulin on the market in 2008 or 2009, "the new generation of insulins is so clearly superior and there is such a change in attitude by doctors and patients toward it that they will not go back." And by the time the patents on the analogues expire he said that Novo would already have its next generation insulin products on the market.

Indeed, WHO says some countries are spending substantial proportions of their drug budget on analogue insulins.⁶ And an International Insu-

lin Foundation report shows that Kyrgyzstan, for example, now spends 57% on analogues.²⁸

Sensing the market potential in countries with growing type 2 diabetes problems, companies seem keen to introduce the patented analogue insulins to low and middle income countries and are recruiting large numbers of patients and doctors into research studies.

Novo Nordisk is currently running the "largest ever observational study" in low and middle income countries. The study, given the name A1CHIEVE, has recruited over 60 000 participants in 28 countries and, according to a press release, "involves more than 3300 physicians."

The protocol describes A1CHIEVE as a 24 week, international, prospective, multicentre, open labelled, non-interventional study in people with type 2 diabetes previously treated with other anti-diabetic medication.

The study focuses on the "safety and efficacy of insulin analogues in less well resourced countries," says Professor Home, the lead investigator. "We are also interested in baseline data to capture information on the circumstances of people starting insulin or insulin analogues."

Commenting on the study, Patrick Loustau, senior vice president of global marketing at Novo

Nordisk, told investors: "To do our job well, we need to know everything there is to know about these groups of people."²⁹

"NN [Novo Nordisk] is traditionally a much more global company than other insulin manufacturers, and is therefore more alert to the

shift of medical expertise interest and resources from the West," Professor Home told the *BMJ*.

Keeping out the generics

And Novo Nordisk is determined to hang on to its global reach. A position paper on essential medicines from the NCD Alliance, a federation of societies representing people with chronic diseases, called for "fair competition"¹⁴—but it will be difficult for any newcomers to compete. Rather than lose market share to generics, Novo Nordisk offers human insulin to countries such as India at prices "that cannot be met by generic human insulin producers."³⁰

Novo Nordisk also offers human insulin to the poorest countries through its LEAD scheme. Under this initiative, insulin is offered to the least developed countries—as defined by the UN—at prices not to exceed 20% of the average price in North America, Europe, and Japan.

But to date, this pricing scheme is available

only to public hospitals and non-governmental organisations. Patients often have to buy insulin from private pharmacies because of insufficient stock, and then they have to pay the full price.

Developing countries are open to the use of generic insulin. Tanzania, for example, operates an open tendering process to supply the insulin used in government hospitals. It uses human insulin supplied by Novo Nordisk supplied at \$4.20 per vial. According to Kaushik Ramaiya, a consultant physician and the honorary general secretary of the Tanzania Diabetes Association—which operates clinics throughout the country funded by Novo Nordisk—says generic companies have bid, but their price is often no cheaper. "If the costs of generics were lowered, there wouldn't be a problem," Dr Ramaiya says.

But it's not just price and quality that generics are competing on; they have to take on the marketing expertise of the main manufacturers. "In government tendering schemes, generic companies have the added disadvantage of brand recognition," Dr Beran says.

Drug companies must take much of the blame for the costs of drugs, but governments need to share their responsibility—as do the manufacturers of devices needed by insulin users, which are often the most expensive part of treatment. Any reductions that governments receive need to be passed on. In some countries, drugs are taxed or prices are marked up, so lower prices do not necessarily reach patients.

This is something the IDF does speak out about. "We want governments to do whatever is needed now to fulfil their human rights obligations to guarantee access to diabetes medicines and technologies," a spokesperson says. "All governments must reduce barriers to access including tariffs on essential NCD [non-communicable disease] medicines and technologies, inefficient and inadequate procurement, and poor distribution."

Once governments have signed up to the UN declaration that includes access to medicines, cost effective treatment, and evidence based guidelines, it's up to all those who represent people with diabetes to hold them to account.

Deborah Cohen, investigations editor, *BMJ*, London WC1H 9JR, UK dcohen@bmj.com

Competing interests: The author has completed the ICMJE unified disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from her) and declares no support from any organisation for the submitted work; DC has received travel expenses from WHO to speak at a WHO training session for young journalists; she has no other relationships or activities that could appear to have influenced the submitted work.

Publisher's competing interests: The BMJ Group receives funds in the form of unrestricted educational grants from Novo Nordisk, Eli Lilly, and Sanofi Aventis, which produce human and analogue insulin.

Provenance and peer review: Commissioned; externally peer reviewed.

References can be found on bmj.com.

Cite this as: *BMJ* 2011;343:d5782

COMMENTARY

Politics of affordable insulin

The diabetes pandemic increasingly affects low and middle income countries, where most of those affected have type 2 diabetes. Cheap generic versions of current first line treatments, metformin and sulfonylureas, are widely available so why does this not apply to insulin?

Human insulin is off patent, is relatively simple to manufacture, and WHO recently included it in its list of essential medicines in preference to analogue insulin.¹ Generic biosynthetic human insulin would bring down the price of insulin, and several companies have the capacity to produce it, but progress has been confounded by claims that branded analogue insulins—which are typically two to four times the cost of branded human insulin—are better treatment.

This claim does not relate to biological action, for the analogues are simply delivery systems designed to speed or smooth the rate at which insulin reaches its receptor from the injection site. Although these properties are valuable in some situations, Cochrane type reviews of the use of human and analogue insulins have found limited evidence of benefit in type 2 diabetes^{2,3} and NICE has reaffirmed that human insulin should be considered first line therapy in this condition.² Only one study, on people with type 1 diabetes, has compared analogue and human insulin in double blind fashion. This found no change in haemoglobin A_{1c} and a small reduction in nocturnal hypoglycaemia. The participants were unable to tell the insulins apart at the end of the study and expressed no clear preference either way.⁴ In the absence of similar blinded trials in type 2 diabetes, it seems unlikely that these patients would notice a difference either.

If the case for analogues cannot be based on efficacy, it certainly cannot be based on cost. The clinical advantages of analogues may be sufficient to justify a modest mark-up if we use value based pricing, but they are surely inadequate to justify an excess of 200-400%.

The case for generic insulin seems clear, so why the delay? One reason is that insulin is big business. Global sales rose to a predicted \$11.8bn (£7.4bn; €8.4bn) in 2010, as against \$2bn in 1995,⁵ and insulin accounted for 48.4% of the UK drug bill for diabetes related prescriptions in 2008.⁶ Indeed, data released last month suggest that diabetes now accounts for nearly a tenth of the annual NHS drugs bill in England.⁷ Most of this increase was due to increasing use of more expensive analogue insulins, and the three companies now dominate the world insulin market.

The cost of insulin

But even the cost of human insulin varies widely across the world. On 11 May 2010, volunteers from 60 countries visited their local pharmacies to buy 10 mL of 100 IU/mL human soluble insulin. The price varied by a staggering 5000%, and by 2900% for the same brand.⁸ Much of the difference was due to profit taking by pharmacies and other in-country suppliers rather than to factory price, but the fact that branded human insulin is sold in some markets at less than \$5 a vial provides some indication of the true manufacturing costs.

The insulin manufacturers have been prominent in the campaign to make cheap insulin available to some of the world's poorest countries, despite difficulties such as the re-export of donated insulin for sale elsewhere.⁹⁻¹⁰ Nevertheless, children still die because of lack of affordable insulin,¹¹ and the insulin oligopoly remains part of the problem, rather than part of the solution.

The companies are not to blame for this, for they are commercial organisations and must inevitably pursue commercial goals. Their mission is to develop new products, to promote these at the expense of the old, to seek new markets, and to sell their products for the best price the market will bear. They will naturally avoid mutually harmful price cutting. When it comes to diabetes, it has been equally natural for them to support the use of intensified glucose lowering strategies, which inevitably include earlier and more aggressive use of insulin.¹²

Representing the public interest

Open competition between branded and generic insulin, waged in terms of cost and evidence of efficacy, would undoubtedly be the most effective way of driving down the price of insulin, and would also make charitable donations unnecessary. The analogues are undeniably popular with patients and physicians, but they are overpriced, and they have been promoted well beyond the limits of the evidence. Wealthier nations may be willing and able to sustain the excess cost, but people elsewhere are dying because of lack of insulin or enduring unnecessary hardship in the struggle to afford it.

So where are the advocates for cost effective insulin and evidence based guidelines? The WHO Essential Medicines and Supplies Program issues an updated essential medicines list every two years, but neither it nor the non-communicable disease division has generated evidence based guidelines that are applicable to a wide spectrum of socioeconomic settings. The main income of the

International Diabetes Federation (IDF) derives from its biennial World Diabetes Congress, and much of that income is generated by the pharmaceutical exhibition. IDFAfrica recently coordinated the first East African diabetes summit to help identify sustainable models for dealing with diabetes, but the programme was heavily dominated by drug industry symposiums, implying that the federation endorsed the advocated strategies. The federation's dependence on industry may leave it somewhat emasculated when commercial strategies need to be confronted.

Obstacles to affordable insulin

The drug industry is a major source of information about patient management throughout the world, and the dominant source in low to middle income countries. Doctors and specialist nurses attend conferences and symposiums with industry support and learn about the latest advances in patient care, which typically relate to newer patented drugs that are much more costly than medicines on WHO's essential medicines list.¹ The pressure on limited resources may be such that essential medicines, including insulin, can no longer be afforded.¹¹

Would-be manufacturers of generic insulin face many challenges. One is the capital costs to establishing bioengineering facilities. Another is the lack of a marketing force to compete with the huge investment of the insulin giants. Yet another is the lack of suitable delivery devices, since the uptake of new insulins is often driven by the quality of the pen devices that contain them. And, finally, there is not yet in place a WHO prequalification scheme for insulin, as exists for antiretrovirals and antibiotics,¹³ to confirm manufacturing quality. But entrepreneurial ingenuity will, if offered a level playing field, soon overcome such obstacles.

In the last analysis, the main obstacles to generic insulin seem to be a failure of will and an inability to face the facts. Professional societies such as the IDF have yet to commit themselves to advocacy of the only course of action that will guarantee the future of affordable insulin, and we can only wonder why.

Edwin A M Gale, emeritus professor of diabetic medicine, University of Bristol, Bristol, UK
Edwin.Gale@bristol.ac.uk

John S Yudkin, emeritus professor of medicine, University College London, London, UK

Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

References can be found on bmj.com.

Cite this as: *BMJ* 2011;343:d5675