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Sir Michael Rawlins on being NICE – and fair – about drug development and availability

Interviewed by Daniel Clarke

Sir Michael Rawlins
Chairman of the National Institute for Clinical Excellence

Sir Michael Rawlins has been Professor of Clinical Pharmacology at the University of Newcastle since 1973. He is also Consultant Physician and Clinical Pharmacologist to the Newcastle Hospitals NHS Trust. He was Vice-Chairman (1987–1992) and Chairman (1993–1998) of the Committee on Safety of Medicines, and is currently Chairman of the Advisory Council on the Misuse of Drugs. He has been the Chairman of the National Institute of Clinical Excellence (NICE) since its inception in 1999. NICE is an independent organisation responsible for providing national guidance on treatments and care for people using the National Health Service (NHS) in England and Wales.

What are the aims of NICE?

The primary aim of NICE is to increase the quality of care that patients get from their doctors, nurses and other professionals. Part of that is using pharmaceuticals that are effective and cost effective. There is a tension between the effectiveness and cost effectiveness that we recognise; nevertheless, the NHS operates within a finite budget and it has got to get the best value for money. That is a complicated arrangement, partly because although the techniques [for assessing cost effectiveness] are there, they have never been used in this way in any healthcare system in the world. We were moving in a new direction and there wasn't any real precedent.

What is the greatest achievement of NICE to date?

I think the fact that we are now accepted as a fixed part of the NHS landscape by our stakeholders. That includes the pharmaceutical industry, patient organisations, professional organisations, Parliament and politicians – we have support right across the political spectrum for the things we are trying to do. I think that's very important because when we started there was a lot of hostility to us from certain quarters – not all by any means, but there was some suspicion and I think we've managed to break down a lot of that. The pharmaceutical industry was suspicious of us: that was obvious. I think the opposition [political] parties were suspicious of us and what we were up to: not unreasonably; I don't blame any of them. The professions were always onside from the beginning and we always had a lot of support from the medical and other healthcare professionals, and their support and involvement has been critical to us.

> *"If I want to buy a Rolls Royce, it might not be cost effective, but that's my business..."*

How do you interact with the Medicines and Healthcare products Regulatory Agency (MHRA) [a body with a similar regulatory function to the FDA and the European Medicines Agency (EMEA)] and what is the difference?

In a sense there are two important differences. On a formal level, the MHRA decides which drugs go on the market and what their licence indications are, and we pick it up from there and decide from those licence indications whether the product is cost effective. Clinical effectiveness and the bounds between safety and efficacy is a done deal, and we accept that. Our role is to see whether it's cost effective throughout its indications, or only some of them.

I think it is very important to separate these functions. I don't think that it would be right in a democracy for a regulatory authority to decide whether something was cost effective; if I want to buy a Rolls Royce, it might not be cost effective, but that's my business and nobody else's business. It's the same with pharmaceuticals or any other consumer product. The state should not deprive me of the right to spend my money in the way I wish to choose. I don't think that is the right approach.

There was the thought when I was chairing the Committee on Safety of Medicines (CSM): I was asked whether the CSM having decided

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that something was clinically effective should then go on to decide whether it was cost effective. This was before NICE and I actually advised against that for two reasons: one is that you would have to increase the size of the committee to have a competent health-economic component; but also, experience elsewhere in the world suggests that, if you have that arrangement, committees know that in ten minutes' time they are going to have a rotten cost-effectiveness decision, so rather than do it that way, they fudge the safety and efficacy. So I believe the decision making should be separate.

Are there any other similar agencies that NICE was based upon?

The Australians have their Pharmaceutical Benefits Advisory Committee (PBAC) that looks at the cost effectiveness of pharmaceuticals. We, of course, take it further than just pharmaceuticals and looks at devices and diagnostics and so forth, and we also produce guidelines, which again incorporate cost effectiveness. So there isn't a close analogy to NICE although the Australian PBAC is the nearest thing we have.

> *"The pharmaceutical industry...should have their say but not necessarily have their way"*

Has anyone since copied the NICE format?

Oh yes. There has been a huge international interest. We've had contact from over 60 countries. The Swedes are setting an equivalent body up; the Norwegians are; the Germans are. There is a lot of discussion, curiously enough, in the USA about whether the NICE model would work there. In fact, the Commonwealth Fund has recently reported on NICE and similar agencies in relation to the USA (http://www.cmwf.org/publications/publications_show.htm?doc_id=252181).

How are your guidelines enforced?

Pharmaceuticals are included as a technology, and the law is that if NICE says that a technology should be available on the NHS then funds for it have to be made available by the health authority or primary care trust. That doesn't mean to say that doctors need to use it – you can't control that. Very often we are looking at [drug] classes rather than individual products, so it's a question of which member of the class. We are very reluctant to distinguish between two members of a class, for two reasons: one is that it is often impossible and secondly, it would give someone a monopoly which, from the point of view of the NHS, is a crazy thing to do.

When NICE was set up, and it was probably a mistake, implementation was not seen as part of our role, we just produced the guidance. At the time it was a relief; just producing it was enough of a task. But, of course, we are a complete waste of space if our stuff isn't used, and a waste of public money. The way in which we produce our material has a considerable impact on how it's used, so you can't get away from the production and the implementation. Although we can't stand at the shoulder of every prescriber in the country, there are things we can do which I think we will probably act on.

What impact would you say you have had on prescribing practice?

I think there has been a considerable impact, not least of which because we have ensured the availability of products that had previously been subject to very considerable 'postcode' prescribing. I don't think we've eliminated it but the evidence suggests we have major made inroads into unreasonable and inappropriate geographical differences. So I think that hundreds of thousands of people have probably benefited from the advice we have given.

How much lobbying by the drug companies occurs?

Not much in that [the true lobbying] sense. Clearly, companies that are involved in an appraisal have a considerable interest in what we are doing and are involved right from the beginning. When we do an appraisal, we produce a scope of what we are going to look at and we get all the stakeholders involved in that – the manufacturers, the patient groups, the professional bodies – and they are all together in the same room. That's important; they listen to each other and it moves on from there.

How would you describe your relationship with the industry?

Industry collectively was very hostile at the start, or very suspicious. As time has gone on, I think that they have gained more confidence in what we are doing: confidence in the technical side of what we are doing; confidence in the transparency of what we are doing. As a number of them have said to me, it's also fair: 'We may not necessarily agree with the decision, but we understand how it has been reached and it is fair.'

I think, broadly speaking, the industry has become much more willing to engage in the process in the way we would want them to. I think they do accept that we genuinely want a dialogue with them and that they should have their say, but not necessarily have their way. In fact, several Chief Executives of large pharmaceutical companies have said to me that they hope that countries that copy us will do it in the same way.

> *"We couldn't possibly just restrict ourselves to those treatments on the licence"*

What about people pushing unproven, non-conventional or wonder treatments?

We've never looked at complementary or alternative medicines. My view, as I've always said, is that if we were asked to do it, we would be more than happy, but they have to reach the same standards as everything else.

There are occasions when we do look at drugs outside of their licence indications. When we do that, we do it with the full knowledge of the Department of Health. A good example is when we were looking at anti-rejection drugs for renal transplant. When it comes to children, we are devoid of data, and even in adults, the way it's used is not exactly the same as the licensed indication. It's very important for ministers to know that because the ministers are also the licensing authority. There will be circumstances when we look at things outside of their licensed indications. Drugs used to treat leukaemia in children aren't necessarily licensed for that indication, although they are widely used and everybody accepts their safety. The manufacturers have never bothered or got around to the trouble of getting a licence: it's not going to do them any good and I understand that. We couldn't possibly just

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restrict ourselves to those treatments on the licence. The MHRA understand that and can persuade the company to get a licence to tidy the whole thing up.

> "Everything should be reported within a period of time after the completion of the study"

It has been said that the UK (among other countries) is not paying its fair share for drug development. Is this true?

Mark McClellan [who is widely reported to have made this statement] has denied actually saying that! I know what he was saying – I have spoken to him about it – which was that Europe ought to use much more generic products and make savings on those to find the resources for more innovative things. In actual fact, in the UK we have a high level of generic use so it doesn't really apply. I don't really buy the business that the US is paying a price that covers the R&D and we're not. Under the Pharmaceutical Price Regulation Scheme (PPRS), a proportion – 23% or similar – goes to R&D. I think we're paying our share. Whether other countries are, I have no idea.

For appraisals, drug companies submit their evidence, but you don't have the power to compel them submit data. How do you ensure that you have as much evidence as you can obtain?

There are several bits to this. The first is that with new drugs, the information you can get from the EMEA and FDA, which is publicly available, indicates the trials that have been done. The starting point is to go to the publication that the EMEA produces that itemises the drug trials that have been done. I'm confident that we get the same as the regulators do.

For older drugs, that may be more difficult. You cannot be 100% sure. Nor indeed, can the manufacturers or the UK subsidiary – if it's a US company or a Swiss company, they might not have been told either. That is quite possible, and I know from my days at the CSM that that did sometimes happen, that they were unaware of the existence of certain data. Nevertheless, we do the best we can. I take a somewhat purist view about the publication of clinical trials. In essence, all clinical trials, whoever has done them, should be published, whether it has anything to do with a licence or not: every human trial; I don't care that a company says 'it's our intellectual-property rights'. Morally, the patients who have been involved in the studies have put their time and effort, if not their discomfort, into it, and we owe it to them to make sure that the data become publicly available. Even if the trial is stopped halfway through, it ought to be in the public domain. That applies to academic trials as much as it does to pharmaceutical trials. Everything should be registered in advance – how one does it is a separate issue – to stop people doing dangerous or unnecessary trials and everything should be reported within a period of time after the completion of the study: six months, nine months; something like that. That is the principle under which we should be operating. How to enforce that is actually very difficult; although we could make a law that governed UK companies, we couldn't cover companies in the USA, Switzerland, Germany or Japan, for example. It needs something rather more subtle.

> "The non-publication of clinical trials is morally wrong"

Can you see something like this being agreed to by the drug companies in the future? Will regulators start to demand to see all the data from trials, not just the successful data?

I think so. But access must not just be for the regulator; it must be in the public domain. I think regulators are going to have to get over the commercial and confidence limitations, and either should have to produce the data or the companies should have to do it. But it has to be more than the regulator. Academics have to do it as well, not just the pharmaceutical industry.

One of the groups that could play an important role in this is the Research Ethics Committees and the Institutional Review Boards (IRBs). In a way, they could be very influential, if somehow we could arrange for IRBs in North America and Ethics Committees in Europe to ensure that if you've done one study and not published it, you don't get approval for the next one. That would bite quite hard, especially if you could do it globally. That's the kind of thing that could work. I agree with Ian Chalmers that non-publication of clinical trials is morally wrong.

> "The public aren't exactly enamoured with the pharmaceutical industry"

How can drug companies maintain the confidence of the public, especially in light of the Seroxat and COX2-inhibitor problems?

I think confidence has been undermined; there's no question about it. The public aren't exactly enamoured with the pharmaceutical industry. Polling data shows that people by and large think they are a greedy and self-serving bunch, which I think is unfair, although in some circumstances it is fair. I think there are a number of aspects to it. The industry must be very honest with everybody. They are a business and there is nothing wrong with being in business.

However, there is a problem, and that is why we have regulation. That regulatory process needs to capture the fact that pharmaceutical companies are in business but at the same time are producing goods that are of major public health significance. We need an efficient, open and transparent regulatory system. One of the difficulties is that the regulatory system has been too closed. When I chaired the CSM I started every meeting by – it was written out for me on a briefing document – reminding members that proceedings and papers were confidential and could not be disclosed. We have section 118 of the Medicines Act which makes you liable for three years in prison if you reveal information: this has to go.

I do think that, every now and again, drug companies do shoot themselves in the foot, like taking the South Africans to court over HIV drugs: that was just crazy. They have to be more sensitive about the perceptions of ordinary people about what they do; that, they are not very good at.

How about public confidence in NICE?

Opinion poll data by ICM in 2004 showed that 72% of the public thought very positively or quite positively about us, which is not too bad! The problems that have arisen and

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whatever is decided (with COX2 inhibitors, for example) are a done deal by the time they reach us. If they are all wiped off, it makes the next appraisal very simple! Those problems are very regulatory.

How will personalised medicine affect NICE guidelines? Will they be the same, but for a more restricted group of people?

In principle, it will be no great difficulty. Herceptin for breast cancer is an example of a sort of personalised medicine, where you only use it for patients expressing the Her2 receptor on their breast tumour cells. I don't think it's a big deal actually. It's just another way of differentiating people, rather than being old or young and so on.

If there were an appraisal of NICE due, what changes would you recommend? What wouldn't you change?

I think there are a number of things. I'm not sure we've got topic selection right yet. I'm not sure we capture the topics the health service wants, and that's why we've started using our website to ask for suggestions. I think it needs to be 'bottom up' as well as 'top down' [currently, ministers – following expert advice – choose the topics for investigation]. We've already talked about implementation and we're taking steps to do that.

We're still struggling over the business of appraising things early, because if we wait until the licence is granted before we start the appraisal process, then it will take a year, 15 months, 18 months before we produce an answer. That's why we have been trying in the past couple of years to start appraisals in parallel with the licensing. We can't produce an answer until we know what the licence is, but we should be able to do it within about 3–4 months after the goods are on the market. In fact, manufacturers usually know some months before it goes on the market what the licence indications are, so that is possible. We've been slightly wrong-footed because we started the appraisals for all sorts of things and had to stop because the licensing process was stopped. We actually spend quite a bit of time starting appraisals and then abandoning them or putting them on hold. That is an inefficiency that I'm not sure how we can get around; we spend quite a bit of resource starting these things off then have to wait six months, nine months or a year – maybe forever.

I think the process by which we do things, in principle, is the right one: decisions are made by independent advisory groups; the process is transparent as far as it can be. I suppose the other thing I would have on my wish list would be having all committee meetings in public, like the FDA. We don't have a tradition of that in the UK. I've promoted this idea and people are very nervous about it. Not so much on the staff here, but people on the committees themselves, because unless you are very confident you might be intimidated by the fact that you know people are listening and may feel less inclined to change your mind as a result of the debates; it would be terrible if that were to happen. I think it's something that we are going to have to approach gradually. The first thing we are doing is starting to hold our appeals in public. The first one has been held in public and after ten minutes, everyone had forgotten that there were people listening and watching. I think about 25 people turned up, most of them, I think, from drug companies and patient organisations who were particularly interested in the topic. That's the direction in which we need to travel, but it will take time and it's not the kind of thing I can impose.

The other thing that we have done, which is rather unusual, is that we have involved patients and patient organisations. In our guidelines we have what we call 'service users', two of which are on each guideline development group, and they have a very important place in what we do. Finally, we are also capturing the public view of some of the principles of which we should do these things, and that, I think, has been an important little experiment and one that we will certainly continue and which offers dividends for the future, not least because it provides public confidence in the social values that we apply; at least it's being tested by a group of outsiders who aren't necessarily involved in healthcare.

Finally, what do you think will be the next big thing in drug discovery?

There are techniques around the corner that offer the promise of doing stunning things, particularly techniques like intrabodies, RNAi, stem cells and gene therapy. I think they offer very exciting possibilities for the future, but I doubt they will be all that big. It will take time, although the first trials are going on for RNAi and gene therapy.

Sir Michael Rawlins
National Institute for Clinical Excellence,
MidCity Place,
71 High Holborn,
London,
WC1V 6NA UK