Education and debate

Medicines regulation and the pharmaceutical industry

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How does an agency funded by user fees make impartial decisions about the safety of new and licensed drugs?

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A regulatory system for medicines should provide timely access to effective treatments for patients, protect patient safety, and foster research into new treatments. Patients, the medical community, government, and the pharmaceutical industry share a common interest in ensuring that the system is efficient, transparent, and robust and bases its decisions on sound scientific evidence. In the United Kingdom, the regulatory body is the Medicines and Healthcare Products Regulatory Agency. The agency clearly needs to work closely with the pharmaceutical industry but remain independent. In this article, we explore how this is achieved.

Role of the agency

The Medicines and Healthcare Products Regulatory Agency was formed in April 2003 by the merger of the Medicines Control Agency and the Medical Devices Agency. With respect to regulation of medicines, the agency has three main duties:

- To protect public health by ensuring that only medicines with a favourable benefit to risk profile are licensed
- To provide appropriate information on available medicines so that prescribers and patients can make informed decisions on their use
- Not to impose unnecessary regulatory impediments that would prevent innovative medicines from being available to improve public health.

Funding

The agency's work on regulating medicines is funded entirely by user fees. Around 40% of the income is from an annual service fee on each current product licence, which covers the costs of post marketing surveillance and enforcement activities, and the remainder comes from fees for such activities as licensing new products, inspecting manufacturing facilities, and authorising clinical trials. The scales of user fees for licensing and inspection activities are agreed by the Treasury and subject to public consultation. Funding of the regulation of medical devices comes from an annual capital government grant, but we will not discuss this further here. Other countries also use a fee based method of funding the regulation of medicines; user fees account for 100% of funding in the Netherlands, 95% in Sweden, 66% in Canada, and 52%

Production of ciprofloxacin: one of the agency's roles is to ensure good manufacturing practice

in the United States. The European Medicines Agency also gets 67% of its income from fees.

Questions have been raised about whether this method of funding inhibits regulators from taking difficult decisions.¹ However, the National Audit Office's review of the Medicines Control Agency, which was also funded entirely by user fees, found that there were sufficient checks and balances in the system to ensure scientific independence.²

Government funding would not benefit either public health or the industry. It is operationally efficient to link income directly to the volume of business, so that staffing can be adapted to work load. Large backlogs in processing applications existed before 1989, when the government partly funded regulation. The House of Commons Health Committee, in its recent inquiry into the influence of the pharmaceutical industry, again drew attention to the potential dangers inherent in user funded regulation but did not propose an alternative.¹ In other areas of regulation the cost is usually borne by the regulated rather than the taxpayer, and the regulation of medicines is not different in principle.

Conflicts of interest

The pool of experts in regulating medicines in the United Kingdom is limited, and both industry and

regulatory agencies compete for them. Thus it is unsurprising that many of the agency's employees have worked in the pharmaceutical industry. For example, an important role of the agency is to ensure that industry complies with good manufacturing practice and good clinical practice. This requires the agency to inspect manufacturing quality in factories and examine research records. Industrial experience is necessary in this role, but any resulting conflicts of interest need to be identified and managed.

Agency staff are civil servants and must abide by standard rules of conduct and impartiality. Because of the nature of the agency's work, its policy on conflicts of interest goes further than that pertaining generally in the civil service. In addition, from November 2005, European regulations will require that staff have no financial or other interests that could affect their impartiality. At present, all members of staff complete a declaration of interest (shareholding, or other interest in the pharmaceutical industry) and their managers ensure that they do not perform any task that might be compromised by any interests. Under the new code, the agency is creating a comprehensive register of all current interests of agency staff, and they were required to dispose of all such interests by July 2005. The regulations do not apply to pensions accruing from previous employment in industry or to pooled investments where individuals cannot influence investment strategy—for example, in unit trusts.

Conflict of interest is also relevant for members of the agency's advisory committees. Chairs of advisory committees such as the Medicines Commission and the Committee on Safety of Medicines are not allowed to hold personal financial interests (such as shareholdings or paid consultancies) in the pharmaceutical industry. Members of these committees have been allowed to hold such interests, but they must declare them, both in an annual submission to the agency and at each meeting that discusses a relevant product. Anyone with such an interest must leave the room and take no part in the discussion and recommendations of the committee. Furthermore, if a member's department is being paid to work on a specific product, this must also be declared and the member will normally leave the committee while the discussion is taking place.

Another potential interest arises when a member's department is involved in work with a company on products other than those under discussion (with any fees going to their university or department). Most academic departments in the UK collaborate with pharmaceutical companies in this way and are encouraged by government and universities to do so. All members must declare such non-personal, non-specific interests annually and at meetings when any of the company's products are debated. However, they can take full part in the discussion and decision making. All these interests are published in the agency's annual report.

From autumn 2005, the advisory structure of the agency will change. The current Medicines Commission and the Committee on Safety of Medicines will be merged into a single body, the Commission for Human Medicines. Members of the new commission will not be allowed to hold either personal or specific interests in the pharmaceutical industry but, for the reasons presented above, they will be allowed to hold

non-personal and non-specific interests, which will still be declared. None of the members will be employed by the pharmaceutical industry. At present, the Medicines Act of 1968 requires that at least one member of the Medicines Commission must have "wide and recent experience of ... the pharmaceutical industry," but this is no longer considered appropriate. These changes should further allay concerns about conflicts of interest in the advice that the agency receives and are an important step to establishing transparency.

Confidentiality and secrecy

Up to 2005, two rules have governed the approach of the agency towards confidentiality and secrecy. Section 118(1) of the Medicines Act of 1968 made it an offence for anyone to disclose to any other person any information obtained through the regulatory process. In 1994, the code of practice on access to government information was introduced, the basic principle of which was that all information should be released except where disclosure would not be in the public interest—for example, on the grounds of commercial confidentiality.

Section 118 of the Medicines Act has often been criticised for encouraging excessive secrecy, but in reality it does not place an absolute restriction on disclosure. When there is a risk to public health or safety, the agency has an overriding obligation to remove or reduce that risk even if confidentiality is broken, and it has done so on several occasions. The section was amended in 2005 after a review and public consultation prompted by the 1997 white paper on freedom of information.

Even with the full implementation of the Freedom of Information Act in 2005, the agency still has common law duties to those who supply information to it in confidence. For example, information on a new product submitted to the agency for licensing purposes could prove useful to a competitor, and the agency deals with all applications on a confidential basis until regulatory action is completed. This is in line with the policy of other medicines regulatory agencies.

How and when clinical trial data submitted to a regulatory agency for licensing purposes should be made public is provoking much debate.¹ The agency supports recent moves by the associations representing the pharmaceutical industry in Europe, the United States, and Japan to ensure the registration of all clinical trials and to allow that information to be placed in the public domain. It also supports making the results of all clinical trials publicly accessible. Issues such as where such a register of clinical trials should be held, where the results of these trials should be deposited, and when such results should be made publicly available must be resolved.

Improving transparency

The agency is committed to greater transparency of its activities. It has already shown this by starting to publish the minutes of its advisory committees and disclose the evidence underpinning its decisions in areas of public concern. For example, the agency published the data from clinical trials that it used in its reviews of

Summary points

Regulation of drugs by the UK regulatory agency is funded entirely by user fees

Strict rules are in place to ensure staff and committee members have no personal conflicts of interest

Although it has to protect commercial confidentiality, the agency can now disclose assessments used in its decisions

Increased transparency should further reassure the public that the agency's decisions are impartial

selective serotonin reuptake inhibitors in 2003-5 and hormone replacement therapy in 2004.^{3 4}

In January 2005, the agency began to publish on the internet the summary data from the yellow card system for reporting adverse drug reactions as drug analysis prints (www.yellowcard.gov.uk/daps.html). It will consider legitimate applications for data on individual yellow card reports for research purposes, subject to ethical and scientific approval.

In addition, from November 2005, the agency will start producing UK public assessment reports on each medicine that it licenses. These will provide details of

the clinical trials submitted as part of the application. The agency has also established a communications division headed by a board level director. One of the division's main tasks is the wider dissemination of information about the work of the agency and the safety and efficacy of licensed medicines.

Relationships between government, the health professions, and the public have evolved considerably in recent years. The setting up of the agency has been accompanied by wide ranging reviews of all aspects of medicines regulation. The changes now being implemented are intended to ensure that it continues to meet public expectations of scientific rigour, independence, and transparency in the years to come.

Contributors and sources: AB and KW have both worked in academic clinical pharmacology and the NHS for many years and have considerable experience in medicines regulation. This article arose from discussions on changes in UK medicines regulation. Both authors contributed to the writing of the article. AB is guarantor for the content of the article.

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1 House of Commons Health Committee. *The influence of the pharmaceutical industry. Fourth report of session 2004-05*. London: Stationery Office, 2005.

2 National Audit Office. *Safety, quality, efficacy: regulating medicines in the UK*. London: Stationery Office, 2003.

3 Committee on Safety of Medicines. *Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants*. London: Stationery Office, 2005.

4 Medicines and Healthcare Products Regulatory Agency. Review of the evidence on long term safety of hormone replacement therapy. *Current Problems in Pharmacovigilance* 2004;30:4-7.

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How well does the evidence on pioglitazone back up researchers' claims for a reduction in macrovascular events?

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Recent claims that pioglitazone prevents macrovascular events are based on a secondary outcome measure. But ignoring the primary outcome is statistically unsound

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Last month, members of the steering committee of the prospective pioglitazone clinical trial in macrovascular events (Proactive) presented the results at the European Association for the Study of Diabetes meeting in Athens.¹ The audience, which overflowed from the meeting room, heard John Dormandy, chair of the steering committee, conclude that the trial had shown that pioglitazone, "Reduces the composite of all cause mortality, non-fatal myocardial infarction, and stroke." He commented: "We have now shown for the first time that oral glucose lowering medication can prevent macrovascular events." The audience seemed excited by these results and a consensus emerged that the results would change practice. The presentation was certainly positive and upbeat (as readers may judge for themselves from the webcast made available with the support of the study sponsors, Eli Lilly and Takeda¹). Unfortunately, these conclusions are not based on robust standards for the interpretation of evidence from clinical trials.

The trial

The trial studied over 5000 patients with inadequately controlled type 2 diabetes randomised to receive pioglitazone or matched placebo. Participants had raised cardiovascular risk, and most were receiving treatment for cardiovascular disease. The minimum planned exposure to study treatment was 2.5 years. The trial seems to have been carried out to a high standard, as we should expect from an industry sponsored trial that was conducted largely to answer safety concerns among regulatory agencies. So why are the conclusions unsafe?

The answer lies with the choice of composite outcome measure and the undue emphasis given to a secondary end point which provided contrasting results to that from the prespecified primary outcome. It is well known that multiple testing can lead to spurious results. Each statistical test in a neutral trial is the equivalent of rolling a 20 sided dice on which one side is denoted as a success. The more times the dice is