



National Audit Office

MEMORANDUM FOR
THE COMMITTEE OF
PUBLIC ACCOUNTS

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Department of Health

Access to clinical trial information and the stockpiling of Tamiflu

Summary

- 1** The cost of medicines is a major expenditure item for the NHS. In 2011-12, the NHS spent £12.7 billion on medicines. NHS spending on medicines has grown by, on average, 2.3 per cent a year in real terms between 2002-03 and 2011-12. There are obvious value for money considerations in purchasing medicines on this scale. Assurance about the efficacy of medicines (a measure of the beneficial effect of the medicine on patients) comes from the assurance process to which they are subjected by regulators at the national or super-national level, and in the UK assurances about clinical and cost-effectiveness, in particular, through assessment by the National Institute for Health and Care Excellence (NICE, formerly known as the National Institute for Health and Clinical Excellence). In addition, the Department of Health (the Department) purchase some medicines to stockpile them centrally. An obvious stockpiling example is medicines for pandemic influenza emergency preparedness. Assurance to underpin the procurement of stockpiles comes from business cases, which should use the latest evidence on efficacy.
- 2** The National Audit Office received correspondence from a number of Members of Parliament raising questions about access to all clinical trials information for UK regulators when licensing and appraising new medicines, and the decision to stockpile Tamiflu, the antiviral medicine that has been used in the treatment of pandemic influenza. A key concern was that, without full clinical trial information, public money could be spent on ineffective medicines. This was a good opportunity for the NAO to examine the process by which medicines are licensed, appraised and stockpiled in the context of Tamiflu (between 2006-07 and 2012-13, the Department purchased nearly 40 million units of Tamiflu at a cost of £424 million at 2011-12 prices).
- 3** This review reports whether: regulators and NICE have access to the clinical trials evidence they require (Part Two); more specifically whether all the clinical trials information was available to regulators and NICE for the appraisal of Tamiflu for the treatment of seasonal influenza (Part Three); and whether the Department stockpiled Tamiflu for pandemics on the basis of clinical evidence and appropriate advice (Part Three).
- 4** This review does not attempt to independently evaluate the efficacy and cost-effectiveness of Tamiflu, but seeks to establish as clearly as possible the views of experts on its efficacy.

5 While outside the scope of this review, there is a broader issue for the research community concerning the fact that not all clinical trial results are published and the resulting potential for 'publication bias'. The Health Select Committee recently recommended that all clinical trials should be published. In July 2012, the European Commission adopted a proposal for a regulation to replace the existing legislation on clinical trials. A key part of the new regulation will be to increase the transparency of clinical trials conducted in the European Union, including publication of trial results on a publicly accessible database.

Key findings

Licensing medicines and evaluating clinical and cost-effectiveness

6 Manufacturers must submit evidence on products they wish to market in the UK to the UK Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMA). The requirement for manufacturers to provide information on clinical trials is supported by statute. Neither organisation is aware of an application which has been granted on the basis of falsified or incomplete data (paragraphs 2.3 to 2.7, 2.9 and 2.10).

7 The MHRA and EMA do not ask for as much information as the United States Food and Drug Administration (FDA) at the initial application stage. The main difference is that the FDA asks for patient-level data upon which it may conduct its own analysis. The European agencies would require more analytical capacity to be able to do this. The FDA also 'shadows' the development of new medicines alongside the manufacturers' teams (paragraph 2.12).

8 NICE does not have the same statutory powers to demand information from manufacturers (unlike the German body that carries out a similar role to the independent academic centres commissioned by NICE to undertake systematic reviews). The UK medical director of the manufacturer has to declare to NICE that all relevant material has been supplied. It is possible that the medical director would not be aware of research undertaken outside the UK (paragraphs 2.16 to 2.18, 2.20 and 2.21).

9 Although many European regulators and the FDA have a confidentiality agreement that permits sharing of otherwise non-public information, authorities within the UK – MHRA and NICE – do not, although they are both accountable to the Department. This may require NICE to duplicate some of the information-gathering activities of the EMA and MHRA (paragraphs 2.8 and 2.19).

Licensing and effectiveness of Tamiflu for treatment and prophylaxis (prevention of illness) of influenza

10 Tamiflu was first licensed for treatment and prophylaxis of influenza in the European Union in 2002, and was assessed as clinically-effective and cost-effective for individuals in at risk groups by NICE in 2003, in line with standard procedures at the time (paragraphs 3.4 and 3.9).

11 There is a general consensus that Tamiflu reduces the duration of influenza symptoms and, in certain circumstances, prevents influenza, when administered promptly. Regulators state that Tamiflu should be administered within 48 hours of symptoms appearing (paragraphs 3.6, 3.10, 3.20, 3.28 and 3.29, Figures 4 and 5).

12 There is less consensus about the extent to which Tamiflu reduces complications, and hence hospitalisation and death rates. Published evidence analysing the extent to which complications are reduced (generally expressed in terms of reduced reliance on antibiotics) has not been accepted in some of the assessments and has been the focus of critiques by the Cochrane Collaboration of the evidence base for Tamiflu efficacy (paragraphs 3.6, 3.10, 3.12 to 3.15, 3.17, 3.20, 3.28 and 3.29, Figures 4 and 5).

13 The debate about the evidence for Tamiflu's efficacy is part of a broader campaign by members of the research community and medical journals to open clinical trials data to peer review and scrutiny by the medical profession and medical researchers. There is also a movement to have trials conducted independently of manufacturers. In April 2013, Roche informed the Cochrane Collaboration that over the next few months they would release to Cochrane Collaboration researchers the reports of all clinical trials on Tamiflu that they had sponsored. In line with European Union law, each clinical study report will be edited by Roche to ensure patient confidentiality and to protect legitimate commercial interests (paragraphs 1.3 and 3.15).

Stockpiling of Tamiflu by the Department of Health for pandemic influenza

14 Initial stockpiling of Tamiflu in the UK, to cover 25 per cent of the population, was carried out in 2006 as a response to the increasing concerns about avian influenza and the potential for an influenza pandemic. The Department's actions in stockpiling Tamiflu have been guided by World Health Organisation (WHO) guidance on pandemic preparedness. This stated that antivirals are effective for both prophylaxis and early treatment of influenza and that they could reduce influenza-related complications, hospitalisations and, potentially, death rates (Figure 4, paragraphs 3.17 to 3.19).

15 The Department developed a business case for a number of measures including the extension of the antiviral stockpile in 2008 to support the strategy outlined in the *National Framework for Responding to an Influenza Pandemic*, published jointly by the Department and the Cabinet Office. As part of the preparation of the publication of the Framework, the Cabinet Office carried out a review of the evidence base generated by the Department and elsewhere in government, and published a paper covering the results of this review. The paper stated that there was no published evidence on a reduction in mortality due to antiviral use and very limited evidence on reduced complications and hospitalisations. The Scientific Pandemic Influenza Advisory Committee had, however, advised that an assumption of 40 to 50 per cent reduction in both hospitalisations and deaths should be used in the modelling work included in the paper. This assumption was based on inferences drawn from the published evidence on reduced complications and hospitalisation and unpublished evidence on the impact of antivirals on mortality. The Department's business case was based on the modelling in the Cabinet Office review paper (paragraphs 3.21 to 3.24).

16 The business case showed the benefits would considerably outweigh costs (a net annual benefit of around £32 billion in a worst-case scenario) and benefits continued to outweigh costs even if pandemics were less frequent or severe. The business case recommended stockpiling a package of countermeasures, including increasing the stockpile of antivirals from the existing population coverage of 25 per cent to 80 per cent to cover both treatment and prophylaxis (paragraphs 3.21 and 3.22).

17 In the event, although the stockpile briefly reached 80 per cent during the 2009 swine flu pandemic, the Department decided on cost and practicality grounds that it was not realistic to maintain the stockpile above 50 per cent. The business case had shown that stockpiling antivirals for 50 per cent population coverage would yield only small additional benefits to a stockpile of 25 per cent even in the worst case scenario, due to the modelling assumption that the most at risk people would be treated first. The Department stated that, aside from concerns that this assumption might be over-optimistic, other issues such as public confidence in the influenza pandemic preparedness strategy, practicalities of distribution and the inclusion of more than one antiviral in the stockpile were considered by the Department when deciding to maintain 50 per cent population coverage (paragraphs 3.22, 3.23, 3.27 and 3.28).

18 In 2008-09, as part of the increase in the stockpile, Relenza (a similar medicine to Tamiflu, manufactured by GlaxoSmithKline) was purchased to provide a back-up stockpile in the event of a new influenza strain being resistant to Tamiflu, which was endorsed by the Scientific Pandemic Influenza Advisory Committee. This covered 15 per cent of the population. The Department has spent £136 million on Relenza (paragraphs 3.25 and 3.30).

19 The Department's 2013 review of observational studies carried out during the 2009 pandemic suggest that Tamiflu might have been helpful in reducing the most serious outcomes for some at-risk groups and hospitalised patients, though such studies are necessarily less rigorous than other types of medical research. The Scientific Advisory Group for Emergencies had advised during the pandemic that there were benefits in administering antivirals for up to seven days after the onset of symptoms although early treatment was greatly preferable. While the Department took steps to try to ensure people received Tamiflu quickly and its review found there were significantly better outcomes from early treatment, it also indicated that Tamiflu may have frequently been given to patients too late to be of use (paragraphs 3.28 and 3.29).

20 Between 2009-10 and 2012-13, 2.4 million units of Tamiflu were consumed, primarily during the influenza pandemic in 2009-10. Over the same period, 10 million units were written off (given the likely long periods between pandemics it is inevitable that stock will be written off without being used due to reaching end of shelf life). Six and a half million units were written off at a cost of £74 million (2011-12 prices) due to the poor record keeping by the NHS about their storage environment during the 2009-10 pandemic, as recorded in the Department of Health accounts for 2009-10 (paragraph 3.31).

Conclusion

21 Regulators are confident that they are provided with all required and requested information from manufacturers when licensing new medicines, insofar as it is possible to know. We noted that the United States regulator requests more information and may spend more time on performing its own analysis. NICE's legal position is not as strong as that of regulators, as they have no automatic access rights to manufacturer information submitted to either the EMA or MHRA. This means that they have to request data from the manufacturer which has already been provided as part of licensing.

22 Regulators' assessments of Tamiflu for the treatment of influenza have broadly agreed on its ability to reduce the duration of symptoms and to assist in preventing influenza illness. They, and other reviewers, have been generally reluctant to accept that clinical evidence is strong enough to support claims for avoidance of serious illness and death due to complications of influenza. Coming to a conclusion on the efficacy of treatment is, however, complicated by the fact that different reviewers may apply different criteria when evaluating evidence.

23 Stockpiling of antiviral medicines in anticipation of an influenza pandemic is in line with WHO guidance and is likely to be justified even with more cautious assessments of their efficacy. The Department's business case indicated that a stockpile providing 50 per cent population coverage would not provide significant additional benefits to a stockpile providing 25 per cent coverage, but this was based on the optimistic assumption that it would be possible to prioritise the use of the smaller stockpile on those most at risk. In reality this might not be possible. As the nature of a future pandemic virus is unknown, it is not possible to determine the ideal level of population coverage within the 25 to 50 per cent range but all stockpiles in this range are cost-effective. The Department also factored in the desire to maintain public confidence in the pandemic response by being able to make antivirals available to all those who might become ill in a pandemic and that the stockpile comprised both Tamiflu as the primary antiviral and Relenza as the contingency.

Recommendations

- a** NICE and the MHRA should work together, with the EMA where necessary, to ensure that arrangements are in place to allow NICE to access the evidence underlying regulatory decisions to avoid the necessity for duplicated effort by NICE and remove the potential for gaps in the evidence available to them.
- b** NICE should require manufacturers to give assurances that they have confirmed at a global level that the evidence submitted is complete.
- c** NICE should align its policies for the publication of information across single and multiple technology appraisals of medicines or treatments.
- d** When making decisions about the stockpiling of pandemic medicines, the Department and its agencies should concentrate on building up knowledge about the added value of stockpiling through reducing complications and deaths, if necessary by commissioning additional independent research.
- e** To reduce the risk of unnecessary write-offs, NHS England and Public Health England should ensure that all providers of antivirals in a pandemic have robust antiviral storage and quality control in place during a pandemic, which is in line with the Department's Antiviral Distribution Framework Guidance. The Department should seek assurance from NHS England and Public Health England that this is the case.
- f** The Department should review its guidance and methods for ensuring that those in need of Tamiflu receive it quickly enough for it to be of use.