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Department of Health

Access to clinical trial information and the stockpiling of Tamiflu

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National Audit Office

Department of Health

Access to clinical trial information and the stockpiling of Tamiflu

Report by the Comptroller and Auditor General

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Amyas Morse
Comptroller and Auditor General
National Audit Office

17 May 2013

This review reports whether medicines regulators and NICE have access to the clinical trials evidence they require when licensing Tamiflu and other medicines for use in the NHS, and whether the Department of Health stockpiled Tamiflu for influenza pandemics on the basis of clinical evidence.

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This report can be found on the
National Audit Office website at
www.nao.org.uk/tamiflu-2013

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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.

Part One

Introduction

The scope of this review

1.1 The NHS spends billions of pounds a year on medicines. There are obvious value for money considerations in purchasing this amount of medicine, especially where medicines are being stockpiled on a large scale for future use. The National Audit Office is in receipt of correspondence from a number of Members of Parliament raising questions about access to information on all clinical trials for UK regulators when licensing and appraising new medicines, and the decision to stockpile the antiviral medicine Tamiflu, which provides an opportunity to examine these issues. A key concern was that, without full clinical trial information, public money could be spent ineffectively. In response, the NAO carried out a review to establish whether:

- medicines regulators and the National Institute for Health and Care Excellence (NICE – formerly known as the National Institute for Health and Clinical Excellence) assure themselves that they have all clinical trials evidence when licensing and appraising new medicines to be used in the NHS (Part Two);
- all the clinical trials information was available to medicines regulators when they licensed Tamiflu and when NICE undertook its effectiveness assessment of Tamiflu (Part Three); and
- the NHS stockpiled Tamiflu for the treatment of influenza pandemics on the basis of clinical evidence, and on the advice of the appropriate authorities (Part Three).

1.2 This review does not attempt to independently evaluate the efficacy (a measure of the beneficial effect of the medicine on patients) of Tamiflu. It reviews, as clearly as possible, the views of experts on its efficacy (see Figure 4).

1.3 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. This reflects perceptions that information about unfavourable trials is suppressed and available data exhibit 'publication bias', where published clinical trials tend to be those with more favourable results than the unpublished trials. All clinical trials undertaken prior to licensing are sponsored by the manufacturer and there are calls for these trials to be undertaken by independent organisations.

1.4 In its recent report,¹ the Health Select Committee made a number of recommendations on clinical trial information, including:

- There should be both a professional and legal obligation to ensure that all regulators, including NICE, have access to all the available research data about the efficacy and safety of pharmaceutical products.
- All information arising from medicines trials should be in the public domain in an accessible and properly anonymised form.
- The pharmaceutical industry should introduce a new code of practice covering research. This should include an obligation to make public all data about medicines which are in current use.

1.5 In July 2012, the European Commission adopted a proposal for a regulation to replace the existing legislation on clinical trials in the European Union (EU).² A key part of the new regulation will be to increase the transparency of clinical trials conducted in the EU including publication of trial results on a publicly accessible database. The new regulation is likely to come into effect towards the end of 2016.

Licensing medicines and evaluating clinical and cost-effectiveness

1.6 Any new medicine needs to be granted a licence. For medicines intended for use across the EU, licences are granted by the European Commission with the licensing process coordinated by the European Medicines Agency (EMA). UK-only authorisations are granted by the Medicines and Healthcare products Regulatory Agency (MHRA) (see Part Two for a description of the regulatory process). Before a licence is granted, information about the medicine is assessed to ensure its efficacy and that it is safe and also that the product is of sufficient quality. Clinical trials on humans are the key source of information used to understand the efficacy of a medicine and to determine whether it is safe. The majority of clinical trials are undertaken, or sponsored, by the medicine manufacturer.

1.7 In addition to undergoing the licensing process, a number of medicines in England are also appraised by NICE to assess their clinical and cost-effectiveness for use in the NHS. The NICE Technology Appraisal process is described in Part Two. NICE combine clinical trials information with their own economic evaluation to make a judgement about the medicine's clinical and cost-effectiveness.

Spending on medicines

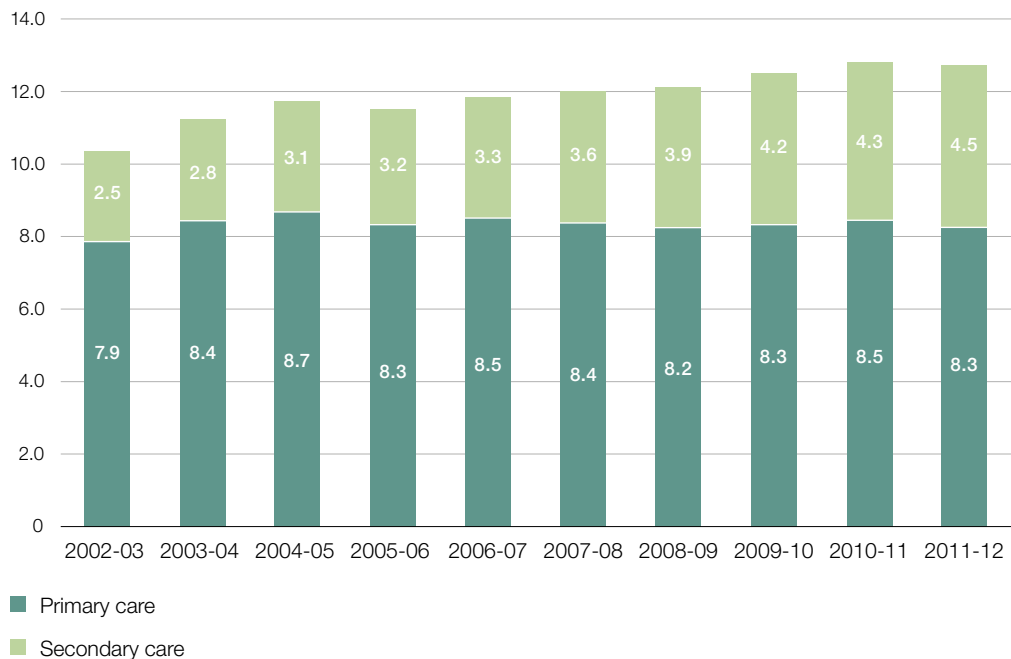
1.8 The cost of medicines is a major expenditure item for the NHS. In 2011-12, the NHS spent £12.7 billion on medicines. NHS spending on medicines has grown by, on average, 2.3 per cent a year in real terms between 2002-03 and 2011-12 (**Figure 1** overleaf). This does not include medicines purchased directly by the Department of Health (the Department), for example, medicines for influenza emergency preparedness. The Department's expenditure on antiviral drugs for pandemic influenza is set out in Part Three.

Figure 1

Annual spending on medicines by the NHS (2011-12 prices)

NHS spending on medicines has grown by, on average, 2.3 per cent a year in real terms between 2002-03 and 2011-12

Expenditure (£bn)



NOTES

- 1 Data have been converted to 2011-12 prices using HM Treasury's GDP deflator.
- 2 The primary care medicines expenditure figures quoted are derived from Department of Health accounts.
- 3 The secondary care medicines expenditure figures quoted are derived from Department of Health Financial Returns and from foundation trust year-end accounts provided by Monitor.
- 4 Primary care expenditure includes amounts paid to pharmacy and appliance contractors and amounts authorised for dispensing doctors and personal administration in England. The data do not cover costs for drugs prescribed in hospital but dispensed in the community or for private prescriptions.
- 5 Secondary care expenditure on medicines includes medical gases. Medicines prescribed in hospitals but dispensed in the community are also included in secondary care data.
- 6 Data do not include direct spending by the Department of Health on medicines for influenza emergency preparedness.

Source: Department of Health

Part Two

How medicines are assessed for safety and effectiveness in the United Kingdom

2.1 This part provides an overview of the licensing of medicines for use in the NHS by UK and European Union (EU) regulators; and also how medicines are appraised for clinical and cost-effectiveness by the National Institute for Health and Care Excellence (NICE – formerly known as the National Institute for Health and Clinical Excellence). It focuses on the processes they follow to establish they have all the information necessary when undertaking their assessments.

Medicines licensing

Overview of licensing for medicines available in the United Kingdom

2.2 The regulator responsible for licensing medicines in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). However, if a manufacturer is applying for an authorisation that is valid in all EU member states they will make a single application through the 'centralised procedure', coordinated by the European Medicines Agency (EMA). This is mandatory for certain types of medicines (e.g. human medicines derived from biotechnology) and optional for others. A large proportion of medicines are evaluated through the centralised procedure (see **Figure 2**). In other cases the national regulator will take the lead in the licensing process.

Figure 2

Key stages of the European Medicines Agency (EMA) centralised licensing procedure

The evaluation of centrally authorised medicines for the EMA is done by the Committee for Medicinal Products for Human Use (CHMP), which is composed of members from each of the European Union member states, and additional scientific expertise.

For each product, the CHMP appoints two of its members to lead and coordinate the evaluation.

A **pre-submission meeting** can be requested by the manufacturer to discuss the format and content of the submission before **submission of the application**. Once the application has been received, there is a scientific evaluation which can last up to a maximum of 210 days (pauses are allowed according to defined criteria), unless the application is withdrawn by the manufacturer. At the end of this period the CHMP must issue a **scientific opinion** on whether the medicine may be authorised or not.

The European Commission has the ultimate authority for granting the **marketing authorisation**.

Source: European Medicines Agency

Assurance on clinical trials information

2.3 The legal basis for medicine licensing in the EU is Directive 2001/83.³ The Directive includes a clear obligation to provide all information on completed, ongoing and abandoned clinical trials: “In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the application and/or completed trials concerning therapeutic indications not covered by the application.”⁴ Each application is accompanied by a signed declaration from the manufacturer confirming inclusion of all relevant information.

2.4 The Directive describes the format in which the manufacturer submits evidence as part of the licensing application. The International Conference on Harmonisation^a has worked to develop consensus guidelines for the format and much of the technical content of the dossiers submitted to licensing authorities. The majority of this guidance has been adopted by the regulatory authorities in the United States, the EU and Japan, and by other national regulators.

2.5 As well as the dossier, the manufacturer submits the parts of their detailed clinical study reports on completed clinical trials^b which describe the methods and results. The other parts, which contain the individual patient level data for the trial, are not submitted. The EMA or national regulator can request these additional parts at 48 hours’ notice.^c

2.6 The manufacturer is also required to submit notification of trials currently under way. The Directive states that, following licensing, any further information that might influence the licensing decision must be provided by the manufacturer, such as reports of adverse reactions suffered by patients. Manufacturers are required to monitor the safety of medicines following licensing, throughout their marketed life. This information should include both positive and negative results of clinical trials. However, there can be complex relationships between manufacturers and data owners. The manufacturer may not be able to access data if the data is owned by the research organisations which undertook the trials. However, they should still notify the regulator of the trial’s existence. The legislation on ongoing monitoring following licensing was updated in 2010 with Directive 2010/84/EU⁵ amending Directive 2001/83, which came into effect in 2012, and was reflected in the Human Medicines Regulation 2012.

a Founded in 1990, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use brings together the regulatory authorities and pharmaceutical industry associations of Europe, Japan and the United States to develop consensus guidance regarding the scientific and technical aspects of drug registration.

b A clinical study report is the detailed report setting out the protocols, methodology, results and patient level data for a clinical trial. They can be several hundred pages long. Their structure and content was harmonised through the International Conference on Harmonisation in 1995.

c Inspections can be undertaken to look into clinical trials that are submitted as part of a licensing application. Trial sites where patients were treated can be inspected to assure the EMA/national regulator that the data are robust and can be used to support the claims made in the application.

2.7 The licensing submission is validated for completeness by the EMA or national regulator which may include searches of clinical trials databases. In the EU, all clinical trials must be authorised by the national regulator, and the relevant ethics committee,^d before they can commence. Since May 2004, as part of the authorisation process, all clinical trials performed in the EU are registered in a database (EudraCT) by the national regulator.⁶ Non-EU trials are not included in the database. Certain parts of the database allow public access to information describing key aspects of trials, based on a World Health Organisation agreed set of data fields. This includes: trial authorisation status; the member states involved; details of the trial protocol; the disease; the patient population; study title; study sponsor; and study purpose. This has been in place since March 2011. The EMA intend to make trial result summaries available towards the end of 2013.

2.8 The EMA and MHRA have had a confidentiality agreement with the United States regulator, the Food and Drug Administration (FDA), since 2003. This allows most of the information, provided as part of the licensing application and information developed by the regulators themselves, to be shared. This is generally high level information but can include assessment reports. Actual clinical trial data is neither requested nor shared under this agreement. Our discussions with the EMA and FDA indicated that, while there is not a systematic process for ‘clearing’ licensing decisions across regulators, there are often discussions about specific applications, especially where final decisions differ across regulators or licensing decisions are ‘close calls’. Regular formal exchanges on specific medicines started with the signing of the confidentiality arrangements. Prior to this, and still today, there are annual formal meetings between the FDA, EMA and the European Commission, and numerous informal communications between them.

Failure to provide information

2.9 A maximum fine of 5 per cent of the manufacturer’s EU turnover in the preceding business year can be imposed by the European Commission for an infringement of the European Regulation on disclosure requirements for evidence submissions.⁷ If the infringement is not corrected then further fines can be imposed. If the facts of any given case also reveal that offences under general criminal law have been committed, then they can be prosecuted under member states national law and are likely to carry heavier penalties. Infringements can carry a maximum penalty of two years imprisonment.

^d Ethics committees are responsible for the research ethics review of all proposals for research which involve human participants. There are 78 ethics committees in England.

2.10 The EMA and MHRA were not aware of an application which has been granted on the basis of falsified or incomplete data. The MHRA has recently prosecuted an individual for falsifying clinical trial results.⁸ There are two cases where manufacturers have failed to report ongoing safety information:

- GlaxoSmithKline (GSK): The MHRA concluded in 2008 that GSK had failed to inform the MHRA of information it had on the safety of Seroxat (anti-depressant medicine) in under 18s in a timely manner although GSK disputed this. A criminal prosecution was not pursued as the legislation in force at the time was not sufficiently strong or comprehensive as to require companies to inform the regulator of safety information when the drug was being used for, or tested outside its licence indications. In response, the UK legislation on reporting requirements was strengthened in 2008. European law was also strengthened, most recently in 2012.
- Roche: The EMA issued infringement proceedings against Roche in October 2012, following an inspection by the MHRA that found that a significant amount of safety data gathered by Roche on 46 medicines authorised in the UK (including 19 centrally authorised medicines one of which is Tamiflu) had not been fully reported. The MHRA agreed a timetable with Roche to provide outstanding data and comply with its requirements. There were no immediate safety concerns, and no action taken on any products. The EMA and the national regulatory agencies in the EU are currently assessing data provided by Roche and evaluating its implications for the relevant market authorisations. The evaluation is due to be completed in June 2013.

Publication of information used in licensing decisions

2.11 For medicines licensed through the centralised procedure, the EMA publish the licensing decision together with a summary of the evidence supporting the decision (European public assessment report) and the procedural steps taken before authorisation. The licensing history, including any variations made at a later date, is also published. For medicines licensed at a national level, a similar public assessment report is published by the MHRA. Detailed clinical study reports are not published.

Comparison with medicine licensing in the United States

2.12 As in the EU, there is a legal obligation on manufacturers to provide all information to the United States FDA as part of the licensing application. There are two significant additional steps in the FDA licensing process. Together they may provide additional rigour to the evaluation process, though there would be inevitable resource implications if introduced to Europe:

- Analysis of manufacturers' submissions: the FDA requires all parts of clinical study reports (including patient-level data – some as case record forms, some as tabulations, some as both) whereas the EU regulatory bodies do not request patient-level data. The FDA has the capacity to rerun, and check, analysis undertaken by the manufacturer and to perform analysis of its own should it choose to do so.
- Knowledge of medicines during development: the FDA team that handles the licensing application will usually already have shadowed the development of the medicine through the Investigational New Drug application process. This includes, for example, discussion sessions with the manufacturer during product development.

2.13 In the United States there is also a clinical trials database (clinicaltrials.gov), launched in 2000, administered by the National Institutes of Health. It is a legal requirement for trials in the United States to be registered and, since 2007, to provide certain trials results. Many trials conducted outside the United States are also registered on the database.

NICE technology appraisals

2.14 NICE provides guidance to UK healthcare professionals in the NHS and elsewhere, one key aspect of which is to assess the clinical and cost-effectiveness of new and existing medicines and treatments within the NHS through 'technology appraisals'.

Overview of NICE technology appraisal process

2.15 Technology appraisals use clinical and economic evidence to assess whether a medicine or treatment provides value for money to the NHS. Technology appraisal can cover either a single medicine or treatment (single technology appraisal); or several medicines or one medicine for use in several different ways (multiple technology appraisal).

Figure 3 overleaf provides an overview of the key steps within a technology appraisal and explains some of the differences in process between the two types. The multiple technology appraisal was the original methodology adopted by NICE. The single technology appraisal was introduced in 2005 to reduce the time taken to assess some medicines.

Figure 3

Key stages of a technology appraisal

For both single and multiple technology appraisals, the manufacturer provides an **evidence submission** with other consultees also invited to submit evidence. For the single technology appraisal the manufacturer provides the evidence in a standard format specified by NICE.

NICE commissions an independent academic centre to review the evidence submission and **prepare an assessment report**. For a single technology appraisal, the academic centre prepares a report based on a review of the manufacturer's evidence submission and expert advice. For a multiple technology appraisal, the academic centre's assessment report is based on a systematic review of the literature, examination of submissions, and advice from clinicians.

An **independent advisory committee** considers the key evidence and hears evidence from nominated clinical experts, patients and carers. Committee discussions are held in public. The Committee will make provisional recommendations and put these out to consultation if it has made recommendations that are more limited than the instructions for use that accompany the medicine or treatment. Following any consultation comments, the committee will make a **final appraisal determination**.

If there are no appeals, or an appeal is not upheld, the final recommendations are issued as **NICE guidance**.

Source: National Institute for Health and Care Excellence

Assurance on clinical trials information

2.16 NICE guidance to manufacturers states that they should:

“identify all evidence relevant to the appraisal. This includes a list of all studies sponsored by them or known to them, in the form of all clinical trials, follow-up studies and evidence from disease registers ... It is important that attempts are made to identify evidence that is not in the public domain. Such evidence includes data from unpublished clinical trials and additional data from trials that have either been published in abstract form only or for which only selected information has been reported.”

2.17 NICE decides what information is ‘relevant’ to its assessment. While there is no legal obligation on manufacturers to provide all information for technology appraisals, NICE requires manufacturers and sponsors to sign a statement declaring that all relevant material has been disclosed, signed by the manufacturer's UK medical director. NICE told us that there is no obligation on the UK medical director to confirm with other offices of the manufacturer that the submission was complete. NICE's requirements contrast with a more legally binding system in Germany, where the Institute for Quality and Efficiency in Healthcare (IQWiG) carry out a similar role to the independent academic centres commissioned by NICE to undertake systematic reviews.^e Since 2011, and following evidence that manufacturers had not always provided full information to IQWiG during assessments, a legal obligation was placed on manufacturers to submit a list of all its sponsored clinical trials and all clinical study reports. Incomplete submission by the manufacturers leads to a negative outcome of the IQWiG assessment.

^e This is part of the process to determine the benefit package (including provision of medicines) of the statutory health insurance system in Germany.

2.18 The academic centres to which NICE delegates the assessment work use a range of search methods to establish whether all relevant information has been submitted by the manufacturer, using standardised guidance.⁹

2.19 NICE does not have formal automatic access rights to information submitted to the EMA or MHRA. It generally relies on the EMA's European public assessment report (see paragraph 2.11) to check completeness of manufacturer submissions before issuing its guidance, and seeks clarifications when required. The European public assessment report is, however, only a summary report and does not allow NICE, and the academic centres commissioned by NICE, to check the extent of information submitted as part of the licensing process. Since many NICE technology appraisals are undertaken in parallel with the licensing process, the EMA's report might not be available to provide real-time validation during initial analysis. NICE therefore has to duplicate some of the regulator's information requests to the manufacturer, but unless the manufacturer consents, or there is an overriding public health interest, it cannot cross-check with the EMA or MHRA that they have received the same unpublished material in response.

Failure to provide information

2.20 NICE confirmed it was not aware of any instances where a manufacturer had deliberately concealed information during a technology appraisal process. However, it may be the case that the UK affiliate of a multinational cannot access research done by other arms of the organisation.

2.21 NICE indicated a number of sanctions that it has available if a manufacturer is found to have not provided all relevant information material to the appraisal:

- the appraisal can be suspended while the manufacturer provides the missing information;
- draft guidance can be published which states that NICE is minded not to recommend the use of the treatment because evidence that it considers material has not been made available; and
- the appraisal could be terminated, with guidance to the NHS stating that NICE is unable to recommend the medicine for use in the NHS as no or insufficient evidence was received from the manufacturer.

Publication of information used in technology appraisal decisions

2.22 NICE's policy is to publish all information that has been considered by the advisory committee. This will include the academic centre's assessment report. For single technology appraisals, the full submission from the manufacturer is published. The full manufacturer submission for multiple technology appraisals is not currently published, so the policies for the two types of assessment are not aligned. Multiple technology appraisals were the initial appraisal methodology adopted by NICE in 2003. At that time, manufacturers' submissions were not published and this policy has not been revised since then. Any reports on clinical trials received from the manufacturer are not published. Commercial or academic-in-confidence information is redacted from published documents.

Part Three

Tamiflu

3.1 Tamiflu is an antiviral medicine that contains the active substance oseltamivir. It acts on the influenza virus, blocking some of the enzymes on its surface known as neuraminidases. When the neuraminidases are blocked, the virus cannot spread. Tamiflu is manufactured by F. Hoffmann-La Roche Ltd (Roche).

3.2 This part of the report describes the licensing of Tamiflu for seasonal influenza and its National Institute for Health and Care Excellence (NICE – formerly known as the National Institute for Health and Clinical Excellence) technology appraisal, focusing on whether all information was provided for these reviews. It also examines the decision to stockpile Tamiflu for use during influenza pandemics including spending on building and maintaining the stockpile.

3.3 **Figure 4** on pages 22 to 25 sets out the assessments of Tamiflu's efficacy made by regulators, other parts of government and the independent Cochrane Collaboration.

Figure 4
Assessments of the efficacy of Tamiflu

Function	Indications for seasonal influenza			Indications for pandemic influenza						
	Licensing		Clinical and cost-effectiveness assessment	Independent evidence assessment			World Health Organisation (WHO) and Department of Health assessments			
Organisation	United States Food and Drug Administration (FDA) (1999 onwards) ¹ – evidence of efficacy based on most up-to-date assessment (paragraph 3.6).	European Medicines Agency (EMA) (2002 onwards) ¹ – evidence of efficacy based on most up-to-date assessment (Figure 5).	National Institute for Health and Care Excellence (NICE) technology appraisals (2003; updated 2008 and 2009) – evidence of effectiveness based on updates (paragraphs 3.9 and 3.10).	Cochrane Collaboration (1999; updated in 2006) (paragraph 3.14).	Cochrane Collaboration (2009. Withdrawn 2010) (paragraph 3.14).	Cochrane Collaboration (2012) (paragraph 3.15 and Figure 6).	World Health Organisation (2004) (paragraph 3.17).	Department of Health – Scientific Evidence Base Review (2007) (paragraph 3.20).	Department of Health – Scientific Evidence Base Review (2011) (paragraph 3.28).	Department of Health – Scientific Evidence Base update (2013) (paragraph 3.29).
Sources of information	Manufacturer's dossier, clinical study reports and patient-level data for all completed trials. Also monitoring of medicine development process.	Manufacturer's dossier, clinical study reports (excluding patient-level data) for all completed trials.	Manufacturer and other consultee's submissions. Systematic review by independent academic centre.	Systematic review of published literature, supplemented by some unpublished data from manufacturers.	Systematic review of published literature.	Systematic review of available clinical study reports, but excludes all published literature. Correspondence with manufacturers and regulators together with regulatory documents from the FDA, EMA and the Japanese regulator.	Review of published literature and WHO consultation held in Geneva on 2 to 4 October 2002. Evidence only available for seasonal influenza.	Review of published literature (significant evidence taken from NICE 2003 technology appraisals). Evidence only available for seasonal influenza.	Systematic review of published literature and databases – primarily seasonal influenza, but does include observational studies of 2009-10 pandemic.	Systematic review of published observational studies from the 2009-10 pandemic influenza period.
Assurance about completeness of information	Submission requirements enforced by law together with validation checks of manufacturer's dossier submission.		Submission signed off by manufacturers' UK medical director. Checks by academic centre on completeness of evidence.	Depends on ability of researchers to identify and access relevant data and information.						
Evidence of efficacy	1 to 1.5 days reduction in duration of symptoms for adults and children (for children the evidence was for 'freedom from illness'). ^{2,3}	1 to 1.5 days reduction in duration of symptoms for adults and children (for children the evidence was for 'freedom from illness'). ^{2,3}	0.5 to 1.5 days reduction in duration of symptoms in healthy adults. ³	1 day reduction in duration of symptoms in healthy adults.	Evidence of reduction in duration of symptoms.	21 hour reduction in duration of symptoms.	1 to 2 day reduction in time to resume usual activities.	0.5 to 1.5 days reduction in duration of symptoms for healthy adults, children, and elderly. ²	Around 1 day reduction in duration of symptoms for healthy adults, children and elderly. ²	Summary of 2011 review findings.

Figure 4 continued

Assessments of the efficacy of Tamiflu

Evidence of efficacy continued	Indications for seasonal influenza			Indications for pandemic influenza						
	Licensing	Clinical and cost-effectiveness assessment	Independent evidence assessment	World Health Organisation (WHO) and Department of Health assessments						
Organisation	United States Food and Drug Administration (FDA) continued	European Medicines Agency (EMA) continued	National Institute for Health and Care Excellence (NICE) continued	Cochrane Collaboration (2006) continued	Cochrane Collaboration (2009) continued	Cochrane Collaboration (2012) continued	World Health Organisation (2004) continued	Department of Health (2007) continued	Department of Health (2011) continued	Department of Health (2013) continued
Prophylaxis from prolonged use during a community outbreak (seasonal prophylaxis)	Evidence of prophylaxis for adults and elderly ³ (not covering prevention of person-to-person transmission).	Evidence of prophylaxis for adults and elderly ³ (no evidence of prevention of person-to-person transmission).	Evidence on prophylaxis, particularly in elderly patients ³ (economic model did not include prevention of person-to-person transmission).	Evidence of prevention.	Evidence of prevention.	Due to limitations in the evidence, not possible to assess the effectiveness of prevention and complications.	Evidence of prophylaxis in elderly.	Evidence of prophylaxis.	Evidence of prophylaxis.	Summary of 2011 review findings.
Prophylaxis after contact with infected person (post-exposure prophylaxis)	Evidence of prophylaxis within households ³ (not covering prevention of person-to-person transmission).	Evidence of prophylaxis within households ³ (no evidence of prevention of person-to-person transmission).	Evidence on prophylaxis within households ³ (economic model did not include prevention of person-to-person transmission).	Evidence of prevention.	Evidence of prevention within households.	Due to limitations in the evidence, not possible to assess the effectiveness of prevention and complications.	Evidence of prophylaxis within households.	Evidence of prophylaxis within households.	Evidence of prophylaxis within households.	Summary of 2011 review findings.
Complications	Meta-analysis evidence on reduced complications not accepted due to lack of statistical significance.	Evidence of reduced complications treated with antibiotics in children, adults and the elderly. The EMA told the NAO that it considers the evidence not particularly extensive in this area.	Overall, data limited with strongest evidence on reduced antibiotic use.	Not mentioned.	No evidence due to exclusion of Kaiser meta-analysis.	Due to limitations in the evidence, not possible to assess the effectiveness of prevention and complications.	Evidence of reduced complications leading to antibiotic use in adults and complications in children.	Evidence of reduced complications requiring antibiotic use in adults and children.	Some evidence of reduced antibiotic use in healthy and 'at risk' adults and in children. Some observational data on reduced likelihood of hospitalisation during 2009 pandemic.	Data suggests reduced mortality and severe outcomes in hospitalised patients.
Hospitalisation and mortality	Not mentioned.	Not mentioned.	No clear evidence on reduced hospitalisation.	Not mentioned.	Not mentioned.	Evidence indicates not effective in reducing hospitalisation.	Preliminary analysis of evidence indicates reduced hospitalisation although evidence on 'at risk' groups is limited.	Evidence of reduced hospitalisation.	No significant evidence on hospitalisation.	Data suggests reduced mortality and severe outcomes in hospitalised patients.

NOTES

- 1 There have been other minor amendments to licences in the US and Europe during the period.
- 2 Children means 1 to 12-year-olds, adults means adults and adolescents 13 years and older, elderly means 65 years and older.
- 3 Positive impact dependent on administering Tamiflu within 48 hours.

Source: National Audit Office analysis of published documents

The licensing and technology appraisal of Tamiflu for use in the treatment of seasonal influenza

The licensing of Tamiflu

3.4 The authorisation of Tamiflu for use across the European Union (EU) was coordinated by the European Medicines Agency (EMA), as described in paragraph 2.2 and Figure 2. The Finnish Medicines Agency carried out the assessment on the EMA's behalf with the assistance of the Portuguese National Authority of Medicines and Health Products. Along with other member states, the UK Medicines and Healthcare products Regulatory Agency (MHRA) had the opportunity to contribute its views during the initial application process. The application was submitted by Roche in February 2001 with the final marketing authorisation approved by the European Commission in June 2002. This covered the use of Tamiflu for treatment and prophylaxis (prevention of illness).

3.5 There have been a number of variations to the original market authorisation, for example extending authorisation for use with children. The overall scientific evaluation of efficacy, however, has remained largely unchanged. The marketing authorisation was renewed by the EMA in 2007 and 2012.

3.6 The key benefits of Tamiflu identified in the EMA's current assessment report¹⁰ are shown in **Figure 5**. The EMA's conclusions closely mirror those of their equivalent body in the United States, the Food and Drug Administration (FDA), for prophylaxis and reduction in symptom duration. The FDA does not accept evidence for reduced complications (see discussion of complication evidence at paragraph 3.12).

Access to data

3.7 At the time of the licensing of Tamiflu, the current directive covering the legal basis for medicine licensing in the EU (Directive 2001/83) was not in place. However, the previous directive also clearly stated that the manufacturer should provide full information, both favourable and unfavourable.¹¹

3.8 The EMA is not aware of any completed clinical trials from that period that were not included in the original licensing application. A clinical trial conducted in China by Roche Shanghai was under way at the time of the original licensing application in 2001. This was requested by the EMA in 2012 as part of its licensing renewal for Tamiflu. While Roche provided the clinical study report in April 2012, this was not in time to be considered as part of the renewal. The EMA told the NAO that the inclusion of this trial would not have changed the outcome of the licensing evaluation.

Figure 5

Key benefits of Tamiflu identified in the EMA's European public assessment report

The following was demonstrated to the satisfaction of the EMA when treatment began within two days of appearance of symptoms or exposure to the virus

Reduction of duration of symptom:

- Evidence of reduction in median duration of symptoms in otherwise healthy adults (around one day) and children (around 1.5 days).
- No statistically significant evidence of reduction in median duration of symptoms for 'at risk' groups (e.g. elderly or people with chronic cardiac and/or respiratory disease) but reduction of one day in the duration of symptoms.

Prophylaxis (prevention of illness):

- Evidence that Tamiflu reduced incidence of illness in people within households who took it after being in contact with someone with influenza.
- Evidence of reduced incidence of illness for adults and the elderly where people took Tamiflu over a prolonged period during an influenza outbreak in their community.
- The EMA told the NAO that this does not cover the prevention of person-to-person transmission.

Prevention of complications:

- Some evidence of reduced complications requiring treatment with antibiotics in children, adults and the elderly. However, the EMA told the NAO that it considers the evidence not particularly extensive in this area.

Adverse events:

- The EMA does indicate that there is some evidence of adverse reactions to the use of Tamiflu. Most common are headaches, nausea and vomiting. More serious adverse events have been rarely reported including, for example, neuropsychiatric disorders.

NOTE

1 Evidence is taken from Annex One – Summary of Product Characteristics, Section 5 (Pharmacological properties).

Source: *European Medicines Agency's European public assessment report 2012*

The NICE appraisals of Tamiflu

3.9 Tamiflu was assessed for clinical and cost-effectiveness in a seasonal influenza outbreak by NICE in 2003. Two appraisals were undertaken, underpinned by the same systematic evidence review.¹² The first recommended Tamiflu as being effective for the treatment of 'at risk' adults and children.¹³ The second recommended Tamiflu as being effective for the prophylaxis of influenza among 'at-risk' and unvaccinated people aged 13 and over. They should have been recently exposed to someone with influenza-like illness and able to start treatment within 48 hours of exposure. Tamiflu is not recommended for post-exposure prophylaxis in healthy people up to the age of 65 years or for the seasonal prophylaxis of influenza.^{f, 14} The appraisals were updated in 2008 and 2009,¹⁵ including two further systematic reviews. The guidance remained broadly unchanged.

f Unless they live in a residential care establishment where a resident or staff member has influenza.

3.10 The reviews in 2003 and the updates in 2008 and 2009 reported:

- evidence on the reduction in the duration of symptoms in healthy adults (0.5 to 1.5 days) which was the primary reason for the positive cost-effectiveness result;
- evidence on both post-exposure prophylaxis (within households) and seasonal prophylaxis following prolonged use during a community outbreak (particularly in elderly patients); and
- only limited evidence on the reduction in complications. The 2009 update highlighted significant limitations in the evidence due to studies with small sample sizes and short duration which were not designed to detect these outcomes. The most consistent evidence was linked to a reduction in the use of antibiotics with no clear evidence on reduced pneumonia and hospitalisations.

Access to data

3.11 NICE guidance states that manufacturers should provide all relevant information. The 2003 systematic review states that clinical study reports were not provided by Roche on two unpublished clinical trials that had been completed at the time of the review. Roche wrote to NICE in May 2002 explaining the reasons for the omissions. One trial was omitted due to Roche not having access to the data which was owned by an independent research organisation. The other trial achieved very low participation numbers and therefore no useful analysis was deemed possible. Roche further confirmed that details of the clinical study reports were subsequently made available to NICE. An unpublished version of a meta-analysis,⁹ which included the two trials, was provided to the systematic review team by Roche. In this way, the review team were able to include the results of the two trials within their economic model.

Cochrane Collaboration reviews of Tamiflu and interpretations of the evidence on complications

3.12 Most assessments have been very cautious about quantifying Tamiflu's impact on 'complications' (that is, its ability to reduce the number of life-threatening cases, for example, those developing pneumonia). For seasonal influenza, complications are rare and therefore trials with a relatively small number of participants will not pick up enough individuals with complications to allow a proper analysis of efficacy. By pooling data from a number of trials, further analysis is possible through a meta-analysis. An unpublished meta-analysis of results, along with reports on individual clinical trials, was provided by Roche to both the EMA and the United States FDA as part of the original licensing submissions and as part of the submission to NICE in 2003. The FDA did not believe the results reached statistical significance. The EMA, however, included evidence from the Roche meta-analysis in its authorisation assessment report.

^g A statistical technique for combining the findings from different studies.

3.13 A different meta-analysis of this data was published in 2003 as a Roche sponsored study,¹⁶ which concluded that Tamiflu reduces complications, antibiotic use and hospitalisations in both healthy and ‘at risk’ adults.

3.14 The Cochrane Collaboration (Cochrane) is an international non-profit organisation that carries out systematic reviews of healthcare interventions by drawing together and evaluating sources of evidence from around the world. In 2006, Cochrane produced a review which indicated that Tamiflu was effective for both the treatment and prevention of influenza. While updating the review in 2009, under commission from the British and Australian governments, the Cochrane review team received a query on its inclusion of the Roche-sponsored meta-analysis. The query related to the fact that eight of the ten trials in the meta-analysis were unpublished and had not been peer reviewed. In response, Cochrane withdrew their 2009 review in February 2010. There followed a prolonged dispute between the Cochrane team and Roche concerning access to the original data, conducted increasingly in the public domain.¹⁷

3.15 Cochrane produced an update on the effectiveness of Tamiflu and Relenza^h in January 2012.¹⁸ Their conclusions are shown in **Figure 6** overleaf. The Cochrane review team has questioned certain elements of the EMA’s assessment of Tamiflu, particularly on prophylaxis and its inclusion within its assessment report of results of a meta-analysis indicating a reduction in complications (see paragraph 3.12). The EMA concluded that no regulatory action was required in response to Cochrane’s questions. In April 2013, Roche informed Cochrane that over the next few months they would release to Cochrane researchers the reports of all clinical trials on Tamiflu that they had sponsored. In line with EU law, each clinical study report will be edited by Roche to ensure patient confidentiality and to protect legitimate commercial interests.

The decision to stockpile Tamiflu for pandemic influenza

3.16 The World Health Organisation (WHO) defines a pandemic as the worldwide spread of a disease. An influenza pandemic occurs when a new influenza virus emerges and spreads around the world and most people do not have immunity. Vaccines are unlikely to be available in the early stages of a pandemic. The severity and timing of pandemics is unpredictable.

Initial stockpiling of Tamiflu

3.17 In the early 2000s, the spread of avian influenza from birds to humans was causing worldwide concerns. The initial Department of Health (the Department) decision to stockpile Tamiflu was based primarily on WHO advice and interpretation of existing evidence on the efficacy of Tamiflu against seasonal influenza. The WHO published guidance on the use of antivirals for pandemic influenza in 2004¹⁹ as part of overall guidance on pandemic preparedness.²⁰ 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.

^h Relenza is another neuraminidase antiviral medicine, manufactured by GlaxoSmithKline.

Figure 6

Conclusions of the 2012 Cochrane review

Evidence used

The reviewers applied selection criteria which led to more evidence being excluded than is usual for Cochrane reviews, although the review drew on more evidence than that used for the 2006 review. They only considered clinical trials where the clinical study reports were available, and there were no outstanding questions about the validity of the methodology. Published literature was not used due primarily to the Cochrane review team's concerns over a number of discrepancies between the clinical study reports and the published literature. Only 15 Tamiflu trials out of a possible population of over 100 met the criteria within the timescale of the review (Roche had not responded to all the team's requests for further information).

Conclusions

The review concluded that:

- Tamiflu shortened the duration of influenza symptoms by around 21 hours;
- there was no evidence of reduced hospitalisation;
- the evidence available was too incomplete to adjudicate on whether complications and onward transmission were reduced; and
- there were increased cases of nausea, vomiting and headache in those taking Tamiflu.

Source: T Jefferson, M A Jones, P Doshi, C B Del Mar, C J Heneghan, R Hama, M J Thompson. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD008965. DOI: 10.1002/14651858.CD008965.pub3

Basis for stockpiling decision

3.18 The Department did not develop a business case for the initial stockpiling of Tamiflu due to the perceived urgency of the situation with increasing concerns about avian influenza and the potential for an influenza pandemic. Key actions were agreed by the Secretary of State for Health in February 2005 following a submission by the then Permanent Secretary. Key actions were:

- stockpile enough antiviral medicines by 2008-09 for 25 per cent population coverage (based on WHO modelling of previous pandemics which showed a population infection rate of between 25 and 45 per cent);
- Tamiflu was chosen as the most effective antiviral based on the evidence available at the time;
- Tamiflu would be used only for treatment of infected people as use for household prophylaxis would require significantly larger stocks; and
- the Tamiflu stockpile would need to be replenished after 2010-11 due to the five-year shelf life.

3.19 Following this decision, the Department established a Scientific Advisory Group on Pandemic Influenza, to advise on the scientific evidence base for health-related pandemic influenza policies to inform future procurements. The Group approved the UK pandemic influenza contingency plan.

Work to build the evidence base in 2007

3.20 Throughout 2006 and 2007, a series of papers to the Scientific Advisory Group developed the evidence base on how to prepare for a pandemic, including the stockpiling of antivirals such as Tamiflu, culminating in a national framework published in November 2007.²¹ The framework was underpinned by a scientific evidence review on antivirals, put together by the Department, which drew on EMA and NICE judgements.²² The review concluded that:

- The Department's interpretation of the available evidence was that Tamiflu reduces the duration of symptoms and there was some evidence on the reduction in complications, antibiotic use and hospitalisation. On prophylaxis, there was evidence of both post-exposure prophylaxis and prophylaxis through prolonged use.
- It was prudent to stockpile in advance of a possible pandemic. Tamiflu and Relenza were the preferred choice for stockpiling, and it would be preferable to stockpile more than one medicine in case the pandemic virus developed resistance.
- While the main clinical intervention during a pandemic would be the treatment of the infected, a more marked impact could come from providing the medicines to household contacts of those infected (as highlighted in WHO guidance), although this would require a significantly larger stockpile.

Business case to increase the stockpile and the 2009 pandemic

3.21 During 2008, the Department developed a business case to establish a number of stockpiles of countermeasures such as antivirals and pre-pandemic vaccine. This included increasing antiviral medicines to 80 per cent population coverage in a two-stage process, underpinned by the scientific evidence review described in paragraph 3.20. This level of population coverage was based on mathematical modelling by the modelling working group of the Scientific Pandemic Influenza Advisory Committee.^{i,23} The business case was endorsed by the Scientific Advisory Committee and was broadly consistent with WHO guidance indicating that up to 45 per cent of the population would be ill during a pandemic.

i Formerly the Scientific Advisory Group on Pandemic Influenza. The Committee membership was expanded and included: academic experts in the field; representatives from the Health Protection Agency and Medical Research Council; hospital consultants and doctors; and a representative from GlaxoSmithKline.

Evidence for effectiveness of antivirals in the business case

3.22 The business case showed that benefits would considerably outweigh costs in a worst-case scenario, and benefits continued to outweigh costs even if pandemics were less severe, or only occurred every 100 years rather than the base case of every 33 years. The Department's chosen option – population coverage of 80 per cent for antivirals, 25 per cent for antibiotics and 45 per cent for vaccines – would yield a net annual benefit of between £10.5 and £32.4 billion for a worst-case pandemic, depending on frequency. An alternative scenario indicated that extending the antiviral stockpile to cover 50 per cent of the population would yield only small additional benefits to a stockpile of 25 per cent in a worst-case scenario, and no additional benefits under other scenarios. This was due to assumptions made in the modelling that the most at-risk groups would be targeted earliest.

3.23 Antivirals provided a net benefit across all scenarios used in the business case, when compared to scenarios with no antivirals. Benefits were calculated by estimating reductions in hospitalisation, complications and death rates due to the use of antiviral medicine and assigning economic values to these benefits. This was based on the Department's review of evidence described in paragraph 3.20 and was agreed by the Scientific Pandemic Influenza Advisory Committee. The evidence base for these assumptions was further reviewed by the Civil Contingencies Secretariat within the Cabinet Office who published a paper presenting the evidence on the government's strategy for responding to pandemics.²⁴ 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, however, advised that an assumption of 40 to 50 per cent reduction in both hospitalisations and deaths should be used in the modelling for 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.^j

3.24 The business case was agreed within the Department by its Revenue and Investment Branch and Finance Director, and was approved by HM Treasury in December 2008. The NHS Purchasing and Supply Agency placed orders in 2009 following a procurement process in line with EU regulations. The WHO announced a 'swine flu' pandemic in June 2009, which ran until August 2010.

Diversifying the stockpile

3.25 At the time of the business case, antiviral stockpile was made up solely of Tamiflu. By March 2009, the stockpile reached 50 per cent coverage with 35 per cent coverage from Tamiflu and 15 per cent from Relenza. Relenza is a similar medicine to Tamiflu, manufactured by GlaxoSmithKline. It was purchased to provide a back-up stockpile in the event of a new influenza strain being resistant to Tamiflu. This was endorsed by the Scientific Pandemic Influenza Advisory Committee.

^j The unpublished evidence was presented at the 2005 European Scientific Working Group on Influenza (ESWI) congress held in Malta, and was based on analysis of insurance claims made to a US insurer.

3.26 Between May and November 2009, the stockpile was further increased to 80 per cent with the additional stock made up of Tamiflu. This was not as part of the planned increase to allow for preventive treatment of households set out in the business case, but to provide additional contingency for treatment during the pandemic following agreement by the Civil Contingencies Committee (COBRA).^k Following the pandemic, the stockpile fell to 60 per cent due to consumption during the pandemic and was forecast to fall below 50 per cent by 2013-14 due to stock reaching end of shelf life (see paragraphs 3.30 to 3.32 for details of consumption and write-offs).

Stockpiling since the pandemic

3.27 In March 2011, the Department decided on cost and practicality grounds that it was not realistic to maintain the antiviral stockpile above 50 per cent population coverage and drew up an addendum to the 2008 business case to maintain the stockpile at 50 per cent. In 2010, additional modelling showed that having a stockpile with 50 per cent population coverage was likely to be highly cost-beneficial compared to having no stockpile. Maintaining the stockpile would be done through procuring replenishments to the stockpile as it reached its end of shelf life. The new UK strategy for pandemic influenza, published in November 2011, confirmed the maintenance of the stockpile.²⁵ As discussed in paragraph 3.22, the calculations within the Department's 2008 business case showed that stockpiling enough antivirals to cover 50 per cent of the population would result in only small additional benefits over the existing stockpile of 25 per cent in the worst-case scenario. This was due to assumptions made in the modelling that the most at-risk groups would be prioritised. In reality this may not be possible due to the nature of the pandemic virus or to the difficulties in the operational prioritisation of 'at-risk' groups. Failure to achieve this would result in the 25 per cent stockpile producing less benefit than estimated with increased benefits from moving to a 50 per cent stockpile. The Department stated that the decision to maintain the stockpile at 50 per cent also factored in the desire to maintain public confidence in the pandemic response by making it available to all those who become ill during a pandemic, practicalities of distribution and the inclusion of more than one antiviral in the stockpile.

^k The Civil Contingencies Committee is a cabinet committee chaired by the Home Secretary intended to deal with major crises.

3.28 To support the strategy a further review of the scientific evidence base on antivirals was commissioned and published in November 2011, which for the first time was able to draw on evidence gathered during a pandemic.²⁶ The review was approved by the Health Protection Agency^l and endorsed by the Scientific Pandemic Influenza Advisory Committee. The systematic review included published literature on studies into seasonal and pandemic influenza up to June 2010. Its conclusions regarding the effectiveness of Tamiflu were:

- Duration of symptoms will be reduced by half to one day and antibiotic use by around 60 per cent, if treatment is started within 48 hours.
- There is strong evidence that illness can be prevented by application before or after contact with infected people.
- A small number of observational studies^m carried out during the 2009 pandemic – some sponsored by Roche, and some carried out by independent researchers – reported that antivirals limited the spread of influenza, although the reviewers had reservations about data collection methods.

3.29 A further update review of the scientific evidence was completed in March 2013.²⁷ This was a systematic review of observational studies carried out during the 2009 pandemic. The review concluded that there was evidence that early treatment with antivirals during the pandemic had reduced death rates and severe outcomes among already hospitalised patients. The Scientific Advisory Group for Emergenciesⁿ had advised during the pandemic, based on evidence from case studies and observational studies, that there were benefits in administering antivirals for up to seven days after symptoms although early treatment was greatly preferable. While the Department looked to ensure people received antivirals quickly by introducing the National Pandemic Flu Service,^o and its review found there were significantly better outcomes from early treatment, it also indicated that antivirals appeared to be frequently administered too late for patients to benefit.

^l The Health Protection Agency's role is to provide an integrated approach to protecting UK public health through the provision of support and advice to a range of organisations including: the NHS; local authorities; and emergency services. On 1 April 2013, the Health Protection Agency became part of Public Health England.

^m Evidence from observational studies is seen as inherently weaker than that from clinical trials, but it is likely to be the only way of gathering evidence from a pandemic.

ⁿ The Scientific Advisory Group for Emergencies (SAGE) is responsible for coordinating and peer reviewing scientific and technical advice to inform decision-making at a UK level. SAGE was activated during the 2009 influenza pandemic.

^o The National Pandemic Flu Service, introduced in July 2009, comprised a dedicated website and call centres to diagnose swine flu quickly and provide an authorisation number to allow antivirals to be collected locally from designated antiviral collection points.

Tamiflu – spending and consumption

3.30 Tamiflu for use in a pandemic is purchased and stockpiled centrally by the Department and distributed at the time of a pandemic. Between 2006-07 and 2012-13, the Department spent £560 million on antiviral medicine (**Figure 7** overleaf). Of this, £424 million was spent on Tamiflu and £136 million on Relenza, as part of the 2011 strategy's intention to avoid being totally dependent on one antiviral medicine.^p Tamiflu was chosen as the primary antiviral medicine due to it being easier to administer, and being available in different dosages for different age groups.

3.31 Between 2006-07 and 2012-13, the Department purchased just under 40 million units of Tamiflu. Between 2009-10 and 2012-13, 2.4 million units were consumed, primarily during the pandemic in 2009-10, with 10 million units written off.^q Of the 10 million units written off, 6.5 million were written off before reaching the end of their shelf life in 2009-10 at a cost of £74 million.^r This was due to the Department being unable to verify that Tamiflu stock, distributed to the NHS during the 2009-10 pandemic, had been stored correctly. This was included in the Department's accounts for 2009-10. In response, the Department issued revised guidance to primary care providers in 2010.²⁸

3.32 As at the end of 2011-12, the value of stock held for Tamiflu was £234 million and for Relenza £129 million.^s Additional stocks of Tamiflu are due to reach their end of shelf life and be replaced during 2013-14 at a cost of £49 million. No stock reaches end of shelf life in 2014-15 due to shelf life being extended to seven years in more recently purchased stock of Tamiflu. Relenza has a shelf life of ten years.

3.33 Since being licensed by the EMA in 2002, Tamiflu has been available to GPs and hospitals to prescribe for use against seasonal influenza. Since 2002, spending in primary and secondary care on Tamiflu has been very small in relation to stockpiling for use in pandemics, totalling £2.7 million (2011 prices) or £2.6 million in nominal terms.

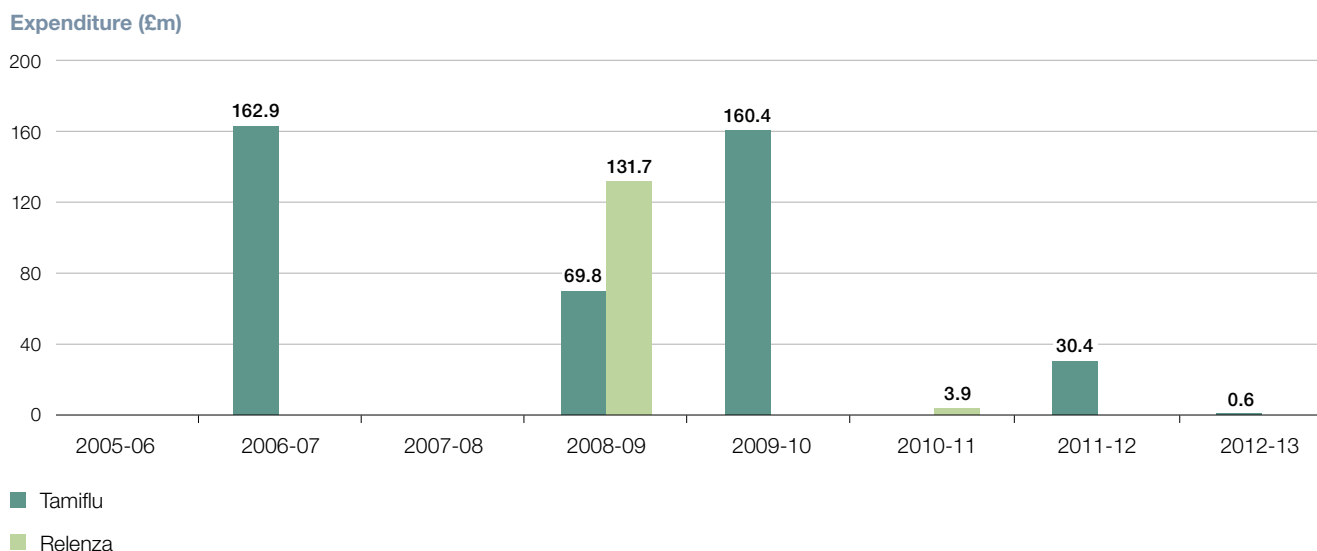
p All amounts are given in 2011-12 prices.

q Included within the units consumed are twelve 7kg drums and five 14kg drums of Tamiflu, equivalent to a significant number of Tamiflu capsules, depending on capsule size.

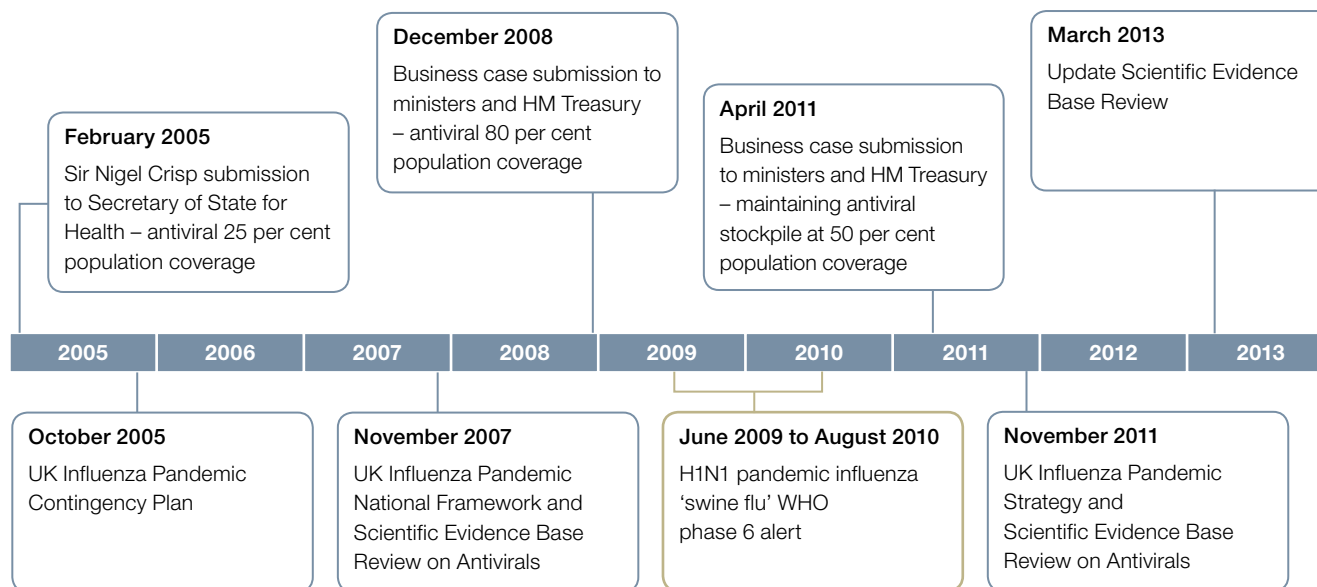
r All amounts are given in 2011-12 prices.

s The Department values the stockpile at current cost and do not depreciate it over its lifetime.

Figure 7
Expenditure on antiviral medicine by the Department of Health (2011-12 prices)



Key policy decisions/advice



NOTES

- 1 Data have been converted to 2011-12 prices using HM Treasury GDP deflator. For 2012-13, deflator based on forecast.
- 2 Includes all purchases of capsules (30mg, 45mg and 75mg), drums (7kg and 14kg) and oral suspension.
- 3 Expenditure is inclusive of VAT at prevailing rate at time of purchase.

Source: Department of Health

Appendix One

Our audit approach and evidence base

- 1 This memorandum reviewed whether:
 - medicines regulators and the National Institute for Health and Care Excellence (NICE) assure themselves that they have all clinical trials evidence when licensing and appraising new drugs to be used in the NHS;
 - all the clinical trials information was available to medicines regulators when they licenced Tamiflu and when NICE undertook its effectiveness assessment of Tamiflu; and
 - the NHS stockpiled Tamiflu for the treatment of influenza pandemics on the basis of clinical evidence, and on the advice of the appropriate authorities.
- 2 This memorandum does not attempt to draw conclusions on whether Tamiflu is value for money. Our conclusions are based on evidence collected using the following methods:
 - Interviews with: The Department of Health; the National Institute for Health and Care Excellence (NICE); the Medicines and Healthcare products Regulatory Agency (MHRA); the European Medicines Agency (EMA); the US Food and Drug Administration (FDA); the Cochrane Collaboration Tamiflu review team; Roche; the Health Research Authority (HRA); the Institute for Quality and Efficiency in Healthcare (IQWiG); Fiona Godlee (Editor of the British Medical Journal); Ben Goldacre (author of Bad Pharma); Sir Iain Chalmers (co-founder of the Cochrane Collaboration and coordinator of the James Lind Initiative); and Professor Jonathan Nguyen-Van-Tam (co-author of the 2011 and 2013 Department of Health antiviral scientific evidence base reviews).
 - Review of published literature, including: EMA and FDA assessments of Tamiflu; NICE technology appraisals of antivirals; Cochrane Collaboration antiviral reviews; Department of Health antivirals scientific evidence base reviews; UK government influenza pandemic strategy documents; World Health Organisation pandemic influenza strategy documents and reviews of antivirals; and various academic articles.
 - Review of key Department of Health internal documentation relating to the decision to stockpile antivirals.
 - Analysis of Department of Health data including data on: total NHS medicines expenditure; antiviral consumption and write-offs; antiviral expenditure; and antiviral stock levels.

Endnotes

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