

MHRA CONTRIBUTION TO THE H1N1 PANDEMIC

SUMMARY

1. The role of the Medicines and Healthcare products Regulatory Agency (MHRA) is to protect public health by ensuring that medicines and medical devices available on the UK market meet the required standards of safety, quality and efficacy. The role of the medicines regulatory regime was therefore central to the authorisation of the vaccines used in the pandemic and the medicines authorised to treat the symptoms of the disease.
2. The regulation of medicines, medical devices and blood is governed by European legislation. The MHRA is one of 27 national medicines authorities that works together to regulate medicines on the EU market. The MHRA is also one of 27 national Competent Authorities medical devices and the national Competent Authority for blood. The MHRA is seen as a strong and effective regulator and leads on both work associated with individual medicines and medical devices' strategy and on input to the development of legislation. This paper provides further information on the role of the MHRA in ensuring that appropriate medicines and medical devices were available in the UK during the pandemic.
3. In preparing for the possibility of a pandemic, the MHRA established a Flu Preparedness group in June 2007 which included representatives from Department of Health. This group's role became critical in 2009 when it became the Flu Business Continuity Management Team and met weekly under the chairmanship of either the Chief Executive or Chief Operating Officer throughout the period of the pandemic as the focus for Agency involvement in all aspects of the flu pandemic. There had also been a considerable amount of preparation done at EU level, for example in the development of an expedited process for assessing new vaccines.
4. The Agency also maintained close links with the wider Department of Health and its pandemic advisory committees in the years of planning prior to the pandemic, as well during the swine flu pandemic. During the planning period the MHRA was represented on the former Surveillance and Clinical Countermeasures Pandemic Influenza Groups (PIGs) and regularly attended the Joint Committee on Vaccination and Immunisation (JCVI) and its influenza sub-group meetings. Kent Woods was also a member of the Chief Medical Officer's National Influenza Pandemic Committee. In responding to the swine flu outbreak, MHRA regularly attended Cabinet Office's Scientific Advisory Group for Emergencies (SAGE), JCVI and internal planning meetings. These regular interactions allowed MHRA to provide critical input into cross-Government planning and response to support effective and safe delivery of vaccines, anti-virals, other medicines, swine flu positive control reagents, swine flu diagnosis algorithms and blood products during the pandemic period.
5. This paper sets out the overall contribution that the MHRA made to the Government's response to the H1N1 pandemic. There were many things that

went well, and we will want to build on these to ensure that we have in place appropriate and tested procedures should we need them in the future. We have also identified in this paper some areas in which we believe further work will be needed if Government is to be fully prepared should we be faced with a much more difficult and challenging pandemic in the future.

INTRODUCTION

6. The role of the MHRA in contributing to the Government response to the H1N1 pandemic was to:
 - Facilitate the authorisation of vaccines made available by the UK health services to protect the public from the disease;
 - Facilitate availability of medicines the anti-virals zanamivir (Relenza) and oseltamivir (Tamiflu) to shorten symptoms of the disease;
 - Monitor the safety of those medicines in use;
 - Ensure that healthcare professionals and patients had access to up to date information about these products;
 - Advise on the distribution and storage of vaccines;
 - Agree a derogation, on humanitarian grounds, for an HPA swine flu positive control reagent, and an HPA Virus Transport Medium and the DH swine flu self-diagnosis algorithm to be used in the UK without having to be CE marked under the Medical Devices Regulations;
 - Monitor the safety of those devices in use;
 - Prepared advice for use of medical devices during a Swine Flu pandemic;
 - Work closely with other parts of Department of Health and wider Government and Agencies to ensure a comprehensive and consistent approach to this exercise.
7. This paper sets out how the medicines and medical devices regulatory system contributed to the overall Government response and also considers what lessons have been learned from this exercise for the future.

THE MEDICINES LICENSING SYSTEM

8. Before they can be placed on the market medicines are assessed for safety, quality and efficacy. The regulation of medicines is governed by European legislation which aims to ensure that the terms in which medicines authorised are harmonised across the European Union (EU). Individual Member States (MS) have national medicines regulatory authorities (the MHRA in the UK) who work together to ensure that licences for medicines (marketing authorisations) are the same in each MS. One MS (known as the Reference Member State) takes the lead in assessing data supplied by the company in support of their application for a marketing authorisation, but the terms of the marketing authorisation are decided by agreement amongst those MS in which the company wishes to market its product.
9. There is also a European Medicines Agency (EMA) which broadly coordinates the work of the national regulatory authorities and which increasingly also takes responsibility for the authorisation of new medicines,

resulting in a single marketing authorisation that is valid throughout the EU. The work associated with assessing new medicines for a marketing authorisation under this “centralised procedure” is undertaken by a nominated MS (the rapporteur) and discussed and agreed by all MS in an EU scientific committee (the Committee for Medicinal Products for Human Use – CHMP) before the marketing authorisation is granted by the European Commission.

10. In both systems the MS that undertook the initial assessment usually leads on subsequent regulatory work associated with the medicine, such as implementing changes to the marketing authorisation arising from the results of monitoring the safety of the medicine in day to day use.

WHAT WORKED WELL

The medicines used in the H1N1 pandemic

11. Three H1N1 vaccines were developed for use in the pandemic – Pandemrix (GlaxoSmithKline), Celvapan (Baxter) and Focetria (Novartis), and two anti-viral medicines were also available – Relenza (GlaxoSmithKline) and Tamiflu (Roche).

The vaccines

12. A European strategy has been developed over a number of years with a view to having in place a robust and rapid procedure for the regulatory approval of a pandemic vaccine. In order to coordinate an expedited assessment of a new vaccine under the pandemic situation, a specific centralised procedure for the evaluation of pandemic vaccines had been previously agreed.

Approving the H1N1 vaccines

13. Prior to the declaration of a flu pandemic, a “mock up” of each vaccine had been prepared using an H5N1 strain and this had been approved by the EMA under the pandemic mock up procedure. After the declaration of Phase 6 of the pandemic by the WHO, the H5N1 strain was replaced with the H1N1 strain responsible for the pandemic and the vaccines manufactured according to the method established in the mock up dossiers. In order to speed up the assessment, quality and non-clinical data were submitted as soon as they became available for a series of “Rolling Reviews” and finally, a variation to the marketing authorisation for the mock-up vaccine was submitted to formally approve the vaccine with the H1N1 antigen. The overall timetable was very fast: the H1N1 strain was identified in April 2009, WHO declared the pandemic in June 2009 and the vaccines were available from October 2009.
14. Because the data had already been reviewed during the Rolling Reviews, the timetable for the final strain change was expedited. The assessment of data in support of each vaccine was carried out and led by the designated rapporteur (which was the UK for Pandemrix: we also provided scientific input to the assessment of Celvapan and Focetria). The assessments prepared by the

rapporteurs were further evaluated and discussed by MS at the CHMP. It is important to note that under this procedure no single MS may make a decision unilaterally - CHMP provides a collective opinion that is translated by the European Commission into a marketing authorisation valid throughout the EU.

15. The two vaccines used in the UK immunisation programme, Pandemrix and Celvapan, were both authorised under the centralised procedure. The MHRA established dedicated assessment teams to facilitate rapid assessment of these pandemic vaccines as data became available during the period.

The anti-virals

16. The two anti-virals (Relenza and Tamiflu) were already available in the UK for treatment of symptoms of influenza. Tamiflu had been authorised under the centralised procedure (Finland was the rapporteur) and Relenza under the non-centralised procedure (Sweden was the Reference Member State).

Approving changes to the anti-virals

17. The MHRA has dedicated assessment teams established for the evaluation of these anti-virals and was involved in the European assessment of various regulatory procedures to rapidly assess data to ensure that the quality, safety and efficacy of Tamiflu and Relenza were maintained when:

- The use of Tamiflu was extended to include the prevention and treatment of HINI infection in paediatric populations previously not covered by the authorisation;
- The shelf life of Tamiflu was extended and recommendations were made on the use of expired stock to increase the availability of the product in the event of supply issues due to increased demand;
- Guidance was provided for the extemporaneous preparation of Tamiflu to ensure that the product could be dosed to paediatric populations;
- Guidance was provided on the use of Tamiflu and Relenza in pregnant and breast-feeding women;
- Approval was given for the use of novel intravenous formulations of Tamiflu and Relenza under the compassionate use programme in a specific, defined critically ill patient population.

Safety monitoring (pharmacovigilance)

18. The MHRA developed a proactive, real-time pharmacovigilance strategy to monitor the anti-virals and vaccines used during the pandemic. Key aspects of this strategy were:

- A dedicated web-based reporting system (the ‘Swine Flu ADR Portal’) for use by patients, the public and healthcare professionals wanting to report suspected adverse reactions to these medicines (via the UK’s Yellow Card reporting system);
- A robust system for rapid identification of emerging trends in adverse reaction reporting on these medicines to ensure a speedy response if problems emerge

- but also, importantly, to provide evidence to counter scare stories in cases of adverse events that are coincidental and not caused by the vaccine;
 - Real-time “observed versus expected” analyses of key adverse events of interest (eg Guillain Barre Syndrome);
 - Active safety surveillance via up to 100 GP practices in the Medical Research Council General Practice Research Framework (MRC-GPRF) with the primary objective of estimating the incidence of any medically attended adverse events in those who have received the vaccine;
 - Communication of the real-time safety experience with key stakeholders.
19. A key achievement of this strategy was the ability to give a rapid indication that the safety profile of the vaccines was broadly as anticipated and similar to that of seasonal ‘flu vaccines. It also gave some assurance, at an early stage in the immunisation programme, that the vaccines were unlikely to be associated with theoretical risks such as a large increased risk of Guillain Barre Syndrome. This was considered to be important because of the incident in 1976 when the US had vaccinated over 40 million people against swine flu, and the outbreak itself caused the death of one person and hospitalised 13, but the vaccine itself was (probably causally) associated with more than 500 cases of Guillain Barre Syndrome, including 32 deaths.
20. We also believe that weekly publication of the overall safety experience contributed to public reassurance of the vaccines’ safety. The MHRA considers that the strategy was successful and provides a model of best practice for future pandemic and other mass immunisation campaigns. The model was adopted by other MS which allowed a consistent approach across the EU to communication of vaccine safety.

Providing information about the medicines and medical devices

21. The MHRA aims to be the authoritative source of information about medicines and medical devices available on the UK market. In the context of the H1N1 pandemic the Agency worked closely with the Department of Health to ensure that information for healthcare professionals and patients about medicines available to treat and prevent H1N1 was expedited. In particular:
- The MHRA published weekly information about reports of adverse reactions received to both vaccines and anti-virals, giving context to the reports received and contributing to a more balanced and fair media coverage. These were coordinated with the Department of Health so as to be available for their weekly media briefing;
 - The MHRA also created a dedicated section on our website to publish all H1N1-related information (including on vaccines and anti-virals) which was promoted in Department of Health literature.
 - The MHRA prepared advice for the use of medical devices in pandemic situations. This advice covered such topics as: the humanitarian derogation; off label use of medical devices and adverse incident reporting.

Medical Devices and the H1N1 pandemic

22. Medical devices are regulated under three main EC Directives. One for general medical devices which range from bandages to high technology scanners. Another for active implantable medical devices such as cardiac pacemakers under which the DH algorithm would be regulated. Lastly for in vitro diagnostic devices which are laboratory tests utilising blood and other human specimens samples to diagnose medical conditions under which the HPA reagents would be regulated. The Directives are transposed into UK law by the Medical Devices Regulations 2002.
23. All three Directives lay down requirements for the safety, quality and performance of medical devices which a manufacturer has to meet before they can CE mark their products and place them on the EC market. The assessment procedures involved are graduated according to risk and all but the lowest risk general medical devices have their conformity assessed to varying degree by notified bodies. These are independent certification organisations designated as competent to carry out this function by EC member states regulatory authorities. The national regulatory authorities – the MHRA in the UK - otherwise have a mainly post market surveillance role including enforcement. This system of controls adopts what is called the “new approach” model which aim to unify safety and other requirements across Europe with the aim of creating a single market.
24. MHRA received a request from the HPA for use of a swine flu positive control reagent without CE marking to increase the amount of testing it could undertake. Under medical device legislation MHRA can agree to such requests via a humanitarian derogation providing it agrees that the benefits outweigh the risks if no CE marked alternative is available. The MHRA reviewed the available data and in May 2009 agreed to a three month derogation with 6 conditions, including ongoing review of performance. This derogation was extended to the end of November 2009 during the course of the swine flu pandemic. This allowed the HPA to reviewed the laboratory and user performance data, such that they were then in position to CE mark the product. The Agency also agreed derogations for virus transport mediums because commercial sources were not able to deliver sufficient numbers at short notice. It should be noted that all these products are now CE marked.
25. Similarly, the MHRA granted a humanitarian derogation for the DH swine flu self-diagnosis algorithm, once it became clear that this needed to be classed as a medical device. MHRA monitored adverse incident reports and reviewed all NPSA swine flu related reported events to ensure that any that arose from the self-diagnosis swine flu algorithm were investigated. No incidents in this category were brought to MHRA’s attention.

LESSONS TO BE LEARNED FOR THE FUTURE

The licensing process

26. It is important to note that as part of an EU wide medicines regulatory regime there is little or no scope for individual national licensing decisions. This has the advantage for industry that they can develop a medicine that they know, once authorised, will be accepted throughout the EU, although the disadvantage for MS is that the regime reduces scope for any individual MS to tailor a medicine to meet its own specific needs.

27. That said, the measures that the EU (EMA, the European Commission and MS) had put in place in preparation for such a pandemic broadly worked well, although we believe there is still scope for improvement. We propose to explore with EMA the possibility of a review of the “Rolling Review” process used for the H1N1 vaccines with a view to introducing a more streamlined procedure – for example by prioritising the review of data critical to vaccine authorisation and supply. The European Commission has also acknowledged that on occasion their own processes held up the formal issue of marketing authorisations for certain medicines, but has already taken steps to address this. The centralised system itself can also hold up the process of authorisation by taking time to determine issues such as acceptable EU-wide names for products and this in turn can cause delays in completing information to accompany national immunisation programmes.

Medical Device humanitarian derogation

28. This swine flu positive control reagent derogation proved safe and effective for the UK. HPA and MHRA were pleased that the derogation enabled HPA to provide an expanded service and gather sufficient information during the course of the derogation to allow CE marking to be applied at the end of the process. This could provide an effective model should a similar situation with a different flu strain develop. It also provided confidence that the medical devices regulatory system was flexible enough to deal with such emergency scenarios.

29. MHRA believe that there are lessons to learn from the DH swine flu self-diagnosis algorithm derogation. The DH should now review the data it has gathered and consider whether there is sufficient data to allow the algorithm to be CE marked, as the HPA has now done for their test (see above).

Safety monitoring

30. In preparation for any future pandemic we will ensure that mechanisms are developed to obtain real-time data on age and risk group-stratified vaccine uptake within the UK. Such data are a critical element to the “observed versus expected” analyses. They were not readily available in a timely manner during the pandemic and, had a serious safety issue emerged, the MHRA may not have been in a position fully to assess the risk this posed. Fortunately this was not an issue on this occasion.

Provision of information

31. The MHRA had enquiries during the pandemic that suggested that Primary Care Trusts (PCTs) were not clear about arrangements for vaccine distribution and storage. For the future there is a need to ensure that there is an established system for

communication to PCTs about the logistics and requirements for vaccine distribution and storage.

Pack sizes and distribution

32. The pandemic vaccines were provided as 'wholesale' packs – for example Pandemrix in 50 multidose antigen vials were packaged together representing 500 doses. Splitting of these wholesale packs is required – for example for delivery to smaller local populations such as rural or 'at-risk' groups – and has a range of consequences. These include the need for new packaging, maintenance of the cold-chain during repackaging, maintenance and provision of package information (labelling, the patient leaflet and technical administration information). These aspects need to be given careful consideration when making a decision on whether a multidose or single dose presentation is desirable or feasible. It would be useful to ensure engagement with MHRA at an early stage of contract development with companies so that associated regulatory issues are addressed in a timely manner.

33. The use of multidose vials is one option to facilitate expedient and efficient production of vaccine for a mass vaccination campaign. However, there are also certain disadvantages such as reduced flexibility for dosing smaller numbers of patients and constraints such as handling and storage after first opening the multidose vial which may need refrigeration.

34. Distribution channels for vaccines and anti-virals need to be licensed so that, for example, medicines do not deteriorate under inappropriate storage conditions. It would be helpful to ensure that the MHRA is involved in discussions at an early stage on proposed distribution chains to ensure that regulatory procedures do not hold up progress.

Business continuity

35. The nature of the pandemic to date has meant that continuity measures put in place by the pharmaceutical industry have not been fully tested. International supply chains of medicinal products, blood components and devices would most likely have been disrupted to some degree if the outbreak had been more severe and prolonged. Measures should be put in place to ensure for the future the robustness of such continuity measures.

Relaxing blood donor acceptance criteria

36. The MHRA was asked by UK Blood Transfusion Service to consider proposals for relaxation in the rules (set out in EU legislation) governing when blood may be taken from donors to ensure continuity of supply during the pandemic. The MHRA received agreement from the Cabinet Office's Scientific Advisory Group for Emergencies (SAGE) to these relaxations in the UK, although this would have represented a less strict application of the EU rules. MHRA then played a key role in working with the European Commission in developing amending EU legislation that gave a firm legislative base for the proposals agreed in the UK. The European Directive 2009/135/EC was adopted on 3 November 2009 and transposed in the UK by SI 2009/3307 on 16 December 2009. These are in force until 30 June 2010. It has

not, however, in this pandemic proved necessary to trigger these emergency relaxations.

MHRA

27 April 2010.