The Regulation of Nicotine Containing Products (NCPs)
MHRA
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Public Summary Report **Page**

Executive Summary 2
- Background 2
- Scientific and market assessment 2
- Stakeholder engagement 2
- Evidence considered 2
- Conclusions 3

Overview of key elements 4
- Nature, quality and safety of unlicensed NCPs 5
- Current use of electronic cigarettes 6
- Potential impact of bringing NCPs into medicines regulation 6
- Levels 7
- Proportionate regulation 7
- Supplementary information 8

Executive Summary

Background

1. In March 2011, the Medicines and Healthcare Products Regulatory Agency (MHRA) published the outcome of a public consultation on whether to bring nicotine containing products (NCPs) within the medicines licensing regime. The response to public consultation showed strong support from the medical and public health communities for the application of the medicines regulatory framework. It was also clear that there was a need for further work to inform a final decision. Since that time, the MHRA has co-ordinated a programme of research on the use, quality and safety of NCPs, their potential impact on public health and how regulation might best be applied.

Scientific and market assessment

2. To inform how this work was taken forward, an expert working group was set up under the statutory committee that advises the UK government on medicines - the Commission on Human Medicines (CHM).

The group devised a programme of work to scope:

- the nature, quality and safety of unlicensed NCPs,
- the actual use of unlicensed NCPs in the marketplace,
- the effectiveness of unlicensed NCPs in smoking cessation,
- and modelling of the potential impact of bringing these products into medicines regulation on public health outcomes.

Stakeholder engagement

3. During the course of 18 months, the MHRA met with a range of stakeholders. This included importers of electronic cigarettes and the Electronic Cigarette Industry Trade Association (ECITA). Meetings were also held with interests across government to establish a common position. This included those with an interest as regulators, like the Health and Safety Executive and local authority Trading Standards, as well as the Department of Health, the Behavioural Insights Team at Number 10 and the Department for Business, Innovation and Skills. The MHRA also worked closely with the National Institute for Health and Care Excellence (NICE) on the development of its draft guideline on smoking harm reduction, published in June 2013. The Agency has also met with key players in the public health community, such as leading researchers in the smoking field, Action on Smoking and Health (ASH) and the British Medical Association, and sought views of medical royal colleges and the NHS.

Evidence considered

4. The CHM advised on the MHRA's assessment of all the available data, for example on the testing of products on the market, from published and unpublished studies and from research on products on the UK market commissioned by the MHRA. Information from

surveys and qualitative data was brought together to provide an analysis of how electronic cigarettes are used in practice and what this means for the potential for public health gain.

Conclusions

5. The Government has accepted the advice of the CHM and its expert group, which concluded that NCPs currently on the market do not meet appropriate standards of safety, quality and efficacy. Testing data confirm that nicotine levels can vary considerably from the labelled content and the amount of nicotine per product can differ from batch to batch. In terms of how well NCPs work, there can be widely differing amounts of nicotine from the same format with one form delivering what could be an effective therapeutic dose, another a “placebo” dose. With regards to safety, toxic elements may be included at unexpectedly high doses which could produce adverse effects, particularly in vulnerable patient groups.

6. The consistent evidence from a variety of sources is that most electronic cigarettes use is to support stop smoking attempts or for partial replacement to reduce harm associated with smoking. This is comparable to how nicotine replacement products (e.g. gums, patches, inhalator), which are licensed as medicines. The current evidence is that electronic cigarettes have shown promise in helping smokers quit tobacco but the quality of existing NCPs is such that they cannot be recommended for use.

7. The public health priority of reducing the harms of smoking is not supported by the current regulatory framework, under the general product safety regulations. To manage the risk of poor and ineffective products and to maximise the potential for public health gain, NCPs should be regulated as medicines to ensure that:

- Standards of quality, safety and efficacy are met
- Monitoring safety in use, including over the long term, is provided for
- Advertising of NCPs is controlled through medicines provisions
- And any emerging risks, e.g. of NCPs acting as a gateway to smoking tobacco, can be effectively managed.

8. To achieve this, the UK Government supports the European Commission’s draft Tobacco Products Directive in relation to the specific provisions for the regulation of NCPs containing defined amounts of nicotine as medicines.

9. In the meantime, the UK Government will encourage applications for medicines licences for NCPs and will make best use of the flexibilities within the existing framework to enable licensed products to be available.

10. This summary should be read in conjunction with the supporting documents published on the MHRA website

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Overview of key elements

11. Smoking is the primary cause of preventable morbidity and premature death, accounting for nearly 80,000 deaths in England. Existing smoking cessation treatments have high failure rates. Smokers who use nicotine replacement therapy (NRT) are more likely to quit smoking than those who try to reduce without NRT. There are a number of nicotine containing products (NCPs) on the UK market, such as electronic cigarettes, which are widely available but are not licensed medicines.

12. Electronic cigarettes are battery powered devices that deliver nicotine through a vapour. Their appearance on the market in around 2006 left regulators the world over with a dilemma of how to most effectively regulate these novel products. At the time of writing, however, there is no international consensus on the regulation of these products. A number of countries have banned NCPs (Canada, Brazil, Turkey etc.), or restricted supply in line with tobacco regulation. Some European Member States have enforced the provisions of medicines regulation on NCPs and some have treated them as medicinal only if medicinal claims are made.

13. Although there are currently no product specific regulations that govern NCPs, there are controls through the "catch-all" General Product Safety Regulations and the Chemicals (Hazard Information and Packaging for Supply Regulations 2002 – CHIP), as well as a number of additional legislative requirements that relate to aspects such as electrical safety or batteries. Whilst these regulations provide a level of basic standards found in other consumer products, there is agreement amongst those who apply the current regulatory controls that they are not designed to manage risks related to the safety, quality and efficacy of such products or to optimise the balance of benefits and risks of products with a potential to benefit public health.

14. When the UK Government consulted on the regulation of NCPs in 2010, although there was strong support from a wide range of stakeholders for regulating NCPs as medicines, it was also clear that there was a need for further work to inform the decision. The consultation highlighted the need for evidence around levels of nicotine that have a significant physiological effect through its pharmacological action and the need for further information on the impact of regulation on public health. The MHRA committed to co-ordinating a period of further scientific and market research with the aim of answering these questions. This work has been informed by the advice of an expert group of the Commission on Human Medicines (CHM). The group devised a programme of work to include:

- The nature, quality and safety of unlicensed NCPs
- The effectiveness of unlicensed NCPs
- The actual use of unlicensed NCPs
- The impact of bringing these products into medicines regulation on public health outcomes
- An investigation of the levels of nicotine which have a significant pharmacological effect

15. During this period the MHRA met with a range of stakeholders, which has included importers of electronic cigarettes and the Electronic Cigarette Industry Trade Association (ECITA). Meetings were also held with other government regulators, like the Health and

Safety Executive and local authority Trading Standards, as well as the Department of Health, the Behavioural Insights Team and the Department for Business, Innovation and Skills. The MHRA also worked closely with the National Institute for Health and Clinical Excellence (NICE) on the development of its draft guideline on smoking harm reduction. Views were sought from key players in academia, the public health community, such as leading researchers in the smoking field, Action on Smoking and Health (ASH) and the British Medical Association.

16. The CHM reviewed the scientific and market research, coordinated by the MHRA, which underpinned the decision on regulation. A brief overview of the assessments that informed this decision follows.

Nature, quality and safety of unlicensed NCPs

17. The data available on the composition of liquids contained in unlicensed NCPs, evaluation of potential toxins, composition of vapour, rate of nicotine delivery, consistency of doses and stability was reviewed.

18. The primary components of electronic cigarette cartridges and vapour are propylene glycol, glycerine, and nicotine. However, studies have shown many other additives and potentially harmful contaminants can be detected in varying amounts across a number of studies. Available safety data is mainly limited to surveys in which patients report only minor side effects, such as mouth and throat irritation, headache, dizziness, and nausea. More serious adverse events have been reported in the literature and media, such as possible aspiration pneumonia, and second-degree burns to the face following the product exploding in consumer's mouth. Although it is reasonable to assume that using electronic cigarettes is a safer alternative than smoking tobacco cigarettes the long term safety of these components to the consumer remains unknown at this stage.

19. Analyses of nicotine levels delivered from electronic cigarettes suggest significant variability exists in the products tested to date. There is no data concerning the manufacture of the cartridge or device to suggest consistent nicotine doses across multiple cartridges or multiple devices. There is insufficient evidence to suggest that electronic cigarettes as currently marketed are safe and effective for their intended use.

20. A MHRA funded study conducted by the Tobacco Dependence Research Unit, Wolfson Institute of Preventative Medicine, Queen Mary, University of London evaluated the rate and consistency of nicotine delivery. The products did not indicate nicotine content clearly; rather they presented % nicotine content in the cartridge solution by volume. Significant differences in nicotine content between the labelled amount and measured amount was noted. There was also variability of up to 26% between batches. Analysis of the nicotine content in vapour showed that different electronic cigarette models varied considerably in nicotine delivery profiles and amount of nicotine in the cartridge that was actually vaporized. The results suggest that nicotine content of the cartridges was only one of the factors contributing to nicotine level in vapour. None of the tested products delivered nicotine levels as high as conventional cigarettes.

21. Consumers who use electronic cigarettes as cessation aids may not achieve success and consequently suffer harm due to quality issues and the inability of the product to

effectively deliver nicotine. The lack of a framework to monitor the safety in use of unlicensed products, and safety in long term use, present public health concerns.

Current use of electronic cigarettes

22. The consistent evidence from a variety of sources is that most electronic cigarettes users use them to stop smoking or partial replacement to reduce harm associated with smoking. This is comparable to how nicotine replacement products (e.g. gums, patches, inhalator), which are licensed as medicines, are used.

23. There is little evidence that electronic cigarettes are being used in a way that may initiate tobacco smoking. There is some evidence from surveys that electronic cigarettes users are having success in achieving their goals with many current electronic cigarette users being ex-smokers.

24. The current evidence is that electronic cigarettes have shown promise in helping smokers quit tobacco, but well-designed safety and efficacy studies are lacking including evaluation of these products in comparison to currently available smoking cessation therapies. The long-term effects of electronic cigarettes are unknown with very few users having been objectively studied.

Potential impact of bringing NCPs into medicines regulation

25. It is estimated that implementing policies to reduce smoking prevalence by 1% per year for 10 years in the UK would prevent over 57 000 deaths in that period. Given that the most recent data from the Smoking Toolkit Study showed that electronic cigarette use by tobacco smokers for any purpose has increased from around 2% in 2011 to between around 6-7% in October 2012, combined with the implementation of tobacco control policies this estimate would seem achievable.

26. NCPs have the potential to enable smokers to change behaviour, impacting on smoking, inequalities and child health. Medicines regulation offers the following benefits:

- The products will have recognised standards of quality, safety and efficacy in line with licensed NRT products.
- Users would have access to accurate information on how to use the product safely, and what is in the product.
- The long term safety of the products could be monitored. Regulatory action could be taken if safety issues are identified.
- The products could be available over the counter, through general sale outlets.
- The products could also be available on prescription
- Users would be assured that the safety of the products was being monitored, and that appropriate action would be taken if safety problems are identified
- Users would have access to an attractive product that mimics smoking

27. The market for NCPs did not exist in 2006. By 2014 it is estimated to be worth around £100m per annum. The WHO predicts that by 2050 to be equivalent to the tobacco products market. Currently there are hundreds of companies offering electronic cigarettes for sale in the UK, mostly operating via websites, although there are a small

number of retail outlets. The majority of companies source from China (accounting for 70% of electronic cigarettes manufactured in the world) and other parts of Asia.

28. The buoyant, competitive UK market in over the counter medicines worth around £2.5 billion annually, of which £100 million is licensed NRT, suggests that medicines regulation need not be a barrier to competition and innovation. As well as an over-the-counter market (e.g. in both supermarkets and pharmacies) the market would be further expanded as these products would be available on prescription. Nor is there evidence that the cost of regulation need affect price or competition, for example there is a competitive over the counter market for painkillers and cough remedies. There are already measures in place that would facilitate the market in this area – for example, the lowest rate of VAT applied to NRT (5%) and existing provisions for staged payments of fees adjusted according to turnover.

Levels

29. To define NCPs as a medicinal product by function[1] usually requires the definition of active substance which has a significant physiological effect through its pharmacological action. CHM considered the evidence and concluded that, even at very low levels, nicotine could have a physiological effect and therefore an impact on smoking behaviour. On this basis, only a product that provided no measurable levels of nicotine could be considered not to have the potential to produce physiological effects. Given these findings, it was not useful to try to define the lowest level of nicotine at which such effects occur through its pharmacological action. CHM also noted that the rate of delivery, as well as "dose", was highly significant and that the nature of nicotine use – in which user titrate their dose to manage cravings, was highly significant.

30. On 20 December 2012 the European Commission (EC) published a draft revised Tobacco Products Directive with specific provisions for NCPs. The EC proposal requires that NCPs below a certain nicotine threshold would be allowed on the market under the existing regulations and above this threshold products would only be allowed if authorised as medicinal products, i.e. as nicotine replacement therapies.

31. The MHRA will further explore with the European Commission, how to develop a pragmatic solution through revisions to the Tobacco Products Directive to address the effective regulation of all products containing nicotine that have a significant physiological effect by means of their pharmacological action.

Proportionate regulation

32. The MHRA has established that there is a cross-Government consensus that proportionate medicines regulation is the most appropriate framework within which to regulate all NCPs. The Department of Health, the Behavioural Insights Team at Number

[1] Article 1 of Directive 2001/83/EC *as amended* defines a "medicinal product" as:
"Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; *["the first limb"]*
Any substance or combination of substances which may be used in, or administered to, human beings, either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis" *["the second limb"]*
Medicinal products may well fall under both limbs of the definition but the European Court of Justice ("ECJ") has confirmed that falling under either limb is sufficient to classify a product as a medicinal product. *[Upjohn 1989* C-112/89*]*:

10, the Department for Business, Innovation and Skills all agree that getting the right form of regulation will support and stimulate innovation of the nicotine market, which will have a positive impact on delivering tobacco harm reduction, as set out in the Government's Tobacco Plan.

33. The medicines regulatory framework could be applied to NCPs in a proportionate way, focussing on managing the risk of poor quality and ineffective products with the potential benefits to public health within a smoking harm reduction regime. This approach would be more proportionate than banning some or all NCPs, restricting supply, as with regulation as a tobacco product, or developing a bespoke framework, which would be likely to take some years, at a time when the market for NCPs is increasing exponentially.

34. Minimising the burden of regulation, achieving a level playing field between big and small businesses and balancing these against consumer protection and public health objectives have been key themes in the work the MHRA has been taking forward in the scientific and market research on regulating NCPs.

Supplementary information

35. The CHM minutes from the meetings that concluded the period of research are available here:

- CHM Working Group on Nicotine Containing Products (17 January 2013)
- Excerpt of CHM meeting (14 February 2013)

36. The CHM Working Group on Nicotine Containing Products scientific papers and minutes that support the above summaries are available via the following links. Whilst all efforts have been made to make the papers available in full, data has been redacted if permission has not been received for its use, or it is personal data. For some of the committee papers relevant new research has been published since the January 2013 meeting and has been included as addenda to the papers.

- Quality, safety and efficacy of unlicensed NCPs
- MHRA funded research on electronic cigarettes
- Current use of electronic cigarettes
- Potential impact of bringing NCPs into medicines regulation
- Draft Tobacco Products Directive and nicotine levels
- Proportionate regulation

37. The MHRA has prepared an impact assessment to support the UK's position in EU negotiations on the regulation of Nicotine Containing Products, which are currently being considered along with changes to the Tobacco Products Directive.

38. The following external links provide further information:

- The National Institute for Health and Clinical Excellence Tobacco – harm reduction guidance
- The European Commission's revisions of the Tobacco Products Directive
- The Human Medicines Regulations 2012