FDA's Approach to Evaluation Nicotine Replacement Therapies; Public Hearing; Request for Comments
Docket No. FDA-2017-N-6529

Deadline: 15th February 2018

Introduction

1. This response is on behalf of Action on Smoking and Health (ASH (UK)), the UK Centre for Alcohol and Tobacco Studies and the UK National Centre for Smoking Cessation and Training.

2. ASH (UK) is a public health charity set up by the Royal College of Physicians in 1971 to advocate for policy measures to reduce the harm caused by tobacco. ASH receives funding for its full programme of work from health charities the British Heart Foundation and Cancer Research UK. It has also received project funding from the Ministry of Health to support tobacco control. It does not receive funding from the pharmaceutical industry or any other commercial funding source.

3. The UK Centre for Tobacco & Alcohol Studies (UKCTAS) was created in 2008 and includes research teams in twelve UK universities. It is one of six Public Health Research Centres of Excellence funded by the UK Clinical Research Collaboration on behalf of the UK Government.

4. The National Centre for Smoking Cessation and Training (NCSCT) was established to support the delivery of smoking cessation interventions provided by local stop smoking services, support the NHS and Local Authorities to deliver effective evidence-based tobacco control programmes, and deliver training and assessment programmes to stop smoking practitioners and other health care professionals. The NCSCT receives core funding from Public Health England and further income from licencing its training and assessment programme to the Health Services Executive (Republic of Ireland), Public Health Wales and the UK Armed Forces. The NCSCT also receives funding for research and for providing face-to-face training courses.

5. This submission has been co-authored by Deborah Arnott, chief executive of ASH (UK); Professor Paul Aveyard (University of Oxford), Professor Linda Bauld (Stirling University), Professor John Britton (University of Nottingham), Professor Ann McNeill (King's College London) and Professor Robert West (University College London), on behalf of UKCTAS; and Dr Andy McEwen, Executive Director, NCSCT.

Responses to the questions

Might there be ways to improve upon the currently available delivery systems to yield new OTC NRT products that might be more effective? If so, what evidence would be needed to support such changes, and how should they be evaluated?

6. There are products, called e-cigarettes, already being used by smokers to help them quit which have been demonstrated to be more effective than NRT bought over the counter.[1] Survey data from the UK show that smokers use e-cigarettes to help them quit smoking, cut down and prevent relapse back to smoking, while ex-smokers primarily use them to quit and prevent relapse, and use by never-smokers is negligible.[2] Because they are popular with smokers they have the potential to have a significant impact on smoking

rates.[3] In England e-cigarettes became the most popular aid for smokers trying to stop from Spring 2013 and have been found to help smokers to quit when used in a quit attempt,[4] a finding supported by a Cochrane review of two randomised controlled trials and 21 cohort studies.[1]

7. A recent US analysis concluded that the substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level.[5] This followed a similar study with very similar results in England.[4] While the recent NASEM report concluded only that e-cigarettes *"might increase adult cessation of combustible tobacco cigarettes"*,[6] it should be noted that currently e-cigarettes cannot be advertised and promoted for smoking cessation in the US, or anywhere else in the world, as no e-cigarette has been granted a medicines license for this purpose and been made commercially available.

8. In the UK specialist stop smoking services provide behavioural and pharmaceutical support to smokers, and a small and growing number are becoming "e-cigarette friendly",[7] [8] supported by the NCSCT.[9] This means that they are willing to support smokers who choose to use e-cigarettes as well as or in addition to licensed stop-smoking medicines although they mostly would not provide the e-cigarettes.

9. Data from stop smoking service returns for England show that smokers using e-cigarettes to quit in conjunction with behavioural support from the services have among the highest success rates in quitting. In 2016/17 7,661 smokers setting a quit date with the services used a licensed medication and unlicensed nicotine containing product (e-cigarette) concurrently, 57% of whom were successful 4 week quitters; 1,915 used licensed and unlicensed products consecutively, 69% of whom were successful; and 2,746 used only unlicensed nicotine containing products with a 59% success rate. This compares to the average success rate of those using pharmacotherapy of 51%.[10] It is not clear, however, that e-cigarettes are the cause of the increased success rates and research is needed to address the issue of causality.

10. In the summary of the NASEM report[6] it states that, *"e-cigarettes are likely to be far less harmful than combustible tobacco cigarettes"* and in the body of the report it clarifies what is meant by this statement, *"Estimates of how harmful they are relative to combustible tobacco cigarettes range from 5 percent estimated by the U.K. Royal College of Physicians (TAG, 2008) to 30 to 50 percent estimated by Glantz (2016), with most agreement concentrated around the lower figure. The committee examined a wide range of values for the relative harm of e-cigarettes compared with combustible tobacco cigarettes, from 0 percent to 50 percent as harmful as combustible tobacco cigarettes. The upper limit of 50 percent was selected as an extreme and improbable value, used to set an upper limit to the potential harm of e-cigarettes. The likelihood that e-cigarettes have none of the harm of combustible tobacco cigarettes is equally extreme and improbable."*

11. Yet in the US perceptions of risk are increasingly out of line with this assessment. In the US the proportion of people thinking that e-cigarettes were just as, or more, harmful than combustible cigarettes rose from 39.8% in 2013[11] to 55.6% in 2017.[12] In comparison the proportion thinking that e-cigarettes were less harmful declined from 39.8% to 29.3%. Even in the UK, where public bodies, academics and clinicians are giving clear messages about relative risk,[13] [14] misperceptions of harm are growing, although not as much as in the US. In the UK the proportion of people thinking that e-cigarettes were more or equally harmful as combustible cigarettes rose from 9% in 2013 to 22% in 2017, although the proportion thinking that e-cigarettes were less harmful was relatively stable at 50% in 2013 and 47% in 2017.[15] In both the UK and the US the proportion thinking, in

line with best estimates, that e-cigarettes are a lot less harmful than smoking tobacco, had declined between 2013 and 2017 to only 5.2% in the US and only 20% in the UK.

12. Providing reassurance to the many smokers who have been unable to quit, but are unwilling to try e-cigarettes because of their concerns about the risks of harm is essential. To this end, as we have in the UK, we recommend that the FDA adopt an abridged medicines licensing process for nicotine containing products which would encourage manufacturers and importers of e-cigarettes to apply for medicines licenses for their products. Having medicinally licensed e-cigarettes available as an alternative option could potentially be beneficial, and provide reassurance to healthcare professionals who are often unwilling to advise smokers about their use of e-cigarettes in the absence of their having a medicinal license for quitting. The British Medical Association also support having some medicinally licensed e-cigarettes available as it *"may provide an important option for some smokers, and would give health professionals confidence in the safety and efficacy of individual devices."*[16].

13. However, abridged medicines licensing should be encouraged as a complement to, rather than instead of, alternative routes of bringing products to the market. E-cigarettes bought as consumer products over the counter are proving successful in the UK[4] and the US[5] in helping smokers quit and appeal to smokers who do not want to use a medicine. Removing this consumer option form the market would be negative for public health. Furthermore medicines licensing brings significant additional costs, which are likely to increase the purchase price of the product. This is a critical issue as we know that one of the motivations cited by smokers in Great Britain as a reason for switching to e-cigarettes is that it is cheaper than smoking.[15]

14. In the UK the medicines authority, the Medicines and Healthcare products Regulatory Authority (MHRA), considers that an abridged medicinal license is appropriate as the efficacy of non-tobacco products that contain nicotine in supporting smokers to quit is well established, and does not need to be proven. Any concerns about the potential additional risks incurred through e-cigarettes as a delivery mechanism can be addressed through post-marketing surveillance by requiring the manufacturer or importer to put in place an appropriate risk management plan.

15. This is the approach taken by the MHRA. On the advice of an expert working group on nicotine containing products, the MHRA decided that a proportionate assessment of any future marketing authorisation applications (MAAs) for e-cigarettes and other nicotine containing products was appropriate. To this end it will accept an abridged application, abbreviated in relation to safety and efficacy by using a comparative pharmacokinetic (PK) study comparing any new product to an appropriate reference medicinal product.[17]

16. The abridged MAA process requires e-cigarettes to use pharmaceutical grade nicotine and meet good manufacturing practice standards.[18] Any flavours used must meet European Phamacopoeia requirements or EU food safety requirements. For medicinal electronic cigarettes and similar NCPs, MHRA would expect the product to meet product quality and safety standards, where relevant, although additional requirements may be needed to meet safety, quality and efficacy criteria under medicines regulations. The British Standards Institute has already developed such standards, and international standards currently under development by CEN (European Committee for Standardisation) and ISO (International Organization for Standardization). The processing time is up to 210 days (excluding the time taken to provide further information or data required), and the fee cost for applying to the MHRA is £25,643 (approximately $35,000 at current exchange rates).[17]

17. In the UK, and other European Union Member States, there is an alternative route to market for e-cigarettes which only requires basic product quality and safety standards to be met. This came fully into force in 2017 on implementation of the EU Tobacco Products Directive[19] as transposed into UK law.[20] In the short-term the notification process has proven more attractive to manufacturers and importers than the licensing authorisation process.

18. As a result to date only one e-cigarette (the e-voke) has received market authorisation from the MHRA, and that was in 2015.[21] It should be noted that, in contrast to traditional NRT, the age of sale for the e-cigarette was set at 18, recognising concerns about potential youth initiation of e-cigarette use. The tobacco company with the license for e-voke recently stated that it will not be putting it on the market.[22] However, at least one other product, produced by NJOY and developed under a Small Business Innovation Research contract from the US National Institute for Drug Abuse, has been submitted for authorisation under the abridged licensing process and other manufacturers have expressed an interest in doing the same.[23]

Are there additional indications or regimens for OTC NRT products that could be explored? Concepts to consider could include relapse prevention, craving reduction, maintenance, reduce to quit, use of short- and long-acting products in combination, or cessation of non-cigarette tobacco products. What evidence would be needed to support each indication or regimen?

19. There are additional indications and regimens for OTC NRT products which should be explored, and which have been put in place in the UK by the MHRA progressively from 2005 onwards. The rationale for relaxations in the licensing of NRT sold OTC has been that it is now widely accepted that there are no circumstances in which it is safer to smoke than to use NRT instead of smoking and that the evidence is that almost no never smokers use NRT. Following a review of the evidence[24] the MHRA concluded that it was sufficient to support NRT OTC license indications for:
    - Adolescents of 12 years and over;
    - Pregnant women – although they should be encouraged to stop smoking without NRT if possible;
    - Smokers with cardiovascular disease – although for those with the severest forms, NRT should be initiated under medical supervision;
    - Combination therapy (use of more than one product at once);
    - Cutting down as a “stepping stone” to quitting completely for smokers unable to stop abruptly;

20. Subsequently the licence indications were extended to include:[25]
    - Temporary abstinence; and
    - All nicotine replacement therapy medicines can be made available for general sale over the counter and are not limited only to pharmacies.

What data would be required to demonstrate health benefits of reduction in consumption of combustible tobacco products?

21. In 2010 the MHRA licensed NRT for harm reduction including long-term partial or complete substitution of smoking. In 2013 this was backed up by guidance[26] developed by the National Institute for Health and Care Excellence (NICE) on tobacco harm reduction. The NICE guidance recommends stopping smoking in one step as the best approach. However, it recognised that for smokers unable to do so there are other ways

of reducing the harm from smoking, even though this may involve continued use of nicotine. This guidance is about helping people, particularly those who are highly dependent on nicotine, and who:

- may not be able (or do not want) to stop smoking in one step
- may want to stop smoking, without necessarily giving up nicotine
- may not be ready to stop smoking, but want to reduce the amount they smoke.

22. Reducing consumption of combustible tobacco products is a common tactic used by smokers to try to reduce harm, to move towards quitting, or to save money.[27] While using NRT to cut down has not clearly been shown to have direct health benefits[28], there is evidence that smokers who use NRT to cut down are more likely to make a quit attempt than smokers who do not, and more likely to quit.[29] [30] [26] [31]

23. The NICE guidance[26] also supports long-term use of licensed nicotine-containing products for those at risk of relapsing back to smoking, which has been found to be cost-effective.[32] Evidence is available from studies with up to 5 years follow-up which suggests that nicotine, in the form available in nicotine replacement therapy (NRT) products, does not pose a significant health risk.[26] [33] Many medications have been approved for a variety of diseases and disabilities because overall the risk–benefit equation is positive, despite the potential to increase risk of significant negative outcomes based on laboratory and human studies. Given the large difference in carcinogen exposure between smoking and NRT it is clear that the risk-benefit equation supports an indication for long-term use of NRT.[34]

Are there OTC NRT products that could be studied for use in combination that might result in reduced tobacco related health impacts? What evidence would be needed to support the safety and efficacy of these products when used in combination?

24. The highest quality evidence comes from the Cochrane review on NRT which found that combination therapy with NRT has been shown to be more effective than single form NRT. Combining the results of these studies shows a clear advantage of combination versus single product NRT use (rate ratio = 1.34; 95% CI: 1.18–1.51). This means that combination NRT is likely to give a 35% increase in cessation rate, but the likely true effect lies between 18% and 51%.[35]

25. Combination NRT has been found to be safe. Nicotine overdose associated with NRT use in smokers is rare. Smokers are used to very large doses of nicotine from tobacco use. Even with combination NRT use smokers are unlikely to receive doses of nicotine that are higher than that they receive from their tobacco use.[36] If smokers experience adverse symptoms such as nausea they can reduce the dose.

Is there other information that could be added to labeling for currently approved or new dosage forms of OTC NRT products that would maximize their ability to be used to support smoking cessation? Please consider the various sections of the Drug Facts labeling, including the Uses, Warnings, and Directions sections.

26. The evidence from the UK is that licensing changes in themselves are unlikely to have a major impact on user behaviour, as reduction as a route to cessation is already well established both in the UK[37] and the US.[38] However, of greater concern is that in the real world, as opposed to clinical trials, smokers have been found to be using NRT in

lower than recommended doses, which is associated with lower success rates in quitting.[39] This may also be associated with misconceptions about the safety of NRT, as surveys in both the US and UK have found approximately two thirds of smokers believed that, or were unsure whether, NRT was as harmful as cigarette smoking.[40] [41] That can be addressed by providing NRT on prescription backed up by behavioural support, which has found to be much more effective than NRT bought over the counter.[42]

27. Changes in labeling need to take this into account and both reassure smokers about the relative risk of NRT compared to smoking and encourage them to use sufficient doses to be effective.

Generally, the labeling of OTC NRT products contains a dosing schedule based on duration of use, and FDA has recommended the labeling on OTC NRT products be modified to include the following: ''If you feel you need to use [the NRT product] for a longer period to keep from smoking, talk to your health care provider.'' What is the impact of longer term NRT treatment? What is the impact on likelihood of cessation or relapse prevention? What data would support an affirmative recommendation to use approved OTC NRT products for durations that exceed those currently included in the Drug Facts labeling of approved OTC NRT products, or would support a chronic or maintenance drug treatment indication for such products?

28. People who use NRT long-term do so because they feel that to stop NRT will cause relapse.[43] There is no strong evidence from trials that this is an effective strategy[44], but it is one pursued by people who were more dependent as smokers.[45] In such a circumstance, it is unhelpful for such people to consult a physician because there is no substantial harm from continued use, particularly when set against the substantial harm that could arise from relapse to smoking if NRT were stopped. The evidence on long-term harms from continued use of snus is strong evidence that NRT, which is less risky than snus, poses minimal risk when used this way.[46] [47]

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