TGA Briefing Document FINAL December 2013

[redacted] to peter.bird 16/12/2013 10:29 AM

Cc: [redacted]

History: This message has been forwarded.

Peter,

As discussed this is a brief summary of Nicoventures, the regulatory situation in EU, our products that are under evaluation with MHRA and some discussion points we would like to cover with the TGA.

If you have any queries please let me know.

Look forward to meeting on Friday Morning.

Regards

[redacted]

[redacted]

Nicoventures Limited

[redacted]

[redacted]

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1 Background to Nicoventures Ltd.

Nicoventures is a consumer healthcare company established to focus exclusively on bringing nicotine products to adult smokers that can be licensed to medicines standards. It is a stand-alone company within the British American Tobacco Group, managed separately from the tobacco businesses. The Nicoventures team has extensive pharmaceutical experience of nicotine replacement therapy (NRT) coupled with an understanding of smoking behaviour, which we believe will be of immeasurable value in providing consumers with products that they want to use and that are substantially safer alternatives in comparison with their usual cigarettes.

The goal of reducing the harm caused by smoking is a public health benefit to which we openly aspire. Alongside healthcare professionals and others concerned with healthcare and tobacco control, we welcome the broader debate that that is on-going in health circles within Australia on the approach to be taken with novel nicotine delivery devices. Similar considerations are also on-going in the UK [redacted]. Unlike in the US or Europe the legal classification for Nicotine containing products is clear in Australia, this is potentially a great step forward. However, we also understand that no sponsors have progressed any applications for these new types of products within Australia, and that there are significant numbers of products being imported either directly by individual users (legally) or commercially for future sale (illegally). This is clearly a situation that creates tension and confusion for smokers and healthcare professionals.

[redacted]. The products are supported with quality, safety and efficacy data that we believe is appropriate to support approval under medicines legislation as Unscheduled Therapeutic Goods. However, due to the innovative nature of this market, and the products we feel it is important to dialogue with the TGA to understand how we can effectively bring these products to market in Australia.

At this stage we appreciate the opportunity to meet with TGA to discuss our experiences in the UK, our proposed first product and regulatory submission options in Australia.

2 The evolving approach to smoking cessation

Smoking is the single greatest cause of preventable illness and early death in England (HM Government, 2011) and most of the western world. Cigarette smokers die on average about 10 years younger than non-smokers (Doll et al., 2004). Unfortunately, at any one time, more than 30% of smokers have no interest in quitting and around another 30% view it as something they would like to do, but in the future (West & Brown, 2011).

Although nicotine, the main psychoactive ingredient in tobacco, is addictive (Stolerman & Jarvis, 1995; US Department of Health and Human Services, 1988) a growing body of evidence suggests that it is also a relatively safe drug (MHRA Consultation Letter MLX 364, 2010). Furthermore, there are no circumstances in which it is safer to smoke than to use NRT products. Experts believe that lifetime use of NRT will be considerably less harmful than smoking (National Institute for Health and Clinical Excellence, 2012).

Short-acting NRTs (e.g. gums, lozenges, microtabs, sprays and inhalators) have been in use for more than 30 years. In addition to helping smokers to quit, they are also effective as part of a reduction strategy, both in reducing cigarette use immediately and in encouraging subsequent quit attempts (Beard et al., 2012). This approach assists many of those who feel unable to quit smoking in taking the first step on that journey.

Controlled clinical trials have consistently shown that currently available forms of NRT, often coupled with varying levels of behavioural therapy, may be effective in aiding smoking cessation among adults. NRT increases the rate of quitting by 50–70%, when compared with placebo or no treatment (Stead et al., 2012). However, on a population level, the impact of NRT in absolute terms is modest (Rose, 1988).

The currently available forms of NRT may fail to help many smokers quit because they do not deliver nicotine in the same way as cigarettes (Schneider et al., 2001). Most currently available NRTs do not replace the unique sensory cues or rituals associated with smoking (Fagerström, 2012; Rose, 2006). The need for more appealing licensed nicotine products to help reduce the prevalence of smoking has been recognised; in the UK, the Royal College of Physicians (RCP) recommend the regulation of new medicinal nicotine products to encourage development and marketing of medicinal-grade formulations that are more acceptable and satisfying alternatives to smoking than current NRT products (Royal College of Physicians, 2008).

The immediate public health need is finding ways to help smokers stop smoking: switching the means by which they access nicotine from the most harmful, burnt tobacco, to safer alternatives. If smoking cessation products can achieve a greater acceptance among smokers by offering craving relief, coupled with rapid absorption and mimicking many of the aspects of a cigarette (pharmacological, physiological, behavioural, social and sensorial) they will enable a greater proportion of the smoking population to begin their journey towards quitting or substitution of cigarettes with medicinal nicotine products. As a consequence, such products could radically reduce the use of burnt tobacco in society, which will, in turn, have a marked impact on public health. Non-combustible forms of tobacco currently purporting to fill this space are e-cigarettes and snus.

Several studies have reported the use of electronic cigarettes as an aid to smoking reduction or temporary abstinence. In one study, the point prevalence of smoking abstinence among electronic-cigarette users was 31%. In addition, a large percentage of respondents reported a reduction in the number of cigarettes they smoked (67%) and almost half reported abstinence from smoking for a period of time (49%) (Siegel et al., 2011). Similarly, in another study, a third of participants sustained a 50% reduction in the number of cigarettes per day, while 13% sustained an 80% reduction after 24 weeks. Sustained smoking abstinence at Week 24 was observed in 22.5% of participants (Polosa et al., 2011).

Electronic cigarettes have also been used as a quitting aid. In a survey of over 200 smokers, those respondents using electronic cigarettes more than 20 times per day reported a quit rate of 70% (Siegel et al., 2011). Also, three smokers with a documented history of recurring relapses were reported to have quit and remained abstinent for at least 6 months using electronic cigarettes (Caponetto et al., 2011). Another study has described the use of electronic cigarettes to reduce nicotine craving, with a significant difference in the level of craving reported with electronic cigarettes compared with placebo (Bullen et al., 2010).

There is also evidence to support the prevention or inhibition of initiation of smoking with Swedish snus. Ramström and Foulds reported that the odds of initiating daily smoking were significantly lower for men who had started using snus than for those who had not. In addition, it was suggested that daily smokers were more likely to quit smoking if they initiated daily snus use (Ramström & Foulds, 2006). Again, the expectation has been, in most countries, that these products be evaluated from a quality and safety standpoint with reference to existing NRT, to determine whether the risk benefit is comparable or advantageous.

As both of these alternative products are currently unregulated, far less information is available in the literature regarding their safety and quality, hence the current review ongoing in Europe as to whether such products should be regulated, and how.

2.1 Australia

Australia has been successful in reducing smoking prevalence over many years, yet still 15.1 per cent of people 14 years or over were smoking daily in 2010 (Intergovernmental Committee on Drugs, 2012). Through the National Healthcare Agreement (NHA) the Council of Australian Governments (COAG), committed to the following performance benchmark:

> 'By 2018, reduce the national smoking rate to 10 per cent of the population, and halve the Indigenous smoking rate, over the 2009 baseline.'

Consistent with this performance benchmark, the COAG National Partnership Agreement on Preventive Health (NPAPH), signed in 2008 and varied in 2012, contained the following public health outcome:

> 'Reduce the proportion of Australian adults smoking daily to 10 per cent within 10 years.'

Currently the approved indications for NRT therapy in Australia are :

- Use as an aid in the cessation of smoking in smokers with nicotine dependence; and
- Relief of nicotine withdrawal symptoms, including nicotine cravings, associated with smoking cessation

- Combination therapy using nicotine transdermal patches and intermittent use products
- Smoking reduction prior to stopping smoking-
- Pre-cessation use of nicotine transdermal patches

No indication for Harm Reduction per-se has been approved in Australia at this time.

In Australia, Roy Morgan research estimates e-cigarette incidence to be at 0.6%1. Further information on the size of the NGP market in Australia is difficult to find, largely due to the illegal nature of the category.

Elusion, the most sophisticated of over 100 Australian-specific e-cigarette companies, sells e-cigarette devices and the banned liquid nicotine on-line and in specialist retailers, Elusion claims that business grew by 200% 20102.

E-cigarettes are most prominent in independent retailers and the peak body representing this sector, the Australian Retailers' Association, discovered in August 2013 that 34% of its members have stocked e-cigarettes and 78% have expressed a desire to do so in the future.

To add to the existing evidence base an NHMRC funded study at the University of Queensland has been commissioned to test the safety and effectiveness of e-cigarettes for smoking cessation by comparing their effectiveness in helping smokers to quit with traditional cessation aids such as nicotine gum and inhalators. (http://www.uq.edu.au/news/article/2013/09/uq-e-cigarettes-research-misrepresented-media)

The current use of electronic cigarettes in Australia is occurring without oversight. The product have not been through due diligence and their purpose for use is outside the currently approved indications for NRT. While supporting the potential role of electronic cigarettes as a tool in tobacco control health groups raise concerns on the oversight of the products currently on the market (http://www.medicalobserver.com.au/news/call-for-regulation-of-electronic-cigarettes)

It is in this context that a pragmatic regulatory approach both facilitates improvement in the quality and safety of the products on the market, reassures companies that investment in innovation is worthwhile and build confidence in these products in the wider community as alternatives to burnt tobacco.

[1] Roy Morgan tracking of total population in an average 7 day period at December, 2012.
[2] http://www.theage.com.au/national/banned-ecigarettes-may-be-a-health-hazard-but-buying-thems-a-wheeze-20101211-18ti7.html

3 Regulatory Approach by MHRA in UK

NRT products were initially recommended for short-term use to help smokers stop abruptly. By 2001, the General Sale List (GSL) availability of some NRT products was approved in the UK and by 2009 all NRT products were classified as GSL thereby maximising accessibility to smokers wishing to change their smoking behaviour. The authorised indications and product types continued to develop over time and in 2010, the MHRA granted an extended indication for NRT to be used for harm reduction, to assist smokers who are unwilling or unable to quit, as a safer alternative to smoking and to reduce the health hazards from second-hand smoke (MHRA, 2009).

The approach taken by the Medicines and Healthcare products Regulatory Agency (MHRA) and other regulators to evaluate NRTs, based on broad pharmacokinetic parameters supported by the standard extensive evidence of quality and a thorough safety evaluation in combination with an appropriate Risk Management Plan, has proved both effective and pragmatic. Users of short-acting NRT, which more closely simulates nicotine intake from a cigarette, self-titrate the amount of nicotine they require. Consequently, clinical trial evidence of efficacy, or even of bioequivalence, has been considered unnecessary for licensing purposes. Provided the pharmacokinetic profile sits within the range already seen by reference to established licensed nicotine products and cigarettes, they are considered to have utility when used by smokers to relieve their cravings. A range of formulations have been licensed, and whilst their actual in use efficacy in terms of achieving quitting is recognised as modest, they do help many smokers wishing to quit and have an excellent safety profile.

In 2010, the MHRA granted an extended indication for NRT to be used for harm reduction, to assist smokers who are unwilling or unable to quit, as a safer alternative to smoking and to reduce the health hazards from second-hand smoke (MHRA Public Assessment Report, 2009). Subsequently, the RCP advised that "harm reduction products should ideally be effective nicotine delivery devices that are less expensive than cigarettes, available in newsagents and other retail outlets in the same way as cigarettes currently are, and supported by purity and safety standards that protect the smoker without stifling product innovation and development" (Royal College of Physicians, 2012).

In 2011, the UK National Institute for Health and Clinical Excellence (NICE) issued the scope for its consultation on tobacco harm reduction. Groups covered by the guidance include smokers of all ages who: want to quit smoking but feel unable to do so abruptly (i.e. they want to reduce their smoking before quitting); are not willing or able to quit but want to reduce the harm that smoking is doing to their health or the health of those around them; want to quit smoking but are not willing or able to stop using nicotine; and those who want to stop smoking temporarily (NICE, 2011). In the recently published draft guidelines, NICE goes on to advocate medicinal nicotine use on a long-term basis when needed to help people maintain a quit attempt or reduce their level of smoking indefinitely as a method of harm reduction (NICE, 2012).

Meeting smokers needs with innovatively designed safer alternatives, over which there is proper regulatory control, should be a priority. It is viewed that this should include acceptance of longer duration of use of existing NRT products, to consider harm reduction as an additional indication and to ensure that the regulatory evaluation is pragmatic. The focus should be on product quality. By a careful evaluation of the product qualitative and quantitative composition throughout its shelf-life,

fully understanding what the user will be exposed to, the safety of the product may be determined. Efficacy can be evaluated with reference to pharmacokinetic parameters (compared with existing NRT and cigarettes), user acceptance and craving relief.

An additional clinical endpoint possibly meriting consideration is craving. As NRT products were initially recommended for short-term use to help smokers stop abruptly (MHRA, 2005), there is very little product-related research that has looked at craving beyond the first weeks and months. It is fairly straightforward to measure craving relief in a clinical trial setting as craving can be reliably provoked by the deprivation of cigarettes and there are a number of widely accepted tools to do this. If evidence can be obtained that a nicotine-containing product is effective for craving relief under these conditions then it is likely to be valid to support the product as a quitting aid and for relapse prevention.

Smokers' cravings are often provoked or cue-induced. We are not aware of any evidence to support the idea that these cravings are any less amenable to medicinal nicotine than those experienced whilst quitting. The key is ensuring that fast-acting NRT, simple to self-titrate, is easily available in these situations so that the ex-smoker utilises such products rather than returning to smoking.

If a clinical endpoint of craving were to be employed, the craving data profile for the test product must at least match that reported for existing products that have been used to successfully help people quit.

Part of the assessment conducted by MHRA is to determine what legal classification the medicinal product should be sold under (i.e. prescription use only, pharmacy or general sales list (OTC)). NRT products currently approved in the UK are all approved with GSL status and therefore are widely available through pharmacies and non-pharmacy retail outlets. With the proposed product designed to be different, meeting the needs of a larger proportion of the smoking population, MHRA must consider whether there are further risks associated with making it available OTC. In order to evaluate these potential concerns, the application includes a risk management plan describing appropriate post marketing surveillance, including assessment of gateway, misuse and overdose.

Data analysed from the National Survey on Drug Use and Health determined the prevalence of smoking in different groups classified by the age at which they first used cigarettes or smokeless tobacco. The study concluded that, compared with boys who started smoking cigarettes, those who started by using smokeless tobacco are less likely to smoke (43% versus 18%), suggesting smokeless tobacco may play a protective role (Rodu & Cole, 2010). Similarly in a Swedish study, the odds of initiating daily smoking were significantly lower for men who had started using snus versus those who had not (Ramström & Foulds, 2006). In a recent UK survey, less than 1% of adults who had never smoked reported having tried electronic cigarettes (ASH, 2010 and 2012).

Although nicotine is addictive, nicotine intoxication is much less pronounced than is the case with opioids and sedatives, and nicotine intoxication occurs rarely in regular tobacco users (Royal College of Physicians, 2007). In addition, the level of nicotine quickly accessible from a nicotine-containing product such as NRT or an electronic cigarette is less than that in a cigarette. Therefore, the risk of deliberate misuse for the purpose of intoxication is low.

Nicotine provides a rapid and effective feedback mechanism, allowing a smoker to easily self-titrate the dose they require from either a cigarette or NRT. Effects related to too much nicotine include: feeling faint, nausea and headache, all of which are likely to further self-limit the administration of the medicinal nicotine product. The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40-60 mg. [redacted]

4 New Products

4.1 Nicotine Delivery Technologies

It is well established that the key pharmacological element of tobacco addiction is the delivery of nicotine to the brain, leading to the release of a range of neurotransmitters such as dopamine which yield powerful feelings of "reward" and "pleasure" to the individual. The tobacco cigarette is a highly efficient nicotine delivery system that achieves rapid pulmonary delivery and sharp increases in the nicotine concentration in both arterial and venous blood. Although nicotine is the predominant addictive chemical in tobacco smoke, it is the other (approximately 4000) chemicals, including carcinogenic agents in the particulate phase, that lead to the well-established adverse health consequences of smoking (Royal College of Physicians, 2007).

The current presentations of medicinal nicotine have different delivery characteristics which vary widely but (with the exception of the nasal and mouth sprays) are generally very much slower than that of a cigarette. This is one of the key factors considered relevant in contributing to the relatively limited usage of NRT when compared to cigarettes. Long term success rates of existing NRT in smoking cessation remain low, with a recent study showing that only 6.75% of smokers receiving NRT therapy attained sustained abstinence for six months, albeit twice the rate of placebo treatment (Moore et al., 2009).

The major limitation with delivery of nicotine by current NRT products is that they do not provide smokers with the combination of a rapid delivery of nicotine and the unique respiratory tract sensory cues of inhaled nicotine (particularly upper airway irritation) which together are of primary importance in relieving craving for cigarettes (Rose, 1988).

There is a clear need for new delivery devices that simultaneously address the behavioural aspects of the smoking ritual together with rapid nicotine delivery combined with respiratory sensory cues. Addressing all these aspects in a single product is likely to be the key to effective craving reduction and increasing adoption by smokers with resultant health benefits to the individual and the general population.

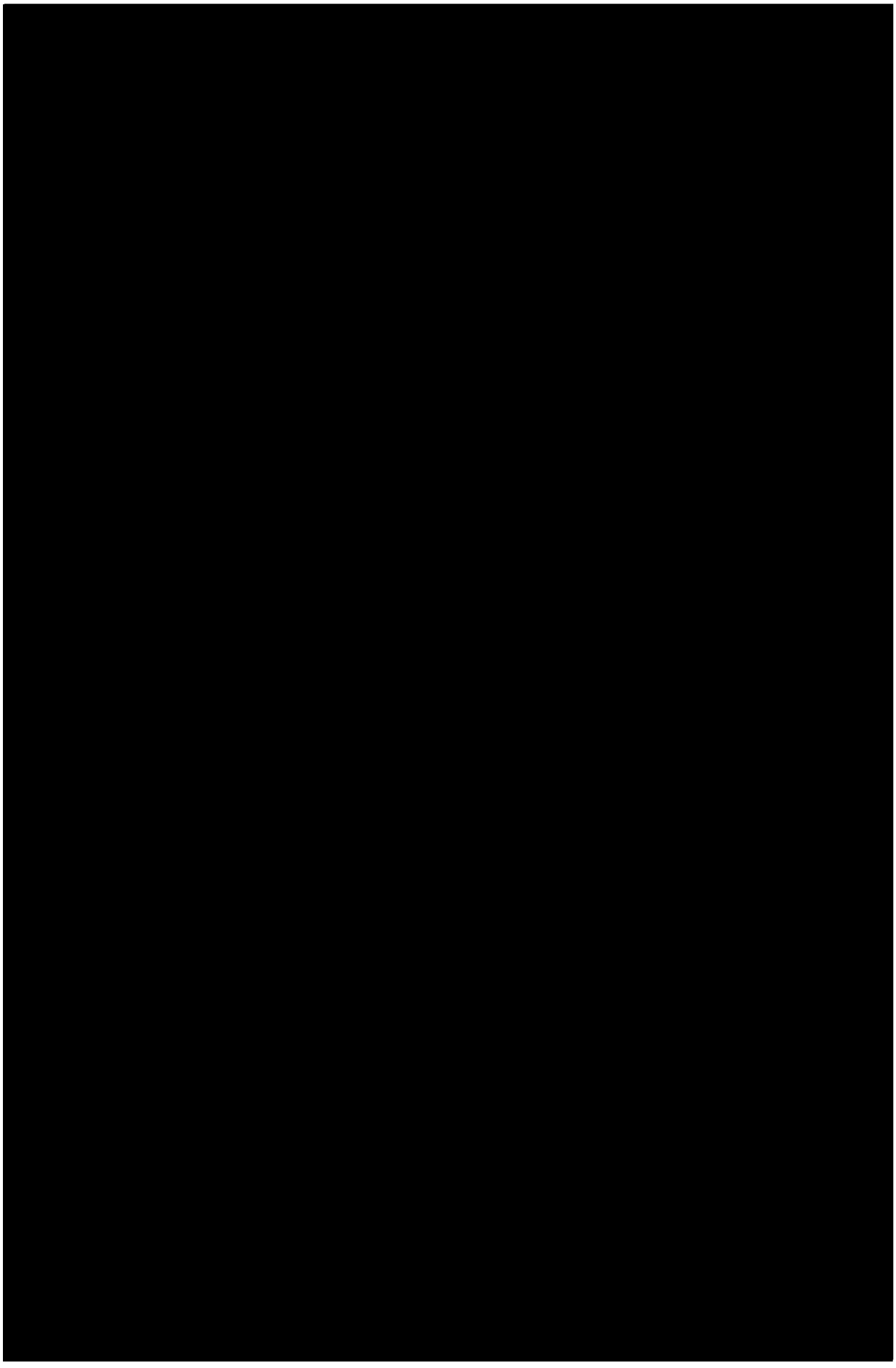
As the most prevalent form of nicotine delivery (along with many of the other harmful elements within tobacco smoke), cigarettes are also an important comparator to any NRT product.

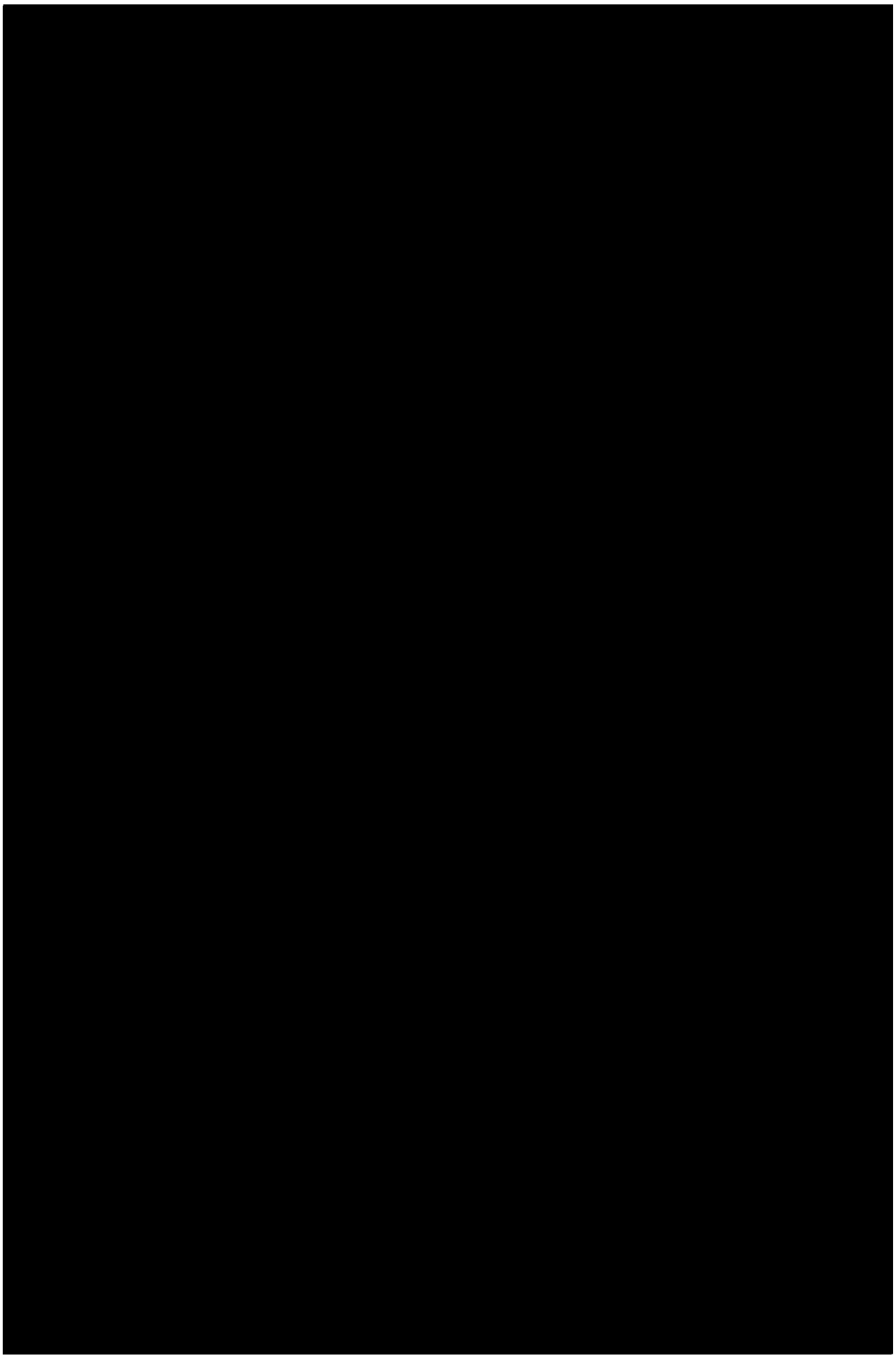
Manufactured cigarettes typically contain approximately 0.7 grams of tobacco and 10-12 mg nicotine per cigarette (a pack of 20 would therefore contain 220 to 240 mg). Of this, only 1-2 mg of nicotine is delivered by a standard cigarette and this rapidly increases the arterial nicotine concentration and reaches the brain within seconds (Royal College of Physicians, 2007). When the cigarette is smoked the combustion is incomplete, and the smoke contains a mixture of carbon particles, tar, water and gases. Particulates form when nicotine vaporises, cools and condenses along

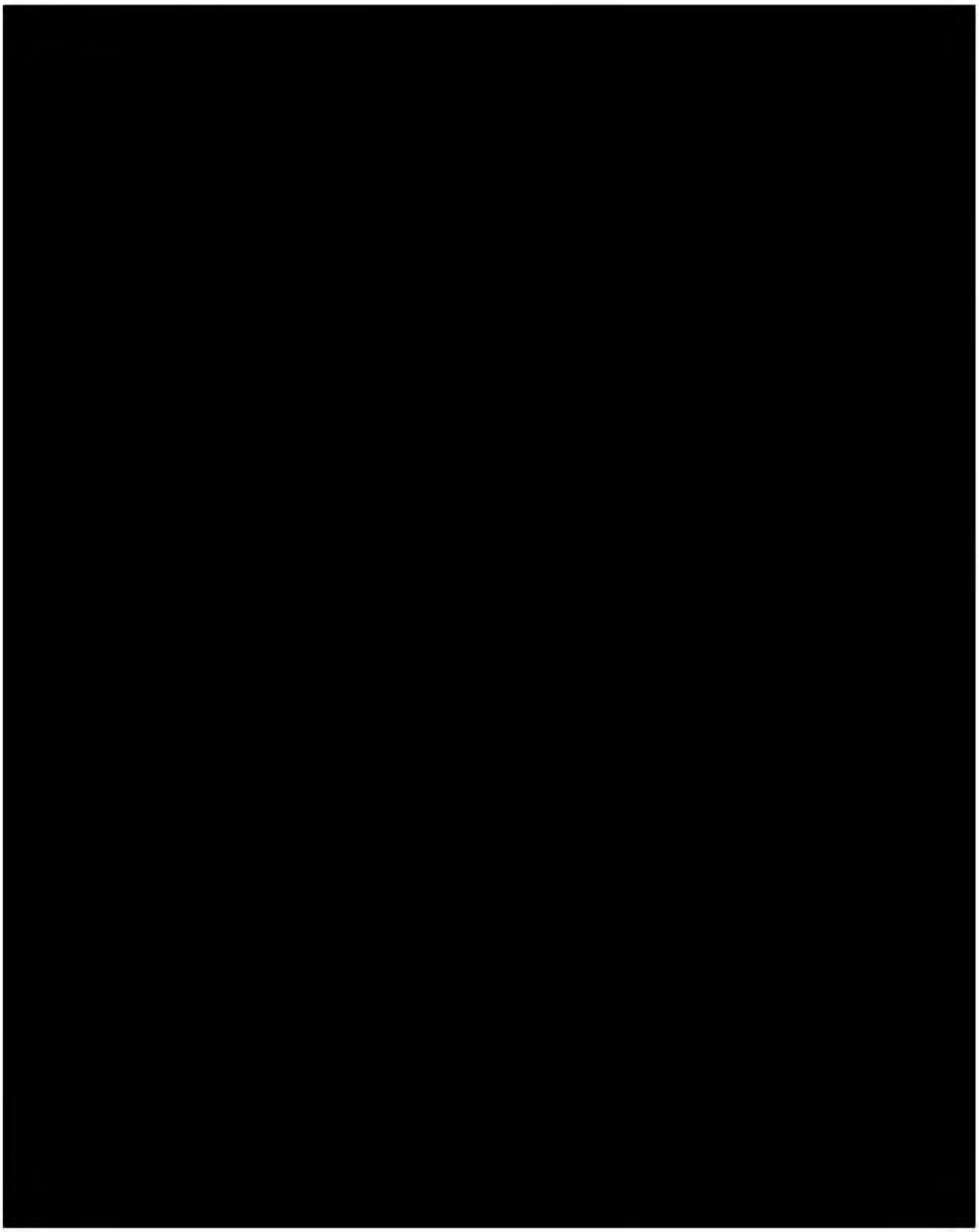
with other products of combustion. Tobacco smoke is inhaled into the lungs, where nicotine is rapidly absorbed into the pulmonary circulation and then into the systemic circulation.

The arterial nicotine concentrations achieved after cigarette smoking are several times higher than those achieved by other nicotine delivery systems. It is the combination of rapid delivery of high concentrations of nicotine to the brain's reward centre via the arterial blood, closely linked to the ritual behaviour of smoking and inhalation throat irritation cues which are considered to enhance the addictiveness of the cigarette (Royal College of Physicians, 2007; Rose, 1988).

There are many studies of venous nicotine concentrations after smoking a cigarette but relatively few studies of arterial pharmacokinetics. The exact profile of concentrations of plasma nicotine generated by smoking depends on the time taken to smoke the cigarette and the rate and depth of inspiration.







5 Potential Regulatory Approaches in Australia

Nicoventures is committed to the reduction of harm caused by the serious health risk of smoking cigarettes.

With the regulatory process now on-going in the UK and EU, Nicoventures is initiating activities in markets outside of the EU to explore the optimum strategy in each, for registration and marketing.

The legislative situation in Australia is clear, [redacted] It is also clear that there are a large number of e-cigarettes, both nicotine containing and nicotine free, being imported into Australia today. These products have questionable quality and their ability to be effective tools in tobacco dependence has not been scrutinised. At Nicoventures we believe we have products that can both comply with the Australian Therapeutic Goods requirements AND the clear desire of smokers for a new form of NRT. Nicoventures is committed to taking our products forward, but within an appropriately regulated system with suitably justified product quality, safety and efficacy.

[redacted]

Given the above key areas that we would value discussion with the TGA are as follows:-

[redacted]

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