Thoracic Society response to TGA Consultation on TGO 110 – Standard for Vaporiser Nicotine

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Introduction

The Thoracic Society of Australia and New Zealand (TSANZ) is a health promotion charity whose mission is to lead, support and enable all health workers and researchers who aim to prevent, cure and relieve disability caused by lung disease. TSANZ is the only Peak Body in Australia that represents all health professionals working in all fields of respiratory health.

TSANZ has a membership base of over 1800 individual members from a wide range of health and research disciplines. TSANZ is a leading provider of evidence-based guidelines for the treatment of respiratory disease in Australia and New Zealand, undertakes a large amount of professional education and training, is responsible for significant research administration, and coordinates an accredited respiratory laboratory program.

As the leaders in lung health, we promote the:

- highest quality and standards of patient care
- development and application of knowledge about respiratory health and disease
- highest quality air standards including a tobacco smoke free society and effective regulation of novel nicotine delivery systems
- collaboration between all national organisations whose objects are to improve the wellbeing of individuals with lung disease and to promote better lung health for the community
- professional and collegiate needs of the Membership.

Last year we published the Electronic cigarettes: A position statement from the Thoracic Society of Australia and New Zealand (1). We will continue to advocate through evidence-based practise and policy to improve lung health.

Preamble

TSANZ notes that the Delegate's decision to classify nicotine as a prescription only medicine essentially clarifies the existing ability of medical professionals to prescribe nicotine containing e-liquids. TSANZ acknowledges this is a practical response and we support the intent of making nicotine containing products available by prescription only, but we have serious reservations about the short circuiting of the TGA regulatory process.

Through the implementation of TGO 110, on-going evaluation and monitoring for impact on public health must occur and the ability to reverse decisions in a timely manner must be possible. The prescription only model is preferable to a retail consumer goods model and it is the position of TSANZ that Alternative nicotine delivery systems (ANDS) are not suitable as a consumer product.

In previous submissions to the TGA and a sequence of other inquiries TSANZ has made its position clear.

1. Alternative nicotine delivery systems have marginal efficacy at best as a tool for smoking cessation,
2. They are toxic to the lung and other systems in short and long-term use
3. Safety relative to combustible tobacco use is uncertain and they may not be any safer at all
4. There is incontrovertible evidence that alternative nicotine delivery systems (ANDS) use in children and young adults is harmful and, regardless of other factors relevant to an individual, increases the likelihood of progression to combustible tobacco use
5. The remaining role of ANDS must
    a. be limited to those smokers for whom other approaches have not been successful
    b. be restricted to short periods of use in a genuine smoking cessation attempt
    c. be under medical supervision with personal support

As it relates to this consultation and although not explicitly part of the consultation document, the availability of nicotine by prescription as envisaged can and must lead to the closure of the current personal importation scheme. TSANZ will strongly and publicly oppose changes within the remit of TGA if that scheme is not shut down. Once onshore supply is assured, there is absolutely no need for a parallel personal importation arrangement.

We remind the TGA of the following concerns of TSANZ:

1. Vaporised nicotine products have not been through the regulatory process and are not listed on the ARTG. The evidence of their effectiveness as cessation products is not yet established and the plethora of products on the market makes it virtually impossible to translate trial outcomes to all ANDS products.
2. We strongly recommend ANDS are submitted to the TGA for inclusion on the ARTG such that prescribers could access reliable evidence about products they are being asked to prescribe.
3. Prescription products require a Product Information (PI) document to assist prescribers to correctly prescribe. The PI must be approved by the TGA and include objective information about the quality, safety and effectiveness of the product. All nicotine products should have an accompanying PI document.
4. Whilst the use of the word therapeutic has been deleted in the amendment to the schedule, it is still the case that the public expect therapeutic actions from prescribers. The TGA is therefore asking doctors to prescribe a poison, in a form with an untested efficacy and safety profile to patients. We are very concerned that advice on dosage and use is being promulgated in the absence of evidence although we note and agree that TGA does not see itself as having a role in specifying or recommending nicotine doses.
5. We strongly recommend suppliers be required to submit their product for independent Quality control testing. Only those products which have successfully been through an independent QC process should be prescribed.

6. To date, no ANDS product has been approved for the purpose of smoking cessation. Given that all the major tobacco companies now have ANDS products, it is not plausible to argue that the cost of supportive research and/or a TGA application fee are prohibiting factors. Likewise, we do not permit small backyard operators to produce and market therapeutic goods without going through a robust regulatory framework. In a regulatory model without compromise, ANDS products would be subject to the regulatory processes of the TGA if they are to be prescribed as a cessation product.
7. The marketing of prescription products is regulated in Australia and prevents direct to consumer advertising. If ANDS products are only available via prescription, then they should be managed under the same marketing regulations as other prescription products. Mechanisms must be in place to prevent vested commercial interests from making therapeutic claims about ANDS.
8. Smokers seeking to use ANDS should not be prescribed as a first line cessation product. Prescribers must ensure combination therapy with behavioural support is completed prior to considering prescribing ECs. The TGA must ensure that robust mechanisms are in place to prevent prescribing of ANDS without first utilising evidence-based tobacco dependence treatment.
9. When prescribing ANDS for cessation the same requirements for accessing currently available tobacco dependence medicines should apply i.e., to attend behavioural support and time limited use. We also advise that there should be no repeat prescriptions without medical review.
10. The authorised prescriber model greatly simplifies the prescribing process. However, there must be mechanisms in place to ensure that the process, if implemented, operates as planned. This includes managing the potential for over-prescribing and ensuring that these products are not prescribed as first line treatment or to non-smokers or smokers not willing to quit or completely substitute away from combustible cigarettes.
11. ANDS devices which dispense prescription nicotine should be considered a medical device to ensure they meet safety standards and should be regulated as a therapeutic device. For example, a recent study demonstrated that use of a nickel-chrome heating element in e-cigarettes at high power induced the potentially lethal lung condition EVALI in the absence of tetrahydrocannabinol, vitamin E, or nicotine (2).
12. TSANZ believes a prescription only approach may assist in reducing uptake amongst young people provided that access to these products through other channels e.g., online, vape shops is restricted.

Consultation Topics

The TGA has requested feedback specific to the following topics:

- The proposed scope of TGO 110,
- The potential requirements for unapproved vaporiser nicotine products, covering labelling, ingredients, packaging, nicotine concentration and container volume, and
- Any other related matters. This covers topics related to vaporiser nicotine products, but covered by TGO 110; specifically, default standards (pharmacopoeia) and nicotine purity, and compounding.

Comments on the Proposed Scope of TGO 110

Q1. Do you think that export only vaporiser nicotine should be required to comply with TGO 110? Why or why not?

Export only vaporiser nicotine should be required to comply with TGO 110. This will ensure the standard quality of products that might be permitted in Australia is maintained in an export market. Australian standards are world leading and will influence the world market. TGA Populations living in smaller countries in our region, in particular, deserve protection.

Q2. Do you think clinical trial products should be required to comply with TGO 110? Why or why not?

TGO 110 should apply to all research. In the case of, for example, a blinded clinical trial, a sticker should be applied over the label when single or double blinding is required in accordance with an approved protocol. All safety features of TGO 110 should be mandatory.

Q3. Do you think products that are the subject of an FDA PMTA marketing order, or that are supplied in the UK, EU, Canada, NZ and/or another country in accordance with the relevant requirements of that country, should be deemed to comply with TGO 110 (in whole or in part)? Why or why not?

All vaporised nicotine products used in Australia need to comply with TGO 110 in their own right. This would ensure that all products brought into Australia meet the required standards. For example, it is possible that the FDA may issue PMTA for a product with a higher nicotine concentration than permitted under a finalised TGO. As has recently been the case with SARS-CoV-2 vaccines, there is no substitute for local regulation and review.

Q4. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

Yes, this would affect management of tobacco dependence treatment. We also have concerns for countries that are our near neighbours.

Q5. Do you have any other comments about the products covered by or excluded from draft TGO 110?

TSANZ notes that many vape liquids do contain nicotine even when they claim not to (3).

Comments on Potential Requirements for Unapproved Vaporiser Nicotine Products

Labelling – ingredients list

Q1. Which option (whether listed above or not) do you prefer? Why?

We recommend option 1, that all active ingredients plus all excipient ingredients (including all component ingredients of any flavours) are listed. We disagree with the TGA's proposal to exclude components of flavours.

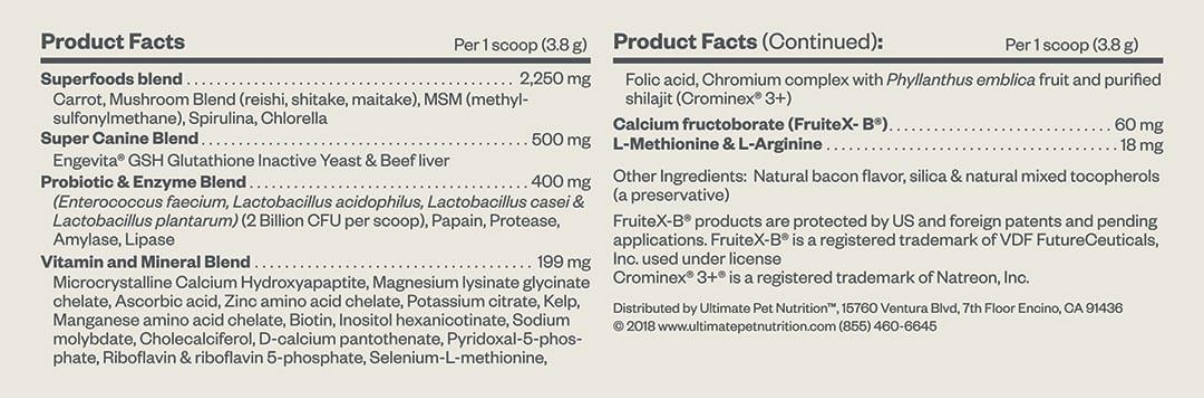
Manufacturers must be fully responsible for accurately informing potential users of the ingredients of the product they seek to sell. TSANZ is concerned that there remains nicotine in non-nicotine e-liquids, along with a host of other ingredients which are not proven safe for inhalation (3). The exemption of inclusion of ingredients that constitute flavour could be exploited as there is no standard definition of what chemical constituents are required to achieve such flavour. If flavourings are included in the

product, these ingredients should be listed. The TGA should consider making flavour component information available on a detailed product information sheet or other publicly available database.

Q2. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

Option 1, listing all ingredients, would provide information to assist with informing patients of what they will be inhaling when vaporising these products. It has the potential to improve the quality of the product as companies will work to produce a more appealing list of ingredients. It creates a loophole for inclusion of ingredients with uncertain effect.

An issue raised by the TGA is that ingredient lists for some products may be too long to fit on a standard label, but we fail to see this as an issue. Regardless of if the liquid needs a double label or an extra sheet for the list of excipients, they should be made to display their entire list of ingredients as to remain transparent and uphold quality assurance on the product. By way of comparison, this is the list of ingredients and levels in a pet food product for oral ingestion. It seems bizarre to TSANZ that a lesser standard could be considered for products designed to be superheated and then inhaled by humans.



Product Facts Per 1 scoop (3.8 g)

Superfoods blend ..... 2,250 mg
Carrot, Mushroom Blend (reishi, shitake, maitake), MSM (methylsulfonylmethane), Spirulina, Chlorella

Super Canine Blend ..... 500 mg
Engevita® GSH Glutathione Inactive Yeast & Beef liver

Probiotic & Enzyme Blend ..... 400 mg
(Enterococcus faecium, Lactobacillus acidophilus, Lactobacillus casei & Lactobacillus plantarum) (2 Billion CFU per scoop), Papain, Protease, Amylase, Lipase

Vitamin and Mineral Blend ..... 199 mg
Microcrystalline Calcium Hydroxyapaptite, Magnesium lysinate glycinate chelate, Ascorbic acid, Zinc amino acid chelate, Potassium citrate, Kelp, Manganese amino acid chelate, Biotin, Inositol hexanicotinate, Sodium molybdate, Cholecalciferol, D-calcium pantothenate, Pyridoxal-5-phosphate, Riboflavin & riboflavin 5-phosphate, Selenium-L-methionine,

Product Facts (Continued): Per 1 scoop (3.8 g)

Folic acid, Chromium complex with *Phyllanthus emblica* fruit and purified shilajit (Crominex® 3+)

Calcium fructoborate (FruiteX- B®) ..... 60 mg
L-Methionine & L-Arginine ..... 18 mg

Other Ingredients: Natural bacon flavor, silica & natural mixed tocopherols (a preservative)

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Manufacturers can make life simple for themselves by having fewer ingredients.

TSANZ notes that many vape liquids do contain nicotine even when they claim not to (3).

Labelling – nicotine concentration

Q1. Which option (whether listed above or not) do you prefer? Why?

We support option 1 (State nicotine concentration or, for nicotine salt products, nicotine base form equivalent concentration (i.e., of nicotine only, not nicotine salt concentration) in mg/mL.) as the most informative option. In addition, we support the inclusion of option 4 where the nicotine concentration or base form equivalent **must be on the label**. It is noted that some products may contain both nicotine and $NicH^+$ and this should be accounted for in when determining the nicotine content (4).

Q2. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

Providing the nicotine content on the label would make it easier for the patient to track and monitor how much nicotine is in the product if they were attempting over time to titrate down their nicotine exposure.

Furthermore, this information provides information which will allow comparison to other NRT products. Awareness of cartridge use per day allows a rough idea of nicotine dose per 24hrs; a concept doctors and pharmacists are very familiar with e.g., NRT 21mg/24hr patch. This is a smoking cessation product and therefore should strive to be comparable with the suite of treatments available.

Labelling – warning statements

Q1. Which option (whether listed above or not) do you prefer? Why?

TSANZ supports Option 2; **Require the provision of warning statements and safety directions AND/OR pregnancy warning AND/OR addictiveness warning and have these included on the label (no option to provide it on an information sheet).**

Having these warnings easily seen on the product labels sends a clear message to the patient. We support a National approach as it would ensure consistent regulations and support a whole-of-nation approach to vaporiser nicotine policy. Warning labels must relate to the whole harm or potential for harm and not be limited to nicotine.

For example:

Vaping nicotine solutions is addictive

Vaping nicotine solution is a health hazard

Vaping nicotine solution is harmful to the lungs

The actual content of any warning can be defined after the update of the NHMRC statement[1] .

Q2. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

Relying on State/Territory regulations risks poor co-ordination. As the peak national body for lung health, we would have to engage in separate discussions with each State/Territory. This is onerous for us. Yes, this would assist in nicotine dependency behavioural therapy.

Ingredients – prohibiting certain ingredients

Q1. Which option (whether listed above or not) do you prefer? Why?

We support Option 3 (Prohibit additional individual ingredients that are associated with health concerns and could be present in flavours) with a substantially stricter implementation. Only nicotine, vegetable glycerine, propylene glycol and flavour (see separate discussions) should be permitted. In supporting this, we in no way endorse that their inhalation is safe. We believe that any other potentially active ingredient should only be permitted if proven not to be harmful.

Q2. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

Yes, it would reduce harm from vaping nicotine products.

Ingredients – flavours

Q1. Which option (whether listed above or not) do you prefer? Why?

[1] https://www.nhmrc.gov.au/about-us/resources/ceo-statement-electronic-cigarettes

TSANZ support Option 1; Allow certain flavours only (e.g., tobacco, mint, menthol).

We are unconvinced of the importance of flavours for a genuine quit attempt. However, we pragmatically submit that there need only be two flavours – tobacco and mint or menthol. All other flavours must be banned. The attraction of fruit and other similar flavours to youth is not in serious question. State and Territory regulators and public health bodies will be able to rapidly identify non-complying products just as non-compliant (illicit) cigarette packs are presently identified.

The flavour restrictions interact with limits on volume and concentration. Currently the majority of State and Territory governments do not restrict the sales of flavoured vaping solutions not containing nicotine. We do not believe that nicotine solution should be sold in a form to which such non-permitted flavour solutions can be subsequently added. The effect of this is that we believe that only closed, pod or cartridge-type systems, should be permitted.

We disagree agree with the TGA's proposal with conditions; there is not a need for flavourings in these products. However, if flavourings are included, they must only be permitted if proven not to cause harm before being permitted.

Q2. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

Yes, it would reduce harm from vaping nicotine products and dramatically reduce the attractiveness of products to children.

Packaging – child resistant packaging

Q1. Which option (whether listed above or not) do you prefer? Why?

We support option 1 to impose requirements equivalent to TGO 95. Child resistant packaging for all products regardless of their country of origin should comply with TGO 95. This will ensure all vaporiser products meet the same standard and will help to ensure children do not accidentally ingest any nicotine. Furthermore, in setting a high standard for CRP, Australia will continue to influence a safer environment for children worldwide.

This submission should be considered in conjunction with separate comments on nicotine concentrations and volume. It is the critical combination of safe packaging and maximum possible nicotine exposures that will prevent further tragic events involving children.

Q2. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

"Child resistant" does not equate to "child proof". This would help reduce accidental harm, including fatal harms, to children(5).

Packaging – tamper-proof/evident packaging

Q1. Which option (whether listed above or not) do you prefer? Why?

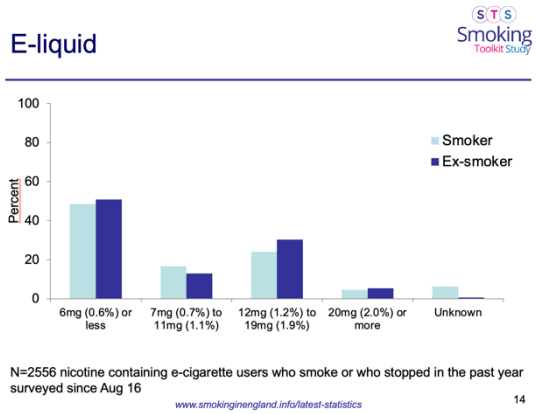
TSANZ supports the TGAs proposal, Option 2; Products packaged for supply within the UK, the EU, Canada, the US and NZ must either comply with CRP requirements imposed in that country OR the requirements applicable to all other products; All other products must meet requirements equivalent to TGO 95 (as described above) (excluding requirement to provide directions for opening/closing).

As vaporiser nicotine products will be prescription only, we agree that tamper-proof packaging is not required.

Nicotine concentration

Q1. Which option (whether listed above or not) do you prefer? Why?

TSANZ supports Option 1; 1. Maximum nicotine concentration of 20 mg/mL OR 66 mg/mL OR another level. We vehemently disagree with the TGA's proposal of no limit on nicotine concentration. Even vaping advocates themselves speak of the success as they see it of these products in EU and the UK that operate on the basis of the EU Tobacco products directive that limits concentration to 20mg/mL (6). Data from the long-running Smoking Toolkit Summary in England highlight that the great majority of current ANDS use is at concentrations below 20mg/ml (7). There is simply no need for higher concentrations – only risk.



Child resistant packaging does not mean child proof, therefore limited concentration adds additional protection. Children have died after drinking 5mls of 10mg/ml liquid (5).

If there is no limit on nicotine concentration or volume, then there is no guarantee that it is for personal use. There should be a limit on the total dose of nicotine prescribed to ensure it is for personal use, dosing safety, and management in line with a therapeutic pathway.

Q2. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

We would argue stridently and publicly and lobby against any proposal for permissible maximum concentration that exceeded 20mg/ml. This should not be necessary.

Volume

Q1. Which option (whether listed above or not) do you prefer? Why?

We support a variation on Option 1; Maximum volume of 10 mL OR 1000 mL OR another level (all concentrations). **As mentioned previously, we will only support the prescription of closed/pod-like systems. The maximum volume per pod must not exceed 10mls.** The standard 28-day prescription will be for enough pods or cartridges to meet the anticipated supply needs of the smoker making a quit attempt.

In the same manner, NRT is limited. Yes, people may need higher doses of nicotine and that is why physicians prescribe combination products and titrate as necessary.

Other questions and comments

We would like to be consulted on any draft guidance prepared for TGO 110.

Comments on Related Matters

Default standards and nicotine purity

Q1. Which option (whether listed above or not) do you prefer? Why?

TSANZ does not support the TGA proposal (Exempt unapproved vaporiser nicotine products covered by TGO 110 from complying with product default standards (see draft *Therapeutic Goods (Exempt Monographs) Determination 2021*). as this in no way ensures that the raw ingredient is pharmacy grade or a pure form. TSANZ supports option 1; **Do not exempt unapproved vaporiser nicotine from complying with the default standards.**

At the very minimum, we encourage the TGA to recommend compliance as per Health Canada's approach.

The e-cigarette market is currently characterised by a lack of quality control and production standards. Approved products are the only products which should be used for smoking cessation. Unapproved products must not be exempt, as this again provides a separate market on unregulated products.

Q2. Would any of these options, particularly the TGA's proposed option, have an impact on you? How?

TSANZ remains concerned as unapproved products are still toxic to the lung and other systems in short and long-term use.

Compounding

Q1. Do you have any comments on the application of TGO 110 to compounded vaporiser nicotine products?

We support the TGO 110 applying to compounded unapproved vaporiser nicotine products in in accordance with the Act and the Therapeutic Goods Regulations 1990 and the Pharmacy Board of Australia's guidance.

Concluding Remarks

Australia and New Zealand must remain focused on proven effective population tobacco control strategies to reduce prevalence rates. We must also ensure smokers have access to behavioural support and, where required, therapeutic products which have been through stringent regulatory approval processes.

TSANZ reconfirms its commitment to Article 5.3 of the World Health Organization (WHO) Framework Convention on Tobacco Control: 'In setting and implementing their public health policies with respect to tobacco control, parties shall act to protect these policies from commercial and other vested interests of the tobacco industry in accordance with national law'.

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