Synthetic nicotine has arrived

Sven-Eric Jordt 1,2

ABSTRACT
The introduction of a new product line of the popular disposable electronic cigarette brand Puffbar, advertised as containing synthetic nicotine, has drawn attention to the increasing use of synthetic nicotine in marketed products and its uncertain regulatory status. A search of the Truth Tobacco Industry Documents revealed that the industry considered using synthetic nicotine already in the 1960s, efforts that were abandoned due to high costs and insufficient purity. Recent patents revealed renewed efforts to develop more efficient strategies for the synthesis of nicotine. Nicotine exists as two stereoisomers, S-nicotine and R-nicotine. While S-nicotine is the prevalent (>99%) form of nicotine in tobacco, a market-leading form of synthetic nicotine contains both stereoisomers at equal amounts, raising concerns about inaccurate labelling and the poorly understood health effects of R-nicotine. Other manufacturers, including a leading vendor of pharmaceutical grade nicotine, developed stereospecific strategies to synthesise pure S-nicotine, now added to electronic cigarette products marketed in the USA and UK. While S-nicotine and R-nicotine can be differentiated by enantioselective High Performance Liquid Chromatography (HPLC), differentiation of synthetic (fossil-derived) from tobacco-derived S-nicotine will require development of methods to measure carbon isotope (13C or 14C) content. Vendors claim that the FDA has no authority to regulate synthetic nicotine as a tobacco product, allowing them to circumvent the premarket tobacco product application process. However, legal analysis suggests that FDA may have the authority to regulate synthetic nicotine as a drug. Alternatively, Congress needs to include nicotine from any source within the legal definition of tobacco products.

In US federal regulations, any product containing tobacco-derived materials is deemed a tobacco product.1 In addition to the conventional tobacco products, the Food and Drug Administration's (FDA) regulatory authority extends to electronic cigarettes (E-cigarettes) that contain highly purified tobacco-derived nicotine, but no other tobacco-derived constituents. Even the market leading products in the recently introduced tobacco leaf-free nicotine pouch category are considered tobacco products since they contain tobacco-derived nicotine.2,3 The tobacco regulatory science community has occasionally discussed a hypothetical scenario in which a company would market a product containing synthetic nicotine.4 Would FDA have regulatory authority over such a product? Such a scenario has ceased to be hypothetical. In February 2021, a countdown clock appeared on the website of Puffbar, announcing a game-changing new product. Puffbar is a popular brand of flavoured disposable E-cigarettes whose market share increased rapidly after FDA prohibited the sale of Juul’s candy and berry-flavoured pods.5 FDA issued a warning letter to Puffbar on 20 July 2020, ordering the company to stop sales due to lack of premarket authorisation.6 However, while the main sales website (puffbar.com) stopped sales, other online vendors, convenience stores and gas stations continued to sell Puffbar-branded disposable E-cigarettes, suggesting that these products were continued to be manufactured or imported illegally, potentially from several sources.

Puffbar revealed the new product as a line of E-cigarettes, stating ‘products are created with tobacco-free nicotine. Our nicotine-based products are crafted from a patented manufacturing process, not from tobacco’ (figure 1A).7 Products are marketed in 3 sizes and with 15 flavours, including a wide range of fruit, berry and candy flavours.

SYNTHETIC NICOTINE: CHEMISTRY AND MANUFACTURERS
Nicotine is a chiral molecule with two stereoisomers, S-nicotine and R-nicotine (figure 2A). Tobacco leaf contains >99% S-nicotine. A search for the term ‘synthetic nicotine’ in the Truth Tobacco Industry Documents revealed that the industry considered the use of synthetic nicotine already in the 1960s. A document by British American Tobacco proposed the addition of synthetic nicotine for adjustment of the nicotine/tar ratio in combustible cigarettes.8 However, this plan was deemed unacceptable since synthetic nicotine was only available as a racemic mixture, containing both S-nicotine and R-nicotine at a 50/50 ratio. S-nicotine extracted from tobacco was considered safer and more economical.9 Analyses by Reynolds in 1967 and Liggert and Myers in 1978 came to the same conclusion.10 11 Stereospecific synthetic pathways for S-nicotine were developed later.12 However, while the tobacco industry eagerly pursued the stereospecific synthesis of L-methanol, developed by Nobel Laureate Ryōji Noyori at the flavour manufacturer Takasago (Tokyo, Japan),13 the Truth Documents library does not contain any more recent evidence considering the use of synthetic racemic or S-nicotine by the major tobacco companies.

Puffbar states ‘Our nicotine-based products are crafted from a patented manufacturing process, not from tobacco’, however, the company neither revealed its source of synthetic nicotine in its products nor the chemical process used to manufacture it. Web searches for tobacco-free nicotine identified additional marketed E-cigarette products containing tobacco-free nicotine. One E-liquid vendor, RXVape, listed a trademarked brand of tobacco-free nicotine (TFN), manufactured by the company, Next Generation Labs (NGL) (figure 1B, table 1).14 15 A patent assigned to NGL describes a synthetic pathway starting from ethyl nicotinate, an ester of nicotinic acid (niacin), a synthetic bulk chemical. Ethyl nicotinate is reacted with...
N-vinyl-2-pyrrolidinone to form myosmine, a tobacco alkaloid. Myosmine is reduced to nornicotine, followed by a methylation step resulting in a racemic (50/50) mixture of the nicotine stereoisomers, (S)-nicotine and (R)-nicotine.16 NGL’s intellectual property was recently recognised by Chinese authorities, enabling the company to enforce its patents in the country where the large majority of E-cigarette products are manufactured.17

At least four other US-based E-cigarette vendors were identified selling TFN-branded synthetic nicotine E-liquids. TFN-branded nicotine was also found marketed as an ingredient in at least two brands of nicotine pouch products, NIIN pouches and 20ne pouches, the latter sold on Amazon.com, with a third pouch product line, FRĒ, stating ‘they do contain a non-tobacco-derived nicotine’ (figure 1C).18–21

In contrast to the vendors listed above, two E-liquid web stores, Five Pawns and Tea Time E-Liquids, state that they...
use pure synthetic S-nicotine in their products, sourced from Contral-Nicotex-Tobacco (CNT, Germany) (table 1). CNT is known as the world’s largest supplier of pharmaceutical grade nicotine extracted from tobacco for pharmaceutical products, including smoking cessation products such as nicotine gum, and the vaping industry. A trade publication cites a CNT executive stating that the company is selling highly pure pharmaceutical grade (USP) synthetic S-nicotine, voicing concerns about sales of racemic nicotine mixtures in consumer products. Patents assigned to CNT describe a manufacturing process first synthesising racemic nicotine from ethyl nicotinate and n-vinylpyrrolidone nicotine acid, followed by a stereoselective purification using L-0,0’-dibenzoyl tartaric acid.

Another E-liquid ingredient supplies vendor, eLiquiTech (Eldersburg, Maryland, USA), lists the company, Zanoprima Lifesciences (London, UK), as a supplier of synthetic S-nicotine (table 1). Zanoprima patented a process involving a biotechnological step for stereoselective synthesis of S-nicotine. The start material is myosmine, first stereoselectively converted to S-nornicotine using a recombinant enzyme (1), a NADH/NADPH-dependent imine reductase. S-nornicotine is then converted to S-nicotine through methylation (2).

Figure 2 Structure and chemistry of synthetic nicotine. (A) Structures of S-nicotine and R-nicotine. The chiral centre of nicotine is labelled with a red asterisk. In tobacco leaf, >99% of nicotine is present as S-nicotine. Synthetic ‘Tobacco-Free Nicotine’ (TFN), marketed by Next Generation Labs, is racemic, containing 50% S-nicotine and 50% R-nicotine. Pure synthetic S-nicotine is chemically indistinguishable from S-nicotine purified from tobacco. (B) Stereoselective synthesis of S-nicotine as described in a patent assigned to Zanoprima involving a biotechnological step. The starting material is myosmine, first stereoselectively converted to S-nornicotine using a recombinant enzyme (1), a NADH/NADPH-dependent imine reductase. S-nornicotine is then converted to S-nicotine through methylation (2).

**Table 1** Manufacturers of synthetic nicotine

<table>
<thead>
<tr>
<th>Manufacturer name</th>
<th>Starting material</th>
<th>Resulting product</th>
<th>Stereoselective step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next Generation Labs</td>
<td>Ethyl nicotinate</td>
<td>Racemic (50/50) R/S-nicotine</td>
<td>none</td>
</tr>
<tr>
<td>Contral-Nicotex-Tobacco</td>
<td>Ethyl nicotinate</td>
<td>S-nicotine</td>
<td>Stereoselective recrystallisation</td>
</tr>
<tr>
<td>Zanoprima Lifesciences</td>
<td>Myosmine</td>
<td>S-nicotine</td>
<td>Enzymatic stereoselective step</td>
</tr>
<tr>
<td>NJOY</td>
<td>Racemic (50/50) R/S-nicotine</td>
<td>Stereoselective recrystallisation</td>
<td></td>
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SYNTHETIC NICOTINE: A CHALLENGE TO FDA’S AUTHORITY

Puffbar’s new product line represents a direct challenge to FDA’s regulatory authority, potentially shortcircuting the premarket tobacco product application (PMTA) requirement for E-cigarette products. While products containing synthetic nicotine were sold before, Puffbar’s brand recognition and popularity among youth E-cigarette users should be a cause for concern. The entry of a market-leading nicotine supplier such as CNT into the synthetic nicotine market is further testing FDA. CNT supplies nicotine to the pharmaceutical industry for cessation products while at the same time supplying both tobacco-derived and synthetic nicotine to vape and smokeless product manufacturers. By selling products containing the more expensive synthetic nicotine, manufacturers demonstrate their willingness to forgo a part of their profits in exchange for staying in the market unimpeded, while manufacturers of products containing tobacco-derived nicotine have to manoeuvre the costly and complex PMTA process. By establishing opaque manufacturing and import networks and multisourced sales channels to web sellers, convenience stores and gas stations, brands such as Puffbar demonstrate their intent to maintain sales even while facing FDA enforcement action. At this time, it is not even clear whether Puffbar products contain synthetic nicotine. The analytical approaches described above should be employed for verification.

The Food, Drug and Cosmetics Act, amended by the 2009 Family Smoking Prevention and Tobacco Control Act (FSPTCA), defines a tobacco product as ‘any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product)’. The FDA seems confident that this definition authorises the agency to regulate at least some recreational synthetic tobacco products, stating that ‘it’s possible that a disposable, closed system device that contains an e-liquid with truly zero nicotine (or synthetic nicotine) would not be regulated by the FDA as a tobacco product, if it is not intended or reasonably be expected to be used in such a fashion. FDA intends to make these determinations on a case-by-case basis, ...’ Manufacturers clearly dispute these claims. For example, the Chief Executive Officer (CEO) of NGL is quoted with ‘All indications from the FDA confirm that Puffbar products containing synthetic nicotine were sold before, Puffbar’s brand recognition and popularity among youth E-cigarette users should be a cause for concern. The entry of a market-leading nicotine supplier such as CNT into the synthetic nicotine market is further testing FDA. CNT supplies nicotine to the pharmaceutical industry for cessation products while at the same time supplying both tobacco-derived and synthetic nicotine to vape and smokeless product manufacturers. By selling products containing the more expensive synthetic nicotine, manufacturers demonstrate their willingness to forgo a part of their profits in exchange for staying in the market unimpeded, while manufacturers of products containing tobacco-derived nicotine have to manoeuvre the costly and complex PMTA process. By establishing opaque manufacturing and import networks and multisourced sales channels to web sellers, convenience stores and gas stations, brands such as Puffbar demonstrate their intent to maintain sales even while facing FDA enforcement action. At this time, it is not even clear whether Puffbar products contain synthetic nicotine. The analytical approaches described above should be employed for verification.

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