

MIRROR IMAGE

Even as synthetic nicotine is gaining acceptance among customers, the product remains in a regulatory void.

By Stefanie Rossel

Though still a niche compared to tobacco-derived nicotine (TDN), the synthetic nicotine (SN) segment has been growing in the past years. In late August, California-based Next Generation Labs (NGL), a producer of bulk R, R-S and S nontobacco-derived nicotine, announced a doubling of its annual production capacity to meet increasing demand. Orders have been coming from vapor product manufacturers and device cartridge fillers, among other customers, with strong demand in the United States and South Korea.

Established in 2014, NGL markets its synthetic nicotine under the tobacco-free nicotine (TFN) trademark. Because adult consumers are displaying an increasing preference for nicotine not sourced from tobacco and free of tobacco-derived components, trade customers have been increasing both order sizes and frequency, according to the company. "Our direct clients have reported transitioning from online and vape specialty retail into the convenience segment," explains Ron Tully, a founding member of NGL.

Tully is reluctant to share customer or production forecasts, however. "What we can say is that over the past five years, NGL has created this market for nicotine that did not exist prior to our innovation and commercialization of TFN," he says. "As we have become more established and our TFN nicotine has gained acceptance with manufacturers, the trade and consumers, we have scaled accordingly. The current market demand for synthetic nicotine has increased annually and continues to grow year on year."

The substance, initially created in a lab, but now manufactured in large-scale production facilities, could play a much greater role in the future, says Torsten Siemann, managing director of Contraf-Nicotex-Tobacco (CNT). "If you think 10 to 15 years ahead and keep in mind the next-generation products market's development of the past 11 years, tobacco-derived nicotine capacity might reach certain limits at one point," he says. "Synthetic nicotine can become important in supplying markets

such as China, India and Russia where you've got many nicotine users who still have to carry out the switch to next-generation products. We see enormous demand there, and the capacity for synthesis of chemicals is unlimited."

Since its creation in 1982, the German company has evolved into the world's leading supplier of tobacco-derived, highly purified nicotine and nicotine derivatives to the pharmaceutical industry. In recent years, CNT has also become a significant provider of pharmaceutical-grade tobacco-derived nicotine to the e-cigarette industry. In 2015, CNT started research on SN. Since 2018, it offers synthetic S nicotine to its customers. The processing takes place at CNT's exclusive manufacturer, Siegfried, in Switzerland. The companies jointly hold a patent on the manufacturing process of synthetic pharmaceutical-grade S nicotine. The share of SN in CNT's business accounts for less than 1 percent, according to Siemann. "Presently, synthetic nicotine clearly is a negligible product for us in terms of volume," he says.

Same but different

Whether manufactured naturally or artificially, the nicotine molecule has the same chemical structure, C₁₀H₁₄N₂, meaning that it comprises 10 carbon atoms, 14 hydrogen atoms and two nitrogen atoms. What makes it special, independent of its origin, is that it is a "chiral" molecule: It has two stereoisomers that are mirror images of each other

The most prevalent form is S nicotine, the physiologically active variant. Its mirror isomer, R nicotine, also occurs in plant-derived nicotine in very small amounts but is basically considered physiologically ineffective. NGL presently focuses on combinations of the R to S isomers for their potential physiological activity. The company has secured a U.S. patent for the use of R-S nicotine in nicotine reduction strategies. But the company also sells full U.S. Pharmacopeia (USP) S nicotine to customers, Tully says.

The easiest product to create is a combination of S and R nicotine. However, to replicate the natural type, meet the

established pharmaceutical monographs and have the same effect, the substance would have to undergo a second process to remove the R isomers. Otherwise, the amount of the combined R-S nicotine would have to be at least doubled.

Opinions about the use of the R form in synthetic nicotine widely differ. “We think R-S nicotine, which contains a significant amount of R nicotine, can only be considered to be an intermediate, which requires further purification to the S form,” says Siemann.

“There is not enough scientific evidence about the effects of the R form, but it is common knowledge in the pharmaceutical industry that enantiomers often exhibit profound differences in pharmacology and toxicology, some of which could be potentially harmful. In the best case, the same quantity of R-S nicotine can be considered to be only 50 percent effective, but we also foresee mislabeling concerns by describing R-S nicotine as equivalent to nicotine USP/EUP. For these reasons, CNT does not sell R-S nicotine.” He adds that his company has tested a number of SN samples, among them products from Chinese and Indian manufacturers, and 100 percent of them were R-S nicotine. “If you look at the European [EUP] and the U.S. Pharmacopeias, the percentage of S isomers in nicotine must be higher than 99 percent,” Siemann explains. “The nicotine used in the pharmaceutical industry needs to have a specific optical rotation that only S nicotine can achieve.”

NGL markets R, R-S and S nontobacco-derived nicotine. “Nicotine has been studied extensively in its naturally derived tobacco form, which includes the naturally occurring S and R isomers, which are metabolized in the consumption of current cigarette, vape and smokeless tobacco products,” explains Tully. “Although the uptake pathway for the R isomer is not fully elaborated, there is nothing to indicate that the R isomer is anything other than a positive attribute to the nicotine molecule. We are at an early stage in the evolution of isomeric nicotine and its utility. NGL is trying to ensure that companies have the option based on their evaluation of the utility and safety of synthetic nicotine in their products.”

Benefits

Synthetic nicotine offers a number of advantages over its natural counterpart. “Manufacturers have access to nicotine in its chiral R and S forms that may offer distinct benefits to consumers in potential uptake pathways for nicotine satiation,” says Tully. In November 2017, the U.S. company reported on research it had carried out on the isomeric character of its SN products. According to a press release, the studies revealed that specific ratios of the R to the S isomers could potentially offer nicotine use at satisfying but nonaddictive or less addictive levels. If proven, the artificially created nicotine might become a useful tool to help producers achieve the U.S. Food and Drug Administration’s (FDA) objective of lowering nicotine content

in tobacco products to minimally addictive levels.

SN can be produced in unlimited amounts independent of nature. In addition, its manufacture doesn’t involve the challenges associated with tobacco cultivation. “Synthetic nicotine requires fewer direct inputs environmentally than tobacco-derived nicotine,” says Tully. “We are not dependent on land availability, soil suitability, fertilizers, herbicides, seeds, labor, firewood, seasonal variations, or any other factor that may impact the finished product as a supply input.”

Due to its artificial character, synthetic nicotine will also remain untouched by general agricultural challenges, Siemann adds. However, he doesn’t buy the frequently heard argument that synthetic nicotine provides a better taste to e-liquids due to

TDN impurities. “This may be true for inferior quality TDN,” says Siemann. “However, CNT’s tobacco-derived nicotine has a purity of more than 99.9 percent, thus ensuring that it is of the highest standard from a sensory perspective.”

For the time being, SN’s greatest downside is price. Siemann estimates that due to difficulty in purifying the synthetic S nicotine from the R-S form and the comparably small amounts in which SN is currently produced, the artificial variant is about 20 to 30 times more expensive to manufacture than its natural counterpart, a factor that will decrease with growing demand and the upscaling of production.

Tully notes that the price of SN has come down dramatically over the past five years. “As demand has gone up and production has scaled, pricing has decreased,” he says.

“We have moved from pricing from a multiple that was 10 times greater than tobacco nicotine to a most favored nation (MFN) pricing level that is only three to four times the current cost of tobacco-derived nicotine. The suggestion that synthetic nicotine manufacturers are not adjusting pricing to meet market demand is simply not true. Any company that commits to a TFN strategy and works with NGL will receive the benefit of MFN pricing as they scale.”

Regulatory void

Despite its growing popularity, SN remains in a regulatory void. Because the product is not derived from tobacco, it does not necessarily fall under the 2009 Family Smoking Prevention and Tobacco Control Act. Neither does SN meet the Federal Food, Drug and Cosmetic Act’s definition of a tobacco product. The FDA has suggested it would evaluate synthetic nicotine products on a case-by-case basis.

“NGL has made clear to manufacturing customers that TFN is a tobacco-free nicotine designed to offer adult consumers the benefits of a nicotine that is free of all tobacco-derived components and contaminants,” says Tully. “It is an alternative recreational nicotine that aims to allow adult consumers to make a choice to separate their nicotine consumption from all forms of tobacco consumption. That is a laudable aim for all companies



Torsten Siemann

in the nicotine business that have the objective of separating nicotine use from tobacco use.”

Various jurisdictions are trying to regulate TFN in the same way as tobacco nicotine. “We believe treating all nicotine within the same regulatory framework is not in the best interests of adult consumers who are seeking an alternative nontobacco recreational nicotine experience,” says Tully. He argues for science-based regulation of SN.

Siemann expects regulation of SN in the U.S. as soon as the market has reached a critical size. He is optimistic, though, that the FDA will find a way to regulate synthetic nicotine differently than TDN. “SN could be taxed differently from TDN,” he suggests. “Perhaps it would be an interesting possibility for health authorities to reach public health goals in cooperation.”

In the EU, SN’s status is similarly unclear. “The revised Tobacco Products Directive, which governs electronic cigarettes in the EU, specifies the use of high purity ingredients,” explains Siemann. “In the case of nicotine, TDN meeting USP/EUP has been adopted as the established norm here. Hence in keeping with this, S form nicotine would be the only equivalent synthetic alternative.”

Future potential

The future for nicotine from the lab looks bright, according to Siemann and Tully. “There will be markets where products containing tobacco-derived nicotine will not be allowed but where

synthetic nicotine will be permitted in consultation with health authorities,” says Siemann. “In the end, we will hopefully see an equivalence between SN and TDN where customers can decide which one to use for their products.”

“Every market in which tobacco is consumed is a potential market for synthetic nicotine in the future for innovative product entrants for those markets,” says Tully. “Specific short-term opportunities for synthetic nicotine may develop in some markets for regulatory definitional or tax reasons, but those aside, the real opportunity will be in finding a commercialization pathway that marries TFN synthetic nicotine isomers with products that adult consumers are seeking,” he says.

“The opportunities for TFN nicotine are limited not by the regulatory framework but by the mindset of the tobacco, vape and pharmaceutical [industries] and their willingness to explore the opportunities that the separated and selectively combined R and S isomers of nicotine offer to adult consumers,” says Tully. “A deeper understanding of synthetic nicotine, the uptake pathways of the isomers and the application of this unique product need to be better funded and developed for synthetic nicotine to find its place as the next big leap in adult nicotine consumption.”

In a world where manufacturers are increasingly promoting products with descriptors such as “natural” and “organic,” it may be difficult to imagine selling a product on its artificial merits. In the case of nicotine, however, “synthetic” may be just the ticket.