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# Will Novel NRT Interest Heat Up In US With First Clearance For ENDS Under Tobacco Control Act?

by Malcolm Spicer

Without mentioning NRT space, FDA's acceptance of one vape device and two replacement nicotine cartridges as tobacco products might reignite interest in proposals for ENDS or other novel products to be approved for smoking cessation claims. To gain clearance as tobacco products, the ENDS were shown to provide a benefit similar to efficacies required for an NRT.

The potential for approval of novel OTC nicotine replacement therapies in the US wasn't mentioned in the Food and Drug Administration's recent announcement of its first clearance for electronic cigarettes to be available under its tobacco product regulations.

The FDA Center for Tobacco Products' announcement also didn't note that its acceptance of three R.J. Reynolds (RJR) Vapor Co. Vuse Solo brand electronic nicotine delivery system (ENDS) products through the premarket tobacco product application (PMTA) pathway came two years after the agency's drug center submitted a Complete Response letter stating concerns about an OTC drug firm's proposed novel NRT with mouth-spray delivery format so far unavailable in the US.

Without mentioning the OTC NRT space, though, the CTP's announcement on 12 October might reignite interest in submitting proposals to the FDA's drug center for ENDS or other novel products to be approved with a smoking cessation indication.

The tobacco center's description of its evaluation of RJR's PMTA suggests that to gain clearance to be available in the US as tobacco products, an ENDS must be shown to provide a benefit similar to efficacies the drug center has said it would consider for products marketed as NRTs.

RJR's data in its PMTA proposal demonstrated its tobacco-flavored products could benefit adult smokers who switch to the Vuse products completely or "with a significant reduction in cigarette consumption," the CTP stated. The benefit is less exposure to harmful and potentially harmful constituents (HPHCs) from using the Vuse products rather than combustible tobacco.

Still, for all the support the FDA drug center has stated for developing novel NRTs and for all the reviews its tobacco center is conducting of ENDS products, the future for the devices in the US smoking cessation space remains clouded.

"It's a gray area," said attorney Marc Scheineson, a partner at Alston & Bird LLP and a former FDA associate commissioner for legislative affairs.

David Clisssold, a director at Hyman, Phelps & McNamara P.C. in Washington, said the announcement could remind stakeholders of FDA's interest in ENDS' potential use as NRTs but doesn't signal a change in its standards for drug product approval.

"I think it certainly signals a willingness to explore the potential for such use. However, FDA's smoking cessation comments regarding Vuse were in the context of explaining the CTP's 'public health' analysis of the Vuse products, which is the legal standard for a PMTA authorization," Clisssold told HBW Insight.

## GSK Novel NRT Stalled

GlaxoSmithKline plc's GSK Consumer Healthcare Holdings LLC business in the US in 2019 submitted to the FDA a proposal for an oral spray that delivers 1 mg per spray of aqueous buffered nicotine solution for oromucosal use.

The proposed use for the product to be marketed under the Nicorette brand was reducing withdrawal symptoms, including nicotine craving, associated with quitting smoking for consumers 18 and up. (Also see "*GSK's Proposal For Mouth Spray Nicorette Delayed By FDA Questions On Label*" - HBW Insight, 8 Jan, 2020.)

Following a Nonprescription Drug Advisory Committee meeting, the FDA in October that year submitted to GSK a Complete Response letter about the proposed OTC product's Drug Facts label.

Although NRT products in other delivery formats already are available OTC in the US, the FDA and its advisors had plenty of questions about consumers' use of GSK's proposed mouth spray without the intervention of a health care professional.

The oral spray already is marketed nonprescription in 45 other countries but isn't available Rx or OTC in the US.

Asking GSK to change the product's DFL reflects FDA Center for Drug Evaluation and

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## Roadmap For ENDS PMTAs

The CTP announcement, coming more than five years after the FDA published a *final rule* adding ENDS to the product categories subject to its regulatory authority under the 2009 Family Smoking Prevention and Tobacco Control Act – *Public Law 111-31*, also noted 10 marketing denial orders for flavored ENDS products RJR submitted under the Vuse Solo brand. (Also see "*FDA Rule Stifles E-Cigarettes' Harm Reduction Role With Grandfather Date, Application Costs*" - HBW Insight, 12 May, 2016.)

The centers' explanations for clearing the three RJR products and rejecting the 10 others provide a roadmap for other manufacturers and marketers to seek PMTA pathway clearance for ENDS or other tobacco or nicotine products.

Research officials' concern about results of actual use trials the firm conducted for the NDA at the agency's request.

Results from GSK's studies prompted the CDER to question the product's "real world" efficacy. In briefing materials for the NDAC meeting, the center also questioned whether study data show the product is safe for OTC access for consumers.

GSK Consumer Healthcare declined in 2019 to make the CRL available; the Philadelphia-based division of the UK pharma declined to comment on potential developments with the mouth spray NRT proposal since it received the CRL.

Additionally, two final rules the CTP published a week earlier provide directions for proposing to introduce or continue marketing products under FDA clearance – *Premarket Tobacco Applications and Recordkeeping Requirements*, and *Content and Format of Substantial Equivalence Reports*.

Directions for navigating CTP reviews, at least.

"The hurdles are too high to go the drug approval route," said Scheineson, who is co-head of Alston & Bird's food and drug practice in Washington.

"I don't think Vuse, or any product authorized under a PMTA, will be able to make a smoking cessation claim," Clissold said.

Smoking cessation similar indications are therapeutic, or drug claims, and efficacy likely will need to be established through clinical trials submitted in new drug applications, just as it was for currently marketed NRT available as patches, gum, or lozenges.

"However, the Vuse product did meet the legal standard of 'appropriate for the protection of the public health' and so marketing claims could be based around the PMTA having been authorized because the product met that legal standard for authorization," Clissold said.

## CDER Open To Novel NRT Proposals

Not that the FDA's Center for Drug Evaluation and Research hasn't attempted to help potential application sponsors clear the hurdles.

The FDA, responding to multiple citizen petitions, in 2013 allowed OTC NRTs to drop duration-of-use limits and warnings about concomitant use with other cessation products from labeling. It denied requests made in the petitions to expand NRT indications, but said those changes would have to be considered via the new drug application or supplemental NDA process, that additional studies would be needed to support expanded indications and it was open to working with sponsors on applications for broader indications. (Also see "*Smoking Cessation Labels Cleared Without Duration-Of-Use Limit*" - HBW Insight, 15 Nov, 2013.)

> ***Without mentioning the OTC NRT space, the CTP's recent announcement might reignite interest in submitting proposals to the FDA's drug center for ENDS or other novel products to be approved with smoking cessation or similar indications.***

Results of a study published in 2020 in the Journal of the American Medical Association suggest ENDS use combined with counseling significantly increased abstinence from smoking cigarettes compared to receiving counseling alone. (Also see "*E-cigarette NRT Outlook Heated By Combining With Counseling, Nicotine-Tapering Strategy*" - HBW Insight, 27 Nov, 2020.)

The researchers recommended investigating nicotine-tapering strategies used for patch, gum and spray NRTs in future ENDS. They said fixed dosing is difficult due to ENDS designs, but a gradual reduction in nicotine e-liquid concentration could achieve a similar effect.

Also in 2020, the CDER published a final guidance on animal studies for novel NRTs and a final guidance is pending on clinical trials for developing novel, inhaled NRTs that could be submitted to the agency for approval as drugs similar to current OTC NRTs. (Also see "*US FDA Finalizes Nonclinical Test Guidance Intended To Spur NDAs For Novel NRTs*" - HBW Insight, 29 Oct, 2020.)

When it published the clinical trials draft guidance in 2019, the FDA acknowledged the potential for "new kinds of NRTs – with different characteristics or routes of delivery" to offer additional opportunities for smokers to quit. (Also see "*Wider Options In FDA's NRT Clinical Trial Guidance, Approval Path Still Narrow*" - HBW Insight, 29 Mar, 2019.)

Despite a contentious history with ENDs manufacturers, beginning with attempting to block sales of all of the products in 2010, agency officials consistently have said the products are eligible to be considered for approval as NRTs through the agency's NDA process.

> *"The hurdles are too high to go the drug approval route." – Marc Scheineson, co-head of Alston & Bird's food and drug practice*

However, clinical trials and other research needed for an NDA proposing ENDS for smoking-cessation labeling likely are too costly for the large majority of companies making the products, and the scientific expertise needed to check all the boxes the FDA would require for safety, efficacy and actual use likely aren't among those companies' assets.

## Potential Benefit Outweighs Risk To Youth

The CTP stated that in its evaluation of RJR's proposal, it considered the risks and benefits to the population as a whole, including users and non-users of tobacco products and youth. It reviewed available data on the likelihood of use of the product by young people.

For the Vuse products – *Vuse Solo Power Unit* and replacement cartridges *Original 4.8% G1* and *Original 4.8% G2* – the center determined the potential benefit to smokers who switch completely, or significantly reduce cigarette use, would outweigh the risk to youth, provided RJR follows post-marketing requirements aimed at reducing youth exposure and access

### CTP Load At Wits ENDS

The CTP's announcements of its rejections of RJR's and other firms' PMTAs for flavored ENDS products explains as much as the center's approvals.

According to the center, it "issued the first marketing denial orders [for ENDS] products after determining the applications for about 55,000 flavored ENDS products from three applicants lacked sufficient evidence that they have a benefit to adult smokers sufficient to overcome the public health threat posed by the well-documented, alarming levels of youth use of such products."

All those ENDS applications were part of a flood of PMTAs the CTP received in August and September 2020 as sponsors met a deadline for non-combustible products. A 2019 court order had shortened

to the products.

The FDA's weekly update to its list of published warning letters typically includes five or more warnings to US and international businesses marketing ENDS that are unapproved new tobacco products because they were not available prior to the Tobacco Control Act and have not been cleared by the agency for sales.

the deadline from August 2022 to May 2020 before the FDA in April 2020 asked the court to extend it to 9 September that year. (Also see "*Application Deadline Ordered To Stop Vaping Industry Evasion Of FDA Approval*" - HBW Insight, 15 Jul, 2019.)

Clissold stated in a recent Hyman, Phelps & McNamara FDA Law Blog post that the agency reported receiving thousands of submissions representing more than 6.5m products, mostly ENDS, by the deadline.

The FDA stated in its approval of RJR's Vuse PMTAs that it had made decisions on more than 98% of applications submitted by the deadline, including MDOs for more than 1m flavored ENDS.

"It should be noted that RJR submitted its Vuse Solo PMTAs on October 10, 2019, about 10 months before the PMTA submission crush, and it still took FDA two full years to review the Vuse Solo PMTAs," Clissold wrote in the blog post.

As with products in other categories under its oversight, the CTP prioritizes removing from the market flavored nicotine juices commonly used by young consumers as well as by adults turning to the products as alternatives to combustible tobacco.

"The agency will continue to issue decisions on applications, as appropriate, and is committed to working to transition the current marketplace to one in which all ENDS products available for sale have demonstrated that marketing of the product is 'appropriate for the protection of the public health'," the CTP stated.

## 'Protection Of Public Health' Appropriate Measure?

There's little else other than "protection of the public health" the FDA could say about ENDS or other nicotine or tobacco products it's evaluating.

"That's the only public health benefit it could have," Scheineson told HBW Insight.

"The question is, is that a reasonable position for the FDA to take? My own view is that is not a reasonable position for the FDA," he added.

That's because while the PMTA pathway requires demonstration that a product is "appropriate

for the protection of public health," the pathway wasn't designed with ENDS as a consideration. E-cigarettes had begun to become available in the US before the Tobacco Control Act was passed in 2009, but at only a fraction of the volume the products available soon after.

"The regulatory structure of the TCA was taken from medical device law where there are two types of applications," Scheineson said.

One type is a 510(k), analogous to a tobacco Substantial Equivalence (SE) Report for review and approval more quickly because it is substantially equivalent to another device the FDA previously reviewed and cleared.

The other is a premarket approval application (PMA), for products with previously undetermined benefit-risk profile or without a predicate already cleared by the FDA.

"It is very difficult, or virtually impossible, for any tobacco derived product to demonstrate to a public health regulator that it protects public health," Scheineson said.