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By Electronic Submission

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-2854; Comment on Premarket Tobacco Product Applications and Recordkeeping Requirements

To whom it may concern,

JUUL Labs, Inc. (JLI or the Company) appreciates the opportunity to comment on FDA's proposed rule for the submission and review of premarket tobacco product applications (PMTAs) and related recordkeeping requirements under the Family Smoking Prevention and Tobacco Control Act (FSPTCA).

The PMTA process is a key part of a public health approach to tobacco and nicotine regulation and policy. As FDA has said, "nicotine — while highly addictive — is delivered through products that represent a continuum of risk and is most harmful when delivered through smoke particles in combustible cigarettes." It is therefore important to encourage "development of innovative tobacco products that may be less dangerous than cigarettes."[1]

Many new electronic nicotine delivery system (ENDS) products in particular will present potential reduced-risk options for current adult users of combustible products who cannot or do not want to quit. They could also potentially incorporate tools and technologies to promote adoption by such users and prevent initiation by nonusers, especially those who are underage.

The proposed rule takes a major step forward by providing the transparency, predictability, and efficiency needed to foster innovation and enable new, alternative products to enter the market when supported by scientific evidence. But there are several areas where we would like additional direction and clarity, as well as changes to assure that the final rule will provide a science-based and robust, but workable, roadmap for both FDA and applicants.

[1] FDA News Release, *FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death* (July 27, 2017).

To that end, we have provided general comments and ideas for specific changes to the proposed rule. JLI believes these proposals will help achieve the purposes of the FSPTCA, maintain the integrity of the PMTA process, and encourage the review of new tobacco products that can compete with, and ultimately eliminate, combustible cigarettes.

I. GENERAL COMMENTS

A. The PMTA regulations should provide a clear, science-based framework to encourage development of new products that can reduce tobacco-associated harms.

To facilitate innovation in potential reduced-risk alternatives for current users, as well as novel solutions to prevent initiation by nonusers, it is essential for FDA to provide industry with clear guidance on the data and other information needed to support PMTA submissions. It is also important for the Agency to review these applications in a scientifically rigorous manner. Both are necessary to facilitate a rational approach to tobacco and nicotine regulation that encourages the development and introduction of new products that can reduce the overall harm of tobacco, now and in the long term.

The existence of a clear path to lawful product marketing is particularly important for ENDS products, which have significant potential to improve public health by providing existing adult smokers with a viable and compelling alternative to combustible cigarettes. At the same time, it is critical to prevent initiation by individuals who do not already use nicotine. As a result, manufacturers of ENDS products and FDA must work together as part of the PMTA process to identify effective strategies for making these products available to existing adult smokers, while also preventing initiation by others, especially those who are underage.

In particular, we agree that FDA's review of PMTAs should involve careful consideration of any voluntary restrictions on sales and distribution proposed by an applicant to decrease the likelihood of initiation among nonusers.[2] Applicants should be encouraged to provide their own input to FDA as to what sales, distribution, and technological controls — including self-imposed marketing restrictions — might be appropriate, feasible, and effective to reduce and prevent nonuser initiation and underage use. There is significant room for innovation in this space, including in product design and how new products are sold through brick-and-mortar retail and ecommerce.

B. The PMTA regulations should accommodate the evolving regulatory framework for new tobacco products and facilitate the adoption of new tobacco product standards.

The rulemaking should focus on developing a PMTA process that will accommodate a regulatory framework that has been evolving rapidly and will continue to do so in the

[2] 84 Fed. Reg. 50566, 50580 (Sept. 25, 2019); *see also* proposed § 1114.7(d)(5).

near future. For example, FDA has not yet issued tobacco product standards, but the proposed rule acknowledges that it could do so in the future. The proposed rule also acknowledges that supplemental PMTAs may be permitted for modifications made to comply with new product standards.[3] JLI supports FDA's development of these standards to improve the public health by establishing category-wide product and quality controls.

The proposed rule, however, does not address how the Agency would implement new product standards that might come into effect between submission and an application decision. Similar issues would arise once FDA promulgates tobacco product manufacturing practice (TPMP) requirements,[4] which will affect the types of information applicants must submit to FDA to obtain a marketing order.[5] Potential judicial and legislative developments also may affect the regulatory landscape for tobacco products.

Accordingly, FDA should ensure that the PMTA regulations will allow applicants to meet evolving requirements, especially if they change while an application is under review. In particular, FDA should consider how its review timeline, review procedures, and requirements for amendments can be crafted to permit a reasonable time for new products, especially deemed products, to come into compliance with new requirements, without delaying or otherwise adversely affecting review of the pending application or continued marketing of the product.

C. FDA should publish a list of deemed products for which PMTAs have not been submitted by the applicable compliance date and take action to remove these products from the market.

As noted above, the PMTA process is a key part of a public health approach to tobacco and nicotine regulation, and will help ensure that new products are appropriate for the protection of public health. A fundamental component of the PMTA process is FDA enforcement against manufacturers that market new tobacco products without a marketing order. Absent rigorous and effective enforcement, the PMTA submission requirement would be of compromised value and the fundamental goals of the FSPTCA would not be achieved. In the case of deemed tobacco products that were on the market as of August 8, 2016, it is imperative that FDA take adequate steps to identify and remove products that are not the subject of required PMTAs submitted to FDA by the applicable compliance date.

Accordingly, once the applicable compliance date has passed, we urge FDA to promptly publish on its website a list of deemed tobacco products for which PMTAs have not been filed with the Agency, including the brand and product names, along with the

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[3] 84 Fed. Reg. at 50612, 50626; *see also* 21 U.S.C. § 387g.

[4] *See* 21 U.S.C. § 387f(e).

[5] *See id.* § 387j(c)(2)(B) (requiring FDA to deny a PMTA and issue a no marketing order if "the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of such tobacco product do not conform to [TPMP requirements]").

corresponding names of manufacturers. This list would be available to distributors and retailers, enabling them to comply with FSPTCA requirements. The list would also clarify for stakeholders generally, including adult users, which manufacturers have not complied with the PMTA submission requirement and highlight the potential risk for FDA enforcement action to address these violations.

FDA has taken a similar approach when transitioning other marketed products into an approval pathway. In particular, after Congress required that new drugs be approved by FDA on the basis of efficacy in addition to safety, FDA published lists identifying drug products for which the manufacturer had not submitted required effectiveness information, as well as the relevant manufacturer names and addresses.[6] Later, FDA disclosed a list of drugs that had remained on the market even though their manufacturers had not submitted required information to FDA.[7] FDA also took action to enforce the drug application requirements against these manufacturers. [8]

In line with that precedent, promptly after the compliance deadline for PMTA submission for deemed tobacco products that were on the market as of August 8, 2016, FDA should publish a list of the names of new tobacco products for which a PMTA has not been submitted, as well as the manufacturers that have failed to make the required submissions.

If, for some reason, the issuance of such a list is impracticable, for example, due to a large number of non-compliant products, FDA instead should publish a list of PMTAs that have been submitted to and are under review by FDA for deemed tobacco products that were on the market as of August 8, 2016, along with the names of the corresponding products and manufacturers.

While FDA typically does not disclose the existence of a premarket product application (unless the applicant has publicly disclosed or acknowledged the existence of the application), the underlying rationale for non-disclosure does not apply in this situation. As explained in the preamble to the proposed rule, confidentiality is warranted where disclosure would reveal the intent of the manufacturer to market the product and could result in a competitive advantage to competitors or disadvantage to the applicant.[9] In the case of tobacco products that are already on the market as part of this transitionary period, the manufacturer's intent to market the product already is public and well-known.

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[6] *See, e.g.,* 40 Fed. Reg. 53609 (Nov. 19, 1975); 42 Fed. Reg. 41917 (Aug. 19, 1977).

[7] FDA, "Computer Generated Listing of Drugs Marketed Without an Unapproved NDA/ANDA" (July 6, 1984) ("Weiss List").

[8] *See, e.g.*, 49 Fed. Reg. 38190, 38192 (Sept. 27, 1984) (discussing the recall of E-Ferol, an aqueous vitamin E solution for intravenous administration marketed without an approved application, after the product showed a possible association with death of premature infants). The E-Ferol incident prompted FDA to require adverse event reporting and recordkeeping for drugs marketed without approved applications.

[9] *See* 84 Fed. Reg. at 50624-25.

Moreover, for such products to be lawfully marketed, they must be the subject of a PMTA (or, if applicable, a Substantial Equivalence Report) and, therefore, disclosure of a pending submission would not reveal any information that is not publicly available.

In sum, we urge FDA to take timely action to notify stakeholders in a clear, transparent manner about which manufactures of marketed, deemed tobacco products that were on the market as of August 8, 2016 have chosen — or not chosen — to comply with FDA's PMTA filing requirements by the applicable compliance date. Doing so would emphasize the Agency's seriousness to enforce this critical requirement to ensure proper oversight over the marketing of new tobacco products. In addition, FDA should take swift action to remove these products from the market, in accordance with the FSPTCA.

II. COMMENTS ON PROPOSED REQUIREMENTS FOR PMTA CONTENT AND FORMAT (PROPOSED § 1114.7)

A. FDA should reconsider the proposed requirements for prototypes and previous or similar versions, which are unclear and potentially onerous for both applicants and FDA.

Proposed § 1114.7(d)(4) would call for a PMTA to include a "description of problems that were identified in prototypes that are the subject of studies in the application and previous or similar versions of the new tobacco product that were marketed, if any." It also states, for any "previous or similar versions that are the subject of studies in the application or were marketed, the application must contain a bibliography of all reports regarding the previous or similar version of the product, whether adverse or supportive."

FDA should reconsider these proposed requirements because they impose potentially onerous requirements for both FDA and applicants, particularly where a manufacturer has evaluated or made many changes to a product to improve adult user experience and product quality — during either premarket development or marketing before being subject to FDA regulation. A requirement to provide information about all "problems" and "reports" associated with all prototypes and previous or similar products could result in submission of large amounts of information, much of which would not be relevant to FDA's evaluation of whether permitting marketing of the product currently under review would be appropriate for the protection of the public health (APPH).

This is largely due to broad, general terms that are not defined in the proposed rule. For example, the term "problems" presumably includes any minor technical defect or other non-health related issue identified during product development.[10]

[10] *See, e.g.*, *Merriam-Webster.com* (last accessed Nov. 21, 2019) (defining "problem" as, among other things, "a question raised for inquiry, consideration, or solution").

The terms "prototype" and "previous or similar version" also are very broad, and it is not clear how they should be interpreted in comparison to each other. For example, a "prototype" may refer narrowly to the first version of a product, or more broadly to early versions of a product.[11] Likewise, it is not clear when a product is a "previous or similar version." For example, companies may split up, consolidate, retire, and introduce new product lines or variants, types, and components or parts, and it is not clear whether any of the above or other product changes would impact whether an earlier-marketed product is a "previous version." The proposed rule does not specify exactly how and in what ways "similar" another product must be to the product being reviewed under the PMTA to be within the scope of this provision.

These issues are exacerbated by the fact that the second sentence of proposed § 1114.7(d)(4) refers only to "previous or similar versions" and introduces the concept of "previous or similar versions that are the subject of studies in the application" without making clear whether or why there are different requirements for "prototypes," "previous or similar versions that are the subject of studies in the application," and "previous or similar versions of the new tobacco product that were marketed."

Finally, the proposed rule does not define what is required in terms of "descriptions" of problems or "reports" regarding previous or similar versions, which makes it difficult to understand what information FDA is seeking to be submitted, or how that information should be identified.

Taken together, the proposed rule requires applicants to assemble a significant amount of information that may be of limited use; this potentially imposes an onerous and unnecessary burden on applicants and FDA reviewers who must analyze and comment on these submissions.

In contrast to the vague and broad terms in the rule itself, the preamble makes clear that FDA is interested only in obtaining information needed to "assess whether known issues with a predecessor product that could affect the health risks of the new tobacco product have been addressed."[12] To achieve that objective, a better approach would be to simply require a bibliography of health risk investigations that: (i) are of the type specified

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[11] *Compare, e.g.*, *Innovation at FDA; What We Do*, *www.fda.gov* (last accessed Nov. 11, 2019) ("Prototype**:** A prototype is an *original model*, form or an instance that serves as a basis for other processes. A prototype helps support a proof of concept in a tangible way. In software technology, the term prototype is a working example through which a new model or a new version of an existing product can be derived.") (emphasis added); *Merriam-Webster.com* (last accessed Nov. 11, 2019) (defining "prototype" as, among other things, "an original model on which something is patterned" or "a first full-scale and usually functional form of a new type or design of a construction (such as an airplane)"), *with, e.g.*, *The Device Development Process; Step 2: Preclinical Research-Prototype*, *www.fda.gov* (last accessed Nov. 11, 2019) (defining a device prototype as "an early version of a medical device").

[12] 84 Fed. Reg. at 50579-80.

at proposed § 1114.7(k)(1)(i); (ii) evaluated products that are "similar" to the product under evaluation; and (iii) identified adverse health effects.

Under this approach, FDA also should clarify that "similar" products are those that have the same essential performance or product characteristics; the Agency should also provide examples. For instance, for ENDS products, essential performance or product characteristics could include the heating mechanism, temperature control, and e-liquid ingredients.

B. FDA should provide more flexibility and clearer guidance regarding the submission of labeling and marketing plans.

Proposed § 1114.7(f) would require that PMTAs include specimens of proposed labeling and marketing plans "developed by the time of filing," including "descriptions of actions that would be taken by the applicant, on behalf of the applicant, or at the applicant's direction for at least the first year the product would be marketed after receiving an order." The provision further describes information the Agency would expect to see in marketing-plan submissions.

JLI supports the proposed requirement that PMTA applicants submit labeling and marketing plans for products to determine whether they would be APPH. Marketing plans play a pivotal role in whether nonusers, and particularly those are underage, might end up being exposed, and then seek access, to a tobacco product. Consequently, it is essential for tobacco product manufacturers to work proactively, voluntarily, and transparently with FDA to establish appropriate controls on labeling, advertising, marketing, promotion, and other consumer-directed activities that will limit exposure to nonusers.

At the same time, carefully crafted regulatory requirements and guidance should provide clarity and flexibility to ensure that FDA receives sufficient and useful information to make a decision on an application.

1. FDA should permit applicants to amend their marketing plans during the review process, as needed to maximize opportunities for limiting exposure to nonusers.

There are several reasons why FDA should revise the proposed rule to give applicants more flexibility in submitting and amending proposed marketing plans.

First, the use of data sources, tools, methodologies, and new technologies to assure that tobacco product marketing reaches only adult users are becoming increasingly sophisticated and effective at a rapid pace. As one example, it has become possible to use information from retailers' loyalty program databases to identify specific age-verified, current adult users of tobacco products. This presents a significant opportunity for targeted marketing to facilitate the transition of adult smokers to innovative, potential risk-reduction products, without exposure to nonusers.

This opportunity is limited, however, if a PMTA applicant must develop, and remain locked into, a marketing plan far in advance of potential authorization and eventual implementation of the plan. This is the case under proposed § 1114.7(f)(2), which would call for a marketing plan to developed by the time of initial PMTA submission and contemplates that this plan must cover an entire year of post-authorization marketing.

Even in a best-case scenario where authorization would occur within 180 days of PMTA submission (*i.e.,* following a review with no extensions or delays), this requires an applicant to commit to a marketing plan at least 6 months before it will be implemented, and remain committed to that plan for at least 18 months. Applicants that submit amendments or experience other delays in review will have to commit even further in advance. Indeed, for the two previously approved PMTAs to date, FDA took an average of 480 days, or roughly 16 months, between initial submission and granting of a marketing order.[13]

Assuming this is an accurate estimate of PMTA review time in the near future, this would require an applicant to commit to a marketing plan over a year in advance before implementation and remain committed to the plan for over two years. In practice, applicants must commit even further in advance, to allow sufficient time for consumer-research testing. This can result in a deadline for development of the marketing plan up to an entire year before submission.

Second, the proposed rule contemplates that the marketing plan will need to be developed before either the applicant or FDA has had the benefit of any substantive review of the application. This could deprive both applicants and FDA of the opportunity to have marketing plans that will best achieve shared goals of moving adult smokers down the risk continuum, while restricting marketing and product exposure from nonusers, especially those who are underage.

In other program areas, FDA has recognized the value of postponing submission of labeling and marketing plans until later in the application review cycle, and otherwise engaging in interactive dialogue about labeling and marketing once the Agency has a full appreciation of the information in an application. For example, FDA requires pre-approval submission of promotional labeling and advertising of accelerated approval drugs and

[13] The marketing orders for Philip Morris Products S.A.'s IQOS products were granted on April 30, 2019, 715 days after the application was initially submitted on May 15, 2017, 685 days after the application was accepted on June 14, 2017, and 634 days after the application was filed for scientific review on August 4, 2017. *See* Marketing Order for PM0000424-PM0000426, PM0000479 (Apr. 30, 2019); PMTA Technical Project Lead Review for PM0000424-PM0000426 & PM0000479, at 14 (Apr. 29, 2019). The marketing orders for Swedish Match North America, Inc.'s General Snus products were granted on November 10, 2015, 245 days after the application was initially submitted on March 11, 2015, 230 days after FDA issued correspondence acknowledging the application on March 23, 2015, and 187 days after the application was filed for scientific review on May 7, 2015. *See* Marketing Order for PM0000010 (Nov. 10, 2015); PMTA Technical Project Lead Review for PM0000010-PM0000017 (Nov. 3, 2015).

biological products, but does not specify exactly when during the review period they must be submitted.[14] The decision about timing is left to discretion of the applicant, with FDA recommending dialogue to inform that decision.[15] Similarly, FDA engages in labeling negotiations with new drug application (NDA) and biologics license application (BLA) applicants at the end of the review cycles for those applications.[16]

Third, the difficulties of developing a plan under an uncertain timeline are compounded by the current lack of experience to determine what marketing plans should look like to satisfy the APPH standard. Both industry and the Agency are still learning about how tobacco products — particularly deemed tobacco products — should be marketed to be APPH, and what information about product marketing is relevant to such an APPH determination.

Finally, the compressed timeframe within which manufacturers of deemed products are currently working to submit PMTAs is a major issue. This imposes constraints on time and resources to conduct consumer research regarding advertising and promotional materials subject to a proposed marketing plan — as contemplated by proposed § 1114.7(f)(2)(iii) and § 1114.7(k)(1)(iv) — and to make adjustments and refinements in response.

To address these issues, proposed § 1114.7(f) should be supplemented to include a statement explicitly acknowledging that applicants may amend or otherwise revise, on their own initiative, any materials or information previously submitted under this provision, based on feedback from FDA or other developments that might occur during the review cycle.

In addition, our interpretation of the proposed rule is that applicants would be permitted to revise and otherwise develop new labeling, advertising, marketing, and promotional materials after authorization, including within the first year of marketing after authorization. We agree with this approach, but we also believe that it is appropriate, at least in many cases, for FDA to use its authority under sections 910(c)(1)(B) and 910(f) of the FDCA to require submission of all such materials at least 30 days prior to initial publication, dissemination, or use.[17]

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[14] *See* 21 C.F.R. §§ 314.550, 601.94.

[15] *Draft Guidance for Industry: Accelerated Approval Products — Submission of Promotional Materials* 2 (Mar. 1999), *withdrawn*, 80 Fed. Reg. 26059, 26060 (May 6, 2015) ("FDA encourages sponsors to begin communication with the appropriate division early in the application review process regarding submission of draft promotional materials for review during the preapproval period").

[16] *See, e.g.*, *CDER 21st Century Review Process Desk Reference Guide* 36-37.

[17] *Cf.* Marketing Order to Philip Morris Products S.A. regarding IQOS System Holder and Charger and Marlboro Heatsticks (April 30, 2019) (requiring "notification of all labeling, advertising, marketing, and/or promotional materials . . . at least 30 days prior to the initial publication, dissemination to consumers, or use in engaging or communicating with consumers of such materials").

2. FDA should clarify the scope of marketing information it expects to see in PMTAs and explain how it plans to engage in a science-based review of labeling and marketing plans.

Although labeling and marketing plans are critical to the APPH assessment, the proposed rule provides little detail as to what specific marketing information the Agency expects to see. For example, proposed § 1114.7(f) requires submission only of specimens of labeling, a "description" of the applicant's plans for labeling, advertising, marketing, promotion, and consumer-directed activities, and "insights" used to inform the marketing plan. In contrast, proposed § 1114.7(k)(iv) requires information about perceptions and use intentions associated with the product's label, labeling, and advertising.

Accordingly, it is unclear whether FDA is proposing to require submission of information about top-line product messaging, or of specific pieces and the advertising and marketing strategies for their use. It is also unclear to what extent FDA expects to see results of consumer research.

Details regarding how FDA plans to review the submitted information also are unclear. For example, the preamble states that product labeling "can be used to help show perception of the risks of the product and the ability of individuals to understand the labeling, including any instructions for use."[18] Yet it remains unknown how the Agency plans to review labeling and what specific considerations or methodologies will guide assessment of consumer risk perception and comprehension.

Similarly, the preamble states that marketing plans can inform consideration of "whether the marketing of the product would increase or decrease the likelihood that those who do not use tobacco products, including youth and young adults, will start using them" and an assessment of "potential uptake of the new tobacco product by current tobacco product users who would have otherwise stopped using tobacco products and how use of the new tobacco product may affect poly use behaviors and subsequent tobacco use."[19] But the preamble does not explain how FDA plans to make these determinations.

The preamble does refer generally to the evaluation of "youth exposure to the labeling, advertising, marketing, or promotion" of a new tobacco product, including through use of specific advertising channels like social media. It also states that "certain kinds of imagery, such as logos and cartoons have an impact on youth tobacco initiation."[20]

JLI agrees with the Agency that preventing initiation by nonusers, especially those who are underage, is a vital component of the tobacco regulatory framework. JLI supports FDA's consideration of, for example, advertising restrictions in the marketing order to

[18] 84 Fed. Reg. at 50580.

[19] *Id*. at 50580-81.

[20] *Id*. at 50581.

reduce nonuser exposure to promotional messaging, voluntary measures and guidelines from applicants, and data-tracking measures to assess the efficacy of the above strategies. FDA, however, should further elaborate on the specific materials it expects to see, the overarching framework for its review, the specific criteria or factors it intends to consider.

C. The final rule should provide clearer, more specific, and scientifically-informed standards for submitting information about HPHCs and other constituents.

Proposed § 1114.7(i)(1)(v) would require that a PMTA include a "full statement" of product's constituents, including "HPHCs and other constituents." This statement would include results of laboratory tests to quantify the constituents. Proposed § 1114.7(k)(1)(i)(A)-(C) would also require information about health effects, toxicity, and pharmacological profile of constituents and HPHCs.

The terms "constituent" and "harmful or potentially harmful constituent or HPHC" are defined broadly in proposed § 1114.3, comprising "any chemical or chemical compound in a tobacco product or in tobacco smoke or emission that is or potentially is inhaled, ingested, or absorbed into the body" and any constituent that "[c]auses or has the potential to cause direct or indirect harm to users or nonusers of tobacco products," respectively.

This language would establish a broad scope for the reporting of constituent and HPHC information. FDA has elsewhere recognized that PMTA applicants need not identify and quantify every chemical and chemical compound that may be introduced into the body through use of the product, as discussed in further detail below. But the proposed rule itself provides no mechanism by which an applicant may reasonably self-determine which constituents should and should not be identified.

There are two distinct problems with this. First, there are practical constraints on the sheer number, capacity, and capability of laboratories that are equipped to do the necessary testing. Thus, it is important for applicants to make reliable determinations about the universe of constituents they need to account for. This is an especially significant issue now, given that many deemed product manufacturers are concurrently preparing PMTAs for submission in the near future.

Second, proposed § 1114.27(a)(1)(ii) and (b)(1)(i) would provide that failure to submit sufficient constituent information could result in refusal either to accept or file a PMTA. As a result, an applicant for a deemed product who fails to identify even a single constituent or HPHC considered important by FDA could end up losing the ability to continue marketing its product based on that deficiency.

FDA has provided some clarifying guidance in the preamble and elsewhere. For example, the preamble refers to the "initial list" of HPHCs published by FDA in 2012, which it "intends to update periodically." The preamble further states:

> An application would not be required to contain testing for all HPHCs on the initial list; rather, it would be required to contain testing for HPHCs that are contained within and can be delivered by the type of product and contain a description of why the HPHCs that were tested are appropriate for the type of product. The HPHC list can be helpful to applicants in preparing a description of why the HPHCs for which it tested are appropriate for the product type, including, where appropriate, why an applicant did not test for certain HPHCs.[21]

The preamble also refers to product-specific recommendations on constituent testing provided in FDA's recently finalized guidance on PMTAs for ENDS products.[22] That document similarly states: "FDA expects that applicants will report the levels of HPHCs as appropriate for each product, so the reported HPHCs will differ among different product categories. The Agency recommends that manufacturers consult with CTP's Office of Science about what is appropriate in the context of a specific application."[23]

FDA also has acknowledged that the universe of potentially relevant constituents and HPHCs is subject to change. For example, FDA is in the process of updating its previously published HPHC list to reflect the deeming of ENDS products,[24] inherently acknowledging that determining HPHCs for such products is an area of uncertainty and continued discussion.

Although FDA has provided helpful guidance on these issues, it should reconcile all of this by modifying the proposed rule to reflect the fact that inclusion of constituent and HPHC information should be based on a comprehensive risk assessment for the particular product, with consideration given to comparator tobacco products such as those within the same category or sub-category and across categories (e.g., combustibles for ENDS products).

For example, the proposed rule could be revised to state that an application must include information only for "relevant" constitutions and HPHCs, and that the list of constituent names required by proposed § 1114.7(i)(1)(v) should be accompanied by a description of why the constituents on the list are appropriate for the product. FDA also should provide applicants with an opportunity to provide additional constituent or HPHC information, if deemed necessary by the Agency, without being subject to a refusal to accept or refusal to file.

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[21] *Id.* at 50585.

[22] *Id.*

[23] *Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems* 28 n.35 (June 2019).

[24] 84 Fed. Reg. at 50576.

D. FDA should set appropriate and reasonable requirements for health risk investigations in PMTAs

Proposed § 1114.7(k) includes requirements for information from "health risk investigations" to be included in a PMTA. The Agency has taken an expansive approach to this term by including, among other things, research on "perceptions" and "use intentions." The rule would further require "full reports of all information, published or known to, or which should reasonably be known to, the applicant" concerning these investigations.

Submission of health risk information is critical to FDA's assessment of whether permitting the marketing of a new tobacco product would be APPH. FDA needs to receive and consider a comprehensive body of scientific information — including information generated both by the applicant and third parties — to make a reasoned and scientifically-rigorous decision on a PMTA. At the same time, however, FDA should provide clarity and a defined scope for health risk information submissions, so that applicants know exactly what to present in PMTAs and to manage the potential burden on applicants and the Agency itself.

1. FDA should require information about health effects of constituents only for normal, customary, and ordinary conditions of use, and should permit use of customary scientific approaches for the generation of such information.

Proposed § 1114.7(k)(1)(i)(A) would require information about health effects of constituents, including HPHCs, at the levels delivered "under the range of conditions under which the product *might* be used" (emphasis added). However, it would be very cumbersome, if not impossible, for an applicant to identify, conduct testing for, and otherwise provide the required information for every condition under which a product "might" be used, including all potential conditions of misuse. FDA therefore should revise the rule to require information only for normal, customary, and ordinary conditions of use.

FDA also should acknowledge that applicants may use customary scientific approaches to conduct testing that addresses the relevant range of use, including "bracketing" and dose-response curves. In the preamble, FDA states that analytical testing for inhaled tobacco products "would be required to be determined using intense and nonintense smoking or aerosol-generating regimens, where established . . . in order to understand the way that constituent yields delivered by a tobacco product can change over a range of different smoking conditions."[25] Thus, FDA accepts a bracketing approach for understanding not only the lowest and highest constituent delivery levels, but also constituent delivery for use that falls somewhere in between these two data points, such as normal or customary use.

[25] *Id.* at 50586.

The proposed rule should itself reflect this accepted approach, by stating that the required information may consist of analyses that are based on investigations of nonintense and intense use regimens, and that employ toxicological principles, such as dose-response curves, to estimate the likely health risks of intermediate levels of exposure.

2. FDA should acknowledge that recommendations in the preamble are binding on the Agency, including recommendations for constituent investigations.

The preamble states that proposed § 1114.7(k)(1)(i)(A) "would not require an applicant to conduct any particular type of studies regarding the health risks of the constituents," but also goes to provide "non-binding recommendations for consideration" where an applicant chooses to conduct its own investigations.[26] While it is appropriate for FDA to say that the recommendations are non-binding *on applicants*, FDA's statements in the preamble are formal statements of policy and binding on the Agency according to its own regulations.[27] It is especially important for manufacturers of deemed products to be able to rely on FDA's statements in the preamble as the deadline for submitting PMTAs rapidly approaches. FDA should therefore clarify that these and other recommendations in preambles are only non-binding with respect to applicants.

3. FDA should make clear that investigations of perceptions and use intentions are required only for prospectively proposed labels, labeling, and advertising.

Proposed § 1114.7(k)(1)(iv) would require reports of investigations regarding the "impact of the product and its label, labeling, and advertising on individuals [*sic*]: (A) Perception of the product; (B) Use intentions; and (C) Ability to understand the labeling and instructions for use and use the product in accordance with those instructions."

This is not explicitly limited to investigations on the prospectively proposed label, labeling, and advertising, but it should be. Because section 910(b)(1)(A) of the FDCA does not provide for inclusion of these kinds of studies in a PMTA, FDA must rely on section 910(b)(1)(G). The latter applies only to "information relevant to the *subject matter of the application* as [FDA] may require" (emphasis added).[28] In this case, the relevant information relates to the label, labeling, and advertising prospectively proposed in the application.

In addition, it would be potentially burdensome for applicants and FDA to require the submission and review of investigations for prior labels, labeling, and advertising,

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[26] *Id.* at 50601.

[27] 21 C.F.R. § 10.85(d)(1) & (e).

[28] 21 U.S.C. § 387j(b)(1)(G).

particularly for products that have been marketed for several years before being subject to the PMTA requirement.

4. FDA should set clear and reasonable requirements on the scope for identification and submission of relevant health risk investigations.

As noted above, proposed § 1114.7(k)(1) would require submission of "all information . . . published or known to, or which should reasonably be known to, the applicant" regarding the specified health risk investigations. Proposed § 1114.7(k)(2) also states that the applicant must conduct a "literature search" as part of compiling this information and describe the search performed.

The scope of these proposed requirements is not clear. Although the proposed rule is based on broad statutory language at section 910(b)(1)(A) of the FDCA,[29] it would set a standard that goes far beyond what is required for other products regulated by FDA,[30] and would be potentially limitless in scope. To address this, FDA should revise the rule to provide clearer limits on how applicants can seek to identify the relevant reports.

For information that is not publicly available, an applicant would know or reasonably know of its own investigations, and perhaps also those of any affiliates. But an applicant is unlikely to know about — let alone have access to — any non-publicly disclosed investigations of competitors and other third parties. FDA should therefore, make clear that an applicant that conducts a reasonable search of its own files will be considered to have satisfied the "known to, or which should reasonably be known to" requirement for non-public information.

To accomplish this, FDA could revise proposed § 1114.7(k)(2) to refer to a "reasonable search" for information that must be performed (instead of the more narrowly conceived "literature search"), and to state that, with respect to non-public information, the search must include: (i) a search of the applicant's own files; and (ii) an inquiry of the applicant's own scientific personnel, requesting that they identify non-public investigations of which they are aware. FDA also should supplement proposed § 1114.7(k)(2) by including a statement that an applicant meets the "known to, or which reasonably should be known to" standard if it has described the search performed and provided its search findings as required by this provision.

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[29] *Id.* § 387j(b)(1)(A).

[30] *Cf., e.g.*, 21 C.F.R. § 314.50(d)(5)(iv) (requiring that an NDA include "A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the NDA, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.").

Finally, FDA should supplement proposed § 1114.7(k)(2) by including a statement that applicants may propose, with justification, a reasonable time limit for their searches. For example, a ten-year lookback period should be considered reasonable for ENDS products, given the very limited distribution and knowledge of such products before 2010.[31]

Imposing clear and reasonable limits on the search requirements for applicants will benefit FDA, applicants, and, most importantly, the public health. These limits would improve the overall quality of the information submitted and applicants' ability to provide the Agency with a helpful summary of the collected information. Another benefit will be the increased emphasis on clinical studies conducted by the applicant.

JLI shares FDA's goal of assuring that PMTA reviews are informed by relevant health risk data, but time and resources to dedicate to the preparation of PMTAs for deemed products before the court-imposed deadline are scarce, as are FDA's resources to review the applications. FDA should seize on this opportunity to focus PMTA applicants' and its own efforts on the most important issues.

III. COMMENTS ON OTHER SPECIFIC PROVISIONS OF THE PROPOSED RULE

A. FDA should revise and provide further clarity regarding the scope of potential amendments and its approach to determining when a "major" amendment has been submitted.

Proposed § 1114.9 would provide that an amendment to a pending PMTA may be requested by FDA or submitted on an applicant's own initiative. It also would provide that FDA may "restart" the 180-day review period after receipt of a "major" amendment or "pause" the review period after receipt of a "minor" amendment.

FDA's proposal to allow PMTA amendments is a welcome addition to the review process. Given the critical but substantial requirements the Agency proposes, the adjustment process that will follow for applicants and FDA as the requirements are first implemented, and the need for manufacturers of deemed products to submit applications under an accelerated deadline should be accounted for to improve efficiency and transparency.

JLI also appreciates, in this circumstance, the text in proposed § 1114.9(a) that an applicant may submit an amendment "on its own initiative." Applicant-initiated amendments may be especially important for soon-to-be submitted PMTAs for deemed products.

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[31] *U.S. Dep't of Health & Hum. Servs., Surgeon General's Report on E-Cigarette Use Among Youth and Young Adults* 149-52 (2016).

For example, it is likely that new data or analyses will become available during the review of PMTAs for such products; applicants should be encouraged to provide this information when it is relevant to FDA's review. It also is important for applicants to submit any new, long-term data that become available under an ongoing scientific program. As another example, a manufacturer of a deemed product may want to make minor modifications to product design or formulation imminently after preparing its initial PMTA submission to improve product quality or its risk-benefit profile. As long as this does not otherwise significantly affect adult user experience, an amendment would provide a prompt, efficient pathway for review of this kind of health-focused development.

Nonetheless, FDA should provide additional clarification, by acknowledging that these kinds of developments may be addressed through PMTA amendments.

Moreover, FDA should revise and clarify its approach to determining whether an amendment is major or minor, given the potentially significant effect this has on the overall review timeline. Currently, the proposed rule does not set forth an overarching principle to guide FDA's determination of whether an amendment will be considered major or minor. It instead provides two examples: (i) an amendment that contains significant new data from a previously unreported study, and (ii) detailed new analyses of previously submitted data. The preamble provides some additional, helpful guidance by stating that major amendments are those "that will require substantial FDA review time," and providing the additional example of substantial new manufacturing information.[32] FDA should provide further clarity by incorporating this general standard and additional example in the text of the rule itself.

B. FDA should clarify the available pathways for authorized product modifications to minimize submissions and reviews that could be unnecessary and onerous for applicants and the Agency.

Several provisions in the proposed rule would address requirements and pathways for modifications and other changes to authorized products.

For example, § 1114.39 would provide that any "modification" resulting in a new tobacco product triggers the need for a new PMTA or supplemental PMTA, "unless the new tobacco product can be legally marketed through another premarket pathway." In contrast, § 1114.41(a)(1)(ii) and (vii) would provide that certain "changes" made to the manufacturing, facilities, or controls, and certain labeling changes must be described in a periodic report.

On the other hand, § 1114.15(a) would provide an opportunity for submission of a streamlined "supplemental" PMTA for certain modifications. This would involve use of a standardized format for cross-referencing information found in a previous PMTA. The proposed rule states that this is limited to "modifications that require the submission of

[32] 84 Fed. Reg. at 50610.

limited new information." It also states that a supplemental PMTA is *not* permitted where, for example, review of a supplemental PMTA would be "confusing, cumbersome, or otherwise inefficient."

JLI welcomes the flexibility presented by this overall approach, given that it has significant potential to reduce the burden of PMTA review for certain modifications and other changes, thereby maximizing relevant FDA resources. This is particularly important now, given that a significant number of PMTAs likely will be submitted for deemed products soon during this transitional period. These initial submission could be followed by applications for modified versions that incorporate innovations designed to drive adult current users of tobacco products down the risk continuum and to reduce the potential for initiation by nonusers. The PMTA process should facilitate this kind of innovation, while also assuring that product changes with potential impact on the risk profile of a product are made with appropriate FDA oversight.

We believe, however, that there are additional opportunities to maximize efficiencies and promote public-health focused innovation, which should be reflected in changes to the proposed rule.

1. FDA should clarify the circumstances in which "changes" are considered "modifications," and the pathways available when modifications are made.

JLI appreciates that the proposed rule makes clear that a new or supplemental PMTA would be required only for "modifications" that result in a new tobacco product, and that the preamble further makes clear that some of these modifications may be made through a request for an exemption from substantial equivalence reporting.[33] We believe that the availability of the latter pathway to PMTA products is plainly reflected in the text of section 910(a)(2)(A)(ii) of the FDCA, which states that a marketing order is *not* required for any new tobacco product that is exempt from the substantial equivalence reporting requirements of section 905(j).[34]

Applicants nonetheless need greater clarity on when a change will be considered a "modification," thus triggering premarket requirements for a new tobacco product. It is helpful, for example, that proposed § 1114.41(a)(ii) would exclude "changes made to the manufacturing, facilities, or controls," subject to FDA evaluation of the applicant's "basis for concluding that each change does not result in a new tobacco product that is outside the scope of the marketing order." This is imperative given the importance of adjusting manufacturing and related process controls during the lifecycle of a product to ensure consistent quality and account for advancements in production technologies.

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[33] *Id.* at 50622.

[34] 21 U.S.C. § 387j(a)(2)(A)(ii); *see also* 21 C.F.R. § 1107.1.

It also is helpful that the preamble excludes certain kinds of co-packaging,[35] which are generally not intended or reasonably expected to alter or affect the tobacco product's performance, composition, constituents, or characteristics. Finally, FDA has elsewhere excluded certain other activities that are not expected to alter the performance of a tobacco product.[36]

FDA should provide further clarity by revising the rule to be consistent with all of this, such as by stating that a change would not trigger the new tobacco product requirements listed in proposed § 1114.39 if it is not intended or reasonably expected to alter or affect the tobacco products performance, composition, constituents, or characteristics.

In addition, our interpretation of the proposed rule is that FDA would not require reporting of any "changes" that do not rise to the level of "modifications" resulting in a new tobacco product, other than the specific types of manufacturing-related and labeling changes described in proposed § 1114.41(a)(1)(ii) and (iv). If that is not the case, FDA should provide additional clarity regarding other changes that should be reported.

2. The final rule should provide clearer and more expansive opportunities for submission of a supplemental PMTA to maximize FDA resources and review efficiency.

JLI welcomes the availability of the supplemental PMTA pathway to reduce the burden of application review and maximize relevant FDA resources. We believe, however, that there are additional opportunities to improve efficiencies, which should be reflected in changes to the proposed rule.

First, the rule should state that a supplemental PMTA may reference any previously submitted PMTA, including one that is still being reviewed by FDA. This would acknowledge that there may be situations where it would be appropriate for an applicant to cross-reference information in another PMTA that is still pending. Such is likely to be the case for manufacturers of deemed products that will soon be submitting original PMTAs closely followed by PMTAs for modified versions of their products. As long as the supplemental PMTA format would help promote efficiency — and not make review confusing, cumbersome, or otherwise inefficient — it should be permitted.

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[35] 84 Fed. Reg. at 50573.

[36] *Guidance for Industry: Interpretation of and Compliance Policy for Certain Label Requirement; Applicability of Certain Federal Food, Drug, and Cosmetic Act Requirements to Vape Shops* 7 (Mar. 2019) (stating that FDA does not intend to enforce premarket authorization and other requirements when a "vape shop modifies a tobacco product consistent with the specifications provided by the original manufacturer" because "FDA does not expect these modifications to alter the performance of the tobacco product as described or intended by original manufacturers").

Second, FDA should revise the rule to state that a supplemental PMTA may be submitted any time that the supplemental PMTA format will facilitate efficient review, not just when it will involve submission of "limited new information." There are many potential circumstances where it would still be in the interest of efficiency for a PMTA to contain a significant amount of new information *and* cross-reference information in another previously submitted PMTA.

This could be the case, for example, with certain manufacturing-related modifications that would subject the product to premarket review requirements. In the analogous context of drug regulation, these kinds of modifications are typically reviewed through supplemental, as opposed to original, applications.[37] It also could be the case with new technologies that reduce potential for underage use. Again, this should be permitted as long as it would not make FDA's review confusing, cumbersome, or otherwise inefficient.

Both changes are also important to encourage applicants to make modifications quickly when they may reduce potential adverse public health effects. They also would give FDA the most flexibility to provide future guidance on specific circumstances where supplemental PMTAs are appropriate, as applicants and the Agency gain more experience with the PMTA process.

3. FDA should revise or interpret the definitions of "accessory," "component or part," and "container closure system" in a manner that limits unnecessary PMTAs for changes to packaging and product-associated items that do not alter or affect performance.

As the terms are interpreted and applied in the preamble, § 1114.3 of the proposed rule would define the terms "accessory," "component or part," and "container closure system" in a manner that could result in a wide variety of packaging materials and product-associated items — none of which alters or affects anything actually made or derived from tobacco — being considered components or parts of a tobacco product. This approach has several potentially significant impacts.

For one, packaging materials could be considered components or parts even if they merely maintain the performance, composition, constituents, or characteristics of a product made or derived from tobacco, such as by protecting it from exposure to air and thereby prolonging its shelf life. The proposed rule would define the term "container closure system" to mean "any packaging materials that are a component or part of the tobacco product," and the term "component or part" to include materials, other than "accessories," that are intended to or reasonably expected to (i) alter or affect the tobacco product's performance, composition, constituents, or characteristics, or (ii) be used with or for the human consumption of a tobacco product. The term "accessory" is defined to

[37] *See generally Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (Dec. 2004).

include materials that solely control moisture and/or temperature of a stored product, but not to materials that otherwise keep the product shelf stable.

Interpreting the proposed rule this way poses two issues. First, it could create unnecessary and artificial constraints around ways in which legally marketed products may be co-packaged. The preamble does this by stating that two or more legally marketed products made or derived from tobacco may be co-packaged without creating a new tobacco product if they are shrink-wrapped together, but not if they are put within a single container-closure system,[38] presumably on the basis that this would result in a change in a component or part of the product.

If both products are separately marketed in the same kind of container-closure system, however, this is an artificial distinction that should not affect the outcome of the analysis. For example, if a manufacturer sells one type of closed system e-liquid cartridges in a 2-cartridge blister pack, and another type in a separate 2-cartridge blister pack, combining the packs should be permitted regardless of whether it is accomplished by putting the previously existing blister packs together, or by creating a new version of the blister pack that holds 4 cartridges. Co-packaging also should be permitted if it involves combining the two separate product types in a single 2-cartridge blister pack (i.e., a pack with 1 cartridge of each type). That would involve no change in the physical attributes of the product made or derived from tobacco, including no change in the total quantity of cartridges in a blister pack.

Second, this approach results in the need for a new PMTA or supplemental PMTA whenever there is a change in packaging materials that merely maintain the performance, composition, constituents, or characteristics of a product made or derived from tobacco. This is inconsistent with *Philip Morris USA Inc. v. FDA*, in which the D.C. District Court observed that the FSPTCA defines the term "tobacco product" in a manner that "refers only to the product's physical characteristics." The court further held that the law treats the product's "package" as distinct from the product itself, and that the law's requirements for new tobacco products apply only when there are changes in "the physical attributes of a tobacco product — not its labeling or packaging."[39] In other words, if a packaging change does not affect the physical attributes of a product made or derived from tobacco, it cannot trigger new tobacco product regulation.

There also are significant potential implications for product-associated items, which could be considered components or parts of a tobacco product even though they have no impact on the performance, composition, constituents, or characteristics of anything made or derived from tobacco. This is because the term "tobacco product" includes any product

[38] 84 Fed. Reg. at 50573.

[39] 202 F. Supp. 3d 31, 37, 51 (D.D.C. 2016).

made derived from tobacco (and intended for human consumption), as well as any component or part of that product.

As an example, an ENDS device used with closed system e-liquid cartridges is considered both a component or part and a tobacco product in its own right. If another product-associated item is used with the device in some manner, it would also be considered a tobacco product in its own right, and so on. This creates a potentially endless chain of items that could all be considered tobacco products, even though they do not themselves have any impact on any product actually made or derived from tobacco.

There is little benefit to be gained by FDA regulation of all these kinds of materials and items as tobacco products. FDA should recognize this by amending or interpreting the proposed definitions to avoid regulating – as a tobacco product, component, or part – anything that does not alter or affect the performance, composition, or characteristics of a product actually made or derived from tobacco.

C. FDA should amend its proposed acceptance and filing procedures to comply with the FSPTCA and avoid inequitable outcomes for applicants.

Proposed § 1114.27 would set forth acceptance and filing procedures, and list several, overlapping reasons for which the Agency may decline to accept a PMTA or to file a PMTA for substantive review. The overall scheme would reflect FDA's view that acceptance, filing, and substantive review are three sequential, distinct phases in the review of a PMTA. FDA should revise and clarify these provisions, including to address how acceptance and filing procedures impact the 180-day review clock Congress specified in the FSPTCA.

1. FDA should clarify that acceptance and filing reviews do not extend the 180-day review clock, in accordance with the FSPTCA, and that RTA and RTF decisions are subject to judicial review.

The FSPTCA provides that FDA "shall" take action on a PMTA by issuing "an order" determining whether the tobacco product may be marketed as "promptly as possible, but in no event later than 180 days after the receipt of [the] application."[40] Such orders are further defined by the statute to be immediately reviewable in the federal courts of appeal.[41] These provisions are phrased in mandatory terms, and they do not contemplate delays for the "acceptance" or "filing" reviews described in current § 1105.10 or proposed § 1114.27. Nor do the statutory provisions contemplate that FDA could take action on a PMTA other than issuing an order subject to judicial review.

To avoid violating these clear statutory requirements, FDA should make clarifying changes to both § 1105.10 and proposed § 1114.27. First, FDA should make clear that the

[40] 21 U.S.C. § 387j(c)(1)(A).

[41] *Id.* § 387*l*(a)(1)(B).

180-day review clock specified in the statute begins, as required, upon "receipt" of the application. FDA's proposal, particularly proposed § 1114.27(c)(2), suggests that the statutory clock would not begin to run until an application is officially "filed." That view is plainly inconsistent with the statute, which states that the deadline expires 180 days after "receipt."

Second, FDA should clarify that any refuse to accept (RTA) or refuse to file (RTF) letter regarding a PMTA would constitute an "order" and "denial" within the meaning of section 910 (c)(1)(A)(ii) and section 912(a)(1)(B) of the FDCA.[42] FDA's proposed rule, particularly proposed § 1114.27(c)(2), suggests that FDA believes that RTA and RTF letters (as well as letters "administratively closing" an application) are distinct from the orders described in the statute. Congress, however, decreed that FDA has *only two* choices when it receives a PMTA: it must either issue an order approving the application or issue an order denying the application. Congress further took the unusual step of decreeing that any denial should be subject to immediate judicial review at the appellate level. FDA cannot by regulation create third, fourth, or fifth options that are not included in the statute.

Notably, other program areas have taken steps to ensure that acceptance and filing procedures do not vitiate an applicant's right to review. In the drug context, an applicant may respond to an RTF by forcing FDA to file an NDA over protest, review the application, and either approve the application or issue a final order of denial pursuant to section 505(d) of the FDCA.[43] In the device context, an applicant may seek reconsideration of an RTF for a premarket approval application, and FDA's decision is defined to be final agency action subject to judicial review.[44] The absence of an equivalent procedure to ensure the availability of judicial review renders both current § 1105.10 and proposed § 1114.27 *ultra vires*.

2. FDA should continue enforcement discretion for a deemed product after an RTA or RTF decision, so long as the application is revised and resubmitted within a reasonable period of time.

In addition to making changes to comply with the statute, FDA should also address how an RTA or RTF will intersect with its current enforcement discretion policy for deemed products.

In *American Academy of Pediatrics v. FDA*, the District of Maryland ordered FDA to modify its enforcement discretion policy to state that tobacco product applications must be received for all deemed tobacco products by May 2020, and approved by May 2021, for the

[42] *Id.* §§ 387j(c)(1)(A)(ii), 387*l*(a)(1)(B).

[43] 21 C.F.R. § 314.101(a)(3); *see also* 21 U.S.C. 355(d).

[44] 21 C.F.R. § 814.42(d)(2).

product to continue to be legally marketed in the United States.[45] Applicants are now working hard to meet that timeline. However, due to enduring uncertainty about application requirements, limited resources, and the sudden acceleration of the application deadline, most applicants will likely only be able to submit their applications close to, or at, the May 2020 deadline.

In addition, FDA has said in guidance that it will stop exercising enforcement discretion for deemed tobacco products when it renders an RTF or RTA decision on an application:

> FDA is revising the compliance policy relating to the period after FDA receipt of SE EX requests, SE reports, and PMTAs for newly regulated products that were on the market on August 8, 2016. Under this new compliance policy, there will be a continued compliance period pending review of those applications (SE EX requests, SE reports, and PMTAs). This compliance period will continue until the agency renders a decision on an application (*i.e.*, issuance of: a Marketing Order; a No Marketing Order; a Refuse to File; or Refuse to Accept) or the application is withdrawn.[46]

In this circumstance, FDA should clarify that applications that are timely submitted would not lose enforcement discretion as a result of a RTA or RTF decision, so long as the application is revised and resubmitted within a reasonable period of time.[47]

3. FDA should include clear deadlines for acceptance and filing reviews.

Neither current § 1105.10 nor proposed § 1114.27 contain deadlines for RTA or RTF decisions. This is highly prejudicial. For instance, the absence of deadlines means that applicants are unable to schedule the submission of a PMTA to ensure that they know whether the application has been accepted and filed before the end of FDA's enforcement discretion policy. More generally, the lack of deadlines raises the specter of arbitrary agency action and years-long delays.

Here, too, FDA's proposal is inconsistent with requirements and practices related to acceptance and filing reviews in other program areas:

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[45] *Am. Academy of Pediatrics v. FDA*, No. 8:18-cv-00883-PWG, ECF No. 127, at 12 (D. Md. July 12, 2019).

[46] *Guidance for Industry: Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule (Revised)** 3 (Mar. 2019).

[47] Although the district court's decision in *Am. Academy of Pediatrics v. FDA* is under appeal, the same problem would exist even if the decision is overturned. FDA's enforcement discretion policy set deadlines to submit PMTAs by August 8, 2021 (combustible tobacco products) or August 8, 2022 (noncombustible tobacco products). *Id.* at 9-10. Even under this longer timeline, an RTA or RTF decision on a timely submission should be without prejudice to the enforcement discretion policy.

- For NDAs, FDA must determine whether the application will be filed within 60 days of receipt.[48]

- For premarket applications (PMAs), FDA intends to determine whether the application will be accepted within 15 days of receipt.[49] FDA must determine whether the application will be filed within 45 days of receipt.[50]

- For section 510(k) clearance reports, FDA intends to determine whether the report will be accepted within 15 days of receipt.[51]

- For new animal drug applications (NADAs), FDA must determine whether the application will be filed within 30 days of receipt.[52]

In promulgating regulations that specify timelines for acceptance and filing review for applications for other regulated products, FDA has acknowledged that these time limits are "important" to prevent applications from remaining in limbo "for many months, if not years."[53]

We are not aware of any clear justification for deviating, in the tobacco context, from FDA's established practice of setting firm deadlines for communicating RTA and RTF decisions. Indeed, such deadlines seem all the more important in this context, given the significant impact of these decisions under court-mandated deadlines and FDA's compliance policy. Not providing PMTA applicants clear timelines for notification of RTA or RTF decisions is arbitrary, capricious, and an abuse of discretion.

4. FDA should clarify the differences between its RTA, RTF, and substantive review standards.

Finally, FDA should clarify each standard at each phase of review — acceptance, filing, and substantive review — to provide applicants fair notice of their obligations to

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[48] 21 C.F.R. § 314.101(a)(1).

[49] *Guidance for Industry and FDA Staff: Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)* 3-4, 7 (Feb. 2019).

[50] 21 C.F.R. § 814.42(a).

[51] *Guidance for Industry and FDA Staff: Refuse to Accept Policy for 510(k)s* 5 (Sept. 2019).

[52] 21 C.F.R. § 514.110(c).

[53] 47 Fed. Reg. 46622, 46638 (Oct. 19, 1982) (preamble to proposed rule for new drug and antibiotic applications) (noting that instituting a firm deadline for filing review was an "important change" to FDA's prior policy of allowing filing review to merge with the substantive review of an NDA); *see also* 51 Fed. Reg. 26342, 26355 (July 22, 1986) (preamble to final rule for PMA regulations) (agreeing with commenters to establish a time limit for notifying applicants of an RTF decision); 36 Fed. Reg. 18375, 18376 (Sept. 14, 1971) (preamble to final rule for NADA regulations) (agreeing with commenters to establish a time limit for notifying applicants of an RTF decision).

clear each review threshold. As currently written, in proposed § 1114.26(a)(1) and (b)(1), "FDA may refuse to accept an application" that meets at least one of four specified criteria, and "FDA may refuse to file a PMTA" for one or more of five specified reasons. Consequently, it is unclear whether and to what extent any of the specified reasons in the regulation would lead to an RTA or RTF decision.

In contrast, in other product areas, FDA regulations list a number of bases upon which FDA may refuse to accept or file an application, and clearly specify that FDA will refuse to accept or file an application only if one or more of those reasons are present.[54] Alternatively, FDA provides a definitive statement that, if any of the specified reasons is present, the Agency shall refuse to accept or file the application.[55] Given the time, cost, and effort applicants must expend to submit a PMTA, and the considerable business stakes for applicants especially when currently marketed products are subject to PMTA review, FDA should provide clarity as to what grounds will lead to an RTA or RTF decision, following either of the above approaches.

In addition, FDA should clarify the differences between the RTA, RTF, and approval standards. FDA should ensure that applicants have advance notice and can understand the difference between RTA and RTF issues. FDA should also ensure that RTA and RTF decisions are not made based on approvability issues.

For instance, proposed § 1114.27(a)(1)(ii) states that an application can be refused acceptance if it is "administratively" incomplete in so far as it "does not appear to contain" required information. Proposed § 1114.27(b)(1)(i) states that an application can be refused filing if it "does not include sufficient information required . . . to permit a substantive review of the application." It is not clear how an application that is "administratively incomplete" differs from one that does not contain sufficient information "to permit a substantive review." And, experience from other program areas suggests that either or both of these standards could be misapplied to reach premature conclusions regarding the approvability of the application.[56]

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[54] *See* 21 C.F.R. § 314.101(a)(2) ("If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the NDA apply, the Agency will file the NDA and notify the applicant in writing."); *id.* § 814.42(b) ("If FDA does not find that any of the reasons in paragraph (e) of this section for refusing to file the PMA applies, the Agency will file the PMA and will notify the applicant in writing of the filing. The notice will include the PMA reference number and the date FDA filed the PMA.").

[55] *See id.* § 514.110(b) ("An application for a new animal drug shall not be considered acceptable for filing for any of the following reasons . . . .").

[56] In one recent, high profile example, FDA was forced to retract an RTF decision for an NDA from Alkermes. FDA had "taken the position that it is unable to complete a substantive review of the regulatory package, based on insufficient evidence of overall effectiveness for the proposed indication." Alkermes plc., Current Report (Form 8-K), Ex. 99.1 (Apr. 2, 2018) (press release announcing FDA's RTF letter). Alkermes successfully challenged the RTF letter as being based on a substantive review issue, not a filing issue. Alkermes plc., Current Report (Form 8-K), Ex. 99.1 (Apr. 16, 2018) (press release announcing FDA's decision to rescind RTF letter and accept NDA for filing).

D. FDA should amend its definitions and requirements for adverse experience reporting to make reporting obligations clearer and less onerous for both applicants and the Agency.

The proposed rule would require two distinct types of adverse experience reports. Proposed § 1114.41(a)(2) would require expedited reporting, within 15 calendar days, of "all serious and unexpected adverse experiences associated with tobacco product that have been reported to the applicant or that the applicant is aware of." Proposed § 1114.41(a)(1)(v) would require periodic reports that include a "summary and analysis" of all these serious and unexpected adverse experiences, "accompanied by a statement of any changes to the overall risk associated with the tobacco product, and a summary of any changes to the health risks, including the nature and frequency of the adverse experience, and potential risk factors."

Many of the key terms associated with these proposed requirements have unclear or unnecessarily broad definitions at proposed § 1114.3. There are several reasons why FDA should revise and clarify these terms.

First, the current definitions could lead to confusion and reporting of significant amounts unnecessary information, which will only complicate efforts to identify important issues. The definitions differ in several respects from comparable definitions in the well-established adverse experience reporting regimes for other FDA-regulated products, such as drugs and devices.

To the extent any of these differences are unnecessary, they may cause unwarranted confusion and raise unwarranted questions as to how FDA's approach to tobacco products differ from its approach elsewhere. In addition, it is important to make clear that many effects of nicotine exposure (*e.g.*, cough, rapid heart rate, increased blood pressure, nausea, and headache) are well known and have been extensively reported both in scientific literature and in other channels (*e.g.*, through government agencies, the internet, the media). Adverse event reporting requirements for tobacco products should be designed to make sure that experiences related to these effects do not obscure signals of other effects that are currently unlabeled and otherwise unknown.

It is worth noting that some tobacco manufacturers, such as JLI, use the same adverse experience coding standards and terminology as do pharmaceutical and device manufacturers, *e.g.*, the Medical Dictionary for Regulatory Activities (MedDRA). Accordingly, we favor general consistency across FDA-regulated products, absent a compelling rationale for disparate treatment.

Second, the preamble states that FDA would require these reports pursuant to section 910(f) of the FDCA,[57] which requires applicants to "establish and maintain such records, and make such reports" as FDA "may by regulation, or by order with respect to

[57] 84 Fed. Reg. at 50622.

[an] application, prescribe on the basis of a finding that such records and reports are necessary in order to enable [FDA] to determine, or facilitate a determination of, whether there is or may be grounds for withdrawing or temporarily suspending" a marketing order.[58] Given that the reports could serve as the basis for such a significant FDA decision, it is important for the applicable standards to be clearly articulated. Section 909, which also pertains to regulations for reporting of serious and unexpected adverse experiences also explicitly states that such regulations must not be unduly burdensome.[59]

1. FDA should narrow the term "adverse experience" to refer to a health-related event that is adverse.

The term "adverse experience" is defined in proposed § 1114.3 as "any unfavorable physical or psychological effect in a person that is temporally associated with the use of or exposure to a tobacco product, whether or not the person uses the tobacco product, and whether or not the effect is considered to be related to the use of or exposure to the tobacco product."

This definition is overly broad. First, the term "unfavorable" is too subjective a standard to allow for consistent application**.** Under the definition as proposed, for example, an unpleasant smell could be considered to result in an "unfavorable physical or psychological effect."

In contrast, applicable statutory and regulatory provisions for other FDA-regulated products define an "adverse experience" in health-related terms. In the particularly relevant context of reporting for other consumer products — *i.e.*, nonprescription drugs and dietary supplements — the term "adverse event" is defined as "any *health-related* event" that is adverse.[60] It is not clear why FDA should use different language for tobacco products, especially when it results in a more subjective standard.

To address these issues, the definition of "adverse experience" should be limited to an adverse health-related event associated with the use of or exposure to (intended or incidental) a tobacco product.

2. FDA should provide additional context to clarify its definition of "serious adverse experience."

In proposed § 1114.3, the term "serious adverse experience" is defined to include, among other things, a "life threatening condition or illness." This definition is similar to the language found in the post marketing adverse experience reporting regulations for prescription drugs. The drug regulations further define "life-threatening adverse drug

[58] 21 U.S.C. § 387j(f)(1).

[59] *Id.* § 387i(a)(3).

[60] *See id.* §§ 379aa(1), 379aa-1(a)(1) (emphasis added).

experience" as any adverse drug experience that "places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse drug experience as it occurred, *i.e.*, it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death."[61]

It would be useful to further define the term "life threatening condition or illness" in the final tobacco regulations to make clear that the term, as in the prescription drug regulations, contemplates the "immediate risk of death from the adverse experience."

The proposed rule also includes, in the definition of "serious adverse experience," the following "catch all clause":

> Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

In comparable definitions of "serious" adverse experience for other FDA-regulated products, this "catch-all clause" characterizes the events as "important medical events" rather than "any other adverse experience."[62] FDA should adopt similar language in the tobacco regulations for consistency and clarity. The adverse experiences being contemplated here are "serious," and potentially reportable to FDA if also meeting the regulatory definition of "unexpected." The phrase "important medical events" better captures the purpose of the provision and is consistent with FDA's approach to other regulated products.

3. FDA should align its definition of "unexpected adverse experience" with definitions in other product areas to avoid unnecessary and overly burdensome reporting.

In proposed § 1114.3, the term "unexpected adverse experience" is defined to mean:

> an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:
>
> (1) The known or foreseeable risks of adverse experiences associated with the use or exposure to the tobacco product as described in the PMTA and other relevant sources of information, such as the product labeling and postmarket reports;

[61] 21 C.F.R. §§ 310.305(b) (unapproved prescription drugs), 314.80(a) (approved prescription drugs), 600.80(a) (biological products) (emphasis in original).

[62] *See id.*

> (2) The expected natural progression of any underlying disease, disorder, or condition of the persons(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
>
> (3) The results of nonclinical investigations.

This definition is unnecessarily complex and would likely render the processing and assessment of adverse experiences challenging and unduly burdensome in a manner that would not ultimately enhance the ability of FDA and applicants to better understand and characterize the effects of PMTA products. For example, it raises difficult practical issues regarding "foreseeability" and assessment of disease progression. In contrast, comparable "unexpected adverse experience" definitions for other FDA-regulated products more simply define unexpectedness with respect to labeled events (with the exception of events that differ because of severity or specificity as more fully described in the regulations) or events not previously observed.[63] FDA should consider a similar approach with tobacco products by defining an "unexpected adverse experience" is one that is not listed in the current product labeling and postmarket reports.

4. FDA should make clear that required reports do not reflect a conclusion of causality by the applicant or FDA.

FDA's adverse experience regulations for other products include language making clear that submission of a required report does not reflect a conclusion or admission by the applicant or FDA that the product at issue caused or contributed to the adverse experience.[64] FDA should do the same here by adding the following to proposed § 1114.41(a)(2):

> The submission of a report under this section (and any release by FDA of that report) shall not constitute an admission that the tobacco product caused or contributed to an adverse experience. The applicant may deny that any report or information submitted under this provision constitutes an admission that the product caused or contributed to an adverse experience.

E. FDA should amend confidentiality provisions in the proposed rule and Part 20 to align with its approach to other products and recent Supreme Court precedent.

Proposed § 1114.47 includes provisions that would seek to preserve the confidentiality of a PMTA and its contents, before and after FDA has made a decision on the application. While these proposed provisions would address certain FDA practices involving product applications, by specifying that FDA would not publicly disclose the

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[63] *See id.*

[64] *See id.*; 21 U.S.C. §§ 379aa(g) (nonprescription drugs), 379aa-1(g) (dietary supplements); 21 C.F.R. § 803.16 (devices).

existence or contents of a pending PMTA unless the applicant has publicly disclosed or authorized the disclosure of such information, the provisions do not address other key practices and issues. FDA should address these issues to avoid uncertainty and minimize risk of public disclosures that run afoul of federal laws protecting both trade secret and confidential commercial or financial information.

1. The rule should state that a PMTA includes all data and information submitted with or incorporated by reference in the application.

Proposed § 1114.47 refers generally to confidentiality of an "application," but that term is not defined. This could create substantial ambiguity regarding the scope of the confidentiality provisions and, by extension, the scope of the Freedom of Information Act (FOIA),[65] sections 301(j) and 906(c) of the FDCA,[66] and FDA's implementing regulations.

In confidentiality provisions for other program areas, FDA has made clear that an "application" includes all data and information "submitted with or incorporated by reference" in the application, including relevant files on investigational products, master files, supplements, postmarket reports, and other relevant submissions.[67] FDA should follow a consistent approach for PMTAs by adding a sentence to § 1114.47 stating that, for purposes of that section, the "application" includes all data and information submitted with or incorporated by reference in the application, including investigational tobacco product submissions, tobacco product master files, supplements, reports, or any other related submission.

2. Disclosure of a pending PMTA referred to TPSAC should be limited to a summary of relevant portions of the application.

Proposed § 1114.45(b)(4) states generally that "the contents" of a PMTA will be available for public disclosure if FDA refers the application to the Tobacco Products Scientific Advisory Committee (TPSAC). Although the rule also refers to redaction for trade secrets, confidential commercial or financial information, or personal privacy, this approach is labor intensive and runs the risk of disclosing both too much and too little information and would likely would result in disclosures that are irrelevant to pending issues for public consideration.

This is especially true in light of the Supreme Court's recent holding in *Food Marketing Institute v. Argus Leader Media* in which the Court interpreted the scope of Exemption 4 of FOIA to reach beyond commercial or financial information for which public disclosure would cause substantial competitive harm, so as to include all commercial or

[65] 5 U.S.C. § 552.

[66] 21 U.S.C. §§ 331(j), 387f(c).

[67] 21 C.F.R. §§ 314.430(a), 514.11(a), 814.9(a).

financial information that would "customarily not be released to the public by the person from whom it was obtained."[68] In other words, given the expansive scope of Exemption 4 of FOIA as clarified by the Supreme Court, it is unclear what non-public information contained within a PMTA would be subject to public disclosure under § 20.61 and, as a result, it is unclear what relevant information could in fact be disclosed for public consideration of a specific pending issue before an open session of an advisory committee meeting.

In contrast, the confidentiality provisions in other program areas call for disclosure of only a summary of selected portions of the application that are appropriate for public consideration.[69] To assure that FDA adopts a consistent approach across its confidentiality regulations, FDA should revise § 1114.47(a)(4) to state that it may publicly disclose a summary of portions of a PMTA, while under review, during an open session of an advisory committee meeting, if such disclosure is relevant to public consideration of a specific pending issue pertaining to whether permitting marketing of the product would be APPH.

3. The rule should state that all data and information contained within an ITP submission are confidential, including the existence of the submission and identity of the applicant.

FDA should revise § 1114.47 to make clear that all data and information contained within an investigational tobacco product submission is confidential, including the existence of the submission and identity of the applicant, consistent with FDA's other product application regulations.[70]

While FDA has not yet issued regulations for investigational tobacco products, it has issued guidance that encourages voluntary submissions pertaining to investigational tobacco products.[71] Consequently, FDA may receive trade secret or other confidential information pertaining to a tobacco product that is or will be the subject of a PMTA, where the information was submitted before a PMTA was filed with the Agency.

To prevent confusion regarding the confidentiality of such information, FDA should specify that such information is confidential under § 1114.47, particularly if FDA has not yet promulgated regulations for investigational tobacco products at the time the PMTA rule is finalized.

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[68] 139 S. Ct. 2356, 2364 (2019) (internal quotations and citations omitted).

[69] 21 C.F.R. §§ 314.430(d)(1), 514.11(d), § 814.9(d)(1).

[70] *See, e.g.*, *id.* §§ 312.130, 514.12, 812.38.

[71] *See Draft Guidance for Industry and Investigators: Use of Investigational Tobacco Products* (Feb. 2019).

4. FDA should update its Part 20 regulations to correctly describe the current scope of FOIA Exemption 4.

Proposed § 1114.47 cross-references FDA's public information regulations under 21 C.F.R. Part 20, but the Agency has not yet amended those regulations to reflect the Supreme Court's holding in *Argus Leader Media*. To address this, FDA should update its part 20 regulations at least by the time it finalizes its PMTA regulations. In particular, FDA should amend § 20.61 to assure that its regulations describing the scope of Exemption 4 under FOIA follow the Supreme Court's analysis and holding in *Argus Leader Media*.

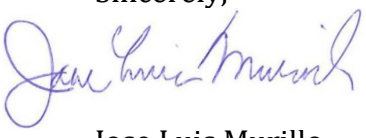
* * *

JLI appreciates FDA's proposal to establish final, binding regulations that will provide much-needed guidance to tobacco product manufacturers as they prepare PMTAs to support the marketing of their products. The PMTA process is vital for manufacturers seeking to market viable alternatives for current users of older, entrenched products — *i.e.*, combustibles — that have dominated the market historically but which may pose greater individual and public health harm.

Consequently, in developing a final version of the PMTA regulations, FDA should ensure a fair playing field for applicants and consider how its requirements will affect both the current and future market for tobacco products. The Company believes that clarifying the Agency's expectations and codifying its review procedures and postmarket requirements will do a great service to both applicants and to the public health.

We thank the Agency for the opportunity to provide comments as it moves forward in finalizing this important rule.

Sincerely,



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