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FDA Application Pitfalls

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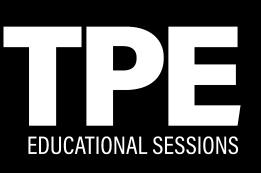


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PMTAS





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PMTA Acceptance Requirements

- FDA may refuse to accept an application that: • Is not submitted using "the form(s) that FDA provides" • Does not contain a comprehensive index and table of contents • Is not well-organized, legible, and written in English • Is not in an electronic format that FDA can process, read, review, and archive, unless FDA has granted a waiver Includes documents that have been translated from another language into English that are not accompanied by: • The original language version of the document, • A signed a statement by an authorized representative of the

- - manufacturer certifying that the English language translation is complete and accurate, and
 - A brief statement of the qualifications of the person that made the translation



Common PMTA RTA Bases

- Does not include an EA
- FDA Forms 4057 and 4057b
- files)

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- Cross-references a TPMF but does not include authorization to reference the TPMF
- Fails to identify an authorized representative or U.S. agent
- Includes a certification statement not signed by a designated authorized representative

Does not include the most recent, and final, versions of

 Does not include a signed statement by an authorized representative of the applicant certifying that the English language translation is complete and accurate (sometimes) caused by a PDF upload stripping issue when combining



PMTA Filing Requirements

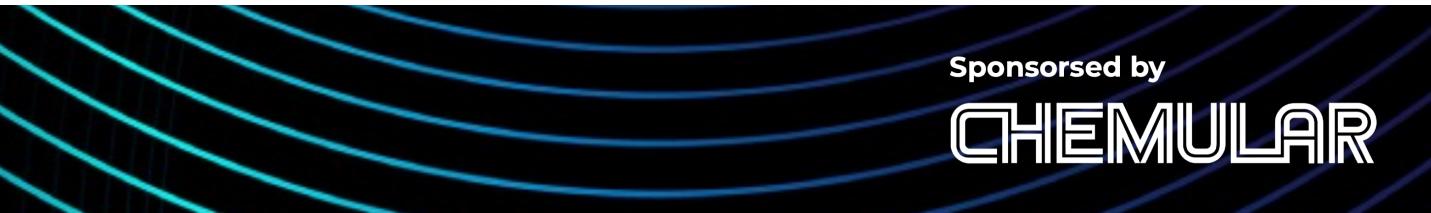
- FDA may refuse to file a PMTA if it does not contain substantive information regarding:
 - The health risks of the NTP
 - The health risks of the NTP compared to the health risks presented by products in the same category and in at least one different category
 - The abuse liability of the NTP

- How consumers would be expected to actually use the NTP
- The potential impact that the marketing of the NTP would have on the likelihood that current tobacco product users would change their tobacco product use behavior



PMTA Filing Requirements (cont.)

- FDA may refuse to file a PMTA if it does not contain substantive information regarding:
 - The impact of the tobacco product and its label, labeling, or advertising, to the extent that advertising has been studied, on tobacco product use behavior of current nonusers of tobacco products
 - The impact of the product and its label, labeling, or advertising, to the extent that advertising has been studied, on individuals' perception of the product and their use intentions
 - The ways in which human factors can affect the health risks of the new tobacco product



FDA's "Fatal Flaw" Approach

- pending PMTAs for ENDS products filed by 9/9/20, FDA established its so-called "fatal flaw" approach
 - then expanded to cover menthol ENDS as well
- include
 - other "reliable and robust evidence")

 - a product includes effective access technology)

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• In late 2021, in order to expedite review of the over one million still-• First applicable only to non-tobacco, non-menthol ENDS but

• If a PMTA for a non-tobacco flavored ENDS does not appear to

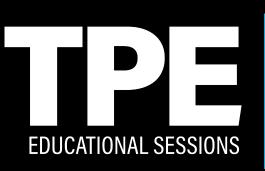
A randomized controlled trial or a longitudinal cohort study (or

• Demonstrating that the flavored product will provide a benefit to adult smokers as compared to a tobacco-flavored product, • It will be denied without further review (except potentially where

 This policy has been the subject of extensive litigation, but FDA has not yet authorized any non-tobacco flavored ENDS products



SE Reports





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Acceptance Criteria

- 2021) if, for example:
 - It does not include the required forms
 - applicable tobacco product standards
 - request

 - It does not include the name and contact agent



 FDA will refuse to accept an SE report that was filed after the effective date of the SE rule (November 4,

 It does not include a statement of compliance with It does not include a health information summary or statement that information will be available upon

 It does not meet the formatting requirements information for the authorized representative or US



- OCE must confirm that each predicate product qualifies as an eligible predicate product
 - Of late, these reviews appear to proceed in tandem with the scientific reviews
- Ensure:
 - Complete predicate product identification information Consistency of identification information with that included in any underlying GF/PX submission (e.g., punctuation, spelling, spacing, capitalization, etc.) Sufficient commercial marketing evidence and "linking

 - information"
 - Complete test marketing statement (i.e., the predicate) was not exclusively in a test market as of Feb. 15, 2007)





- email from ctp-preexisting@fda.hhs.gov
- OCE will request a response within an days)
- Respond with a letter submitted to the an emailed courtesy copy)





 Any perceived "discrepancy" will trigger a request for additional information sent via

extremely short timeframe (e.g., 3-5 business

Document Control Center or CTP Portal (with



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Response Tips

- Reproduce each request and then provide your response
- Overexplain everything; OCE will make no (even obvious) inference for your benefit Use tables to provide corrected identification and linking information Where strategic, consider anticipating follow-up requests when OCE asks about something in one case but not another



- made any GF/PX submission for the predicate product, FDA now seeks the business relationship" between the entities
- predicate product, FDA now requires make a test marketing statement

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 When the applicant differs from the entity that information and documentation to "explain

 When the applicant didn't manufacture the explanation of the applicant's "authority" to



Deficiency Letters

- In general, FDA will now issue only <u>one</u> deficiency letter
- The RHPM will call the contact and offer an emailed courtesy copy, which the applicant should accept to avoid lost days because OS "requests" a response within 90 <u>calendar</u> days of the deficiency letter's issuance
- FDA doesn't "intend" to grant extensions, but the agency does occasionally grant them expressly or implicitly
- Even if FDA requests "missing" stability data, 90 days can suffice for products without established shelf lives



Deficiency Letter Response Tips

- Reproduce each request and then provide your response; make sure to parse the "request" from the (often extensive) background
- If a requested design feature isn't used in the manufacturing process, consider providing "theoretical" targets/limits and test data showing conformance
- Cite Technical Project Lead summaries from prior SE orders to support your position, rebut OS assertions, or push back on inconsistent treatment/demands





Deficiency Letter Updates

- recent deficiency letters curiously have not characterizing flavors
- when the NTP does not have increased water activity relative to the predicate product



 Comparing flavored NTPs to unflavored predicates still results in automatic NSE orders, but some addressed sensory/appeal impacts of changes in

 FDA now consistently takes a stepwise approach to stability data requests, requiring no further testing



Appeal Options

- Appeal of a PMTA MDO:
 - - Within 30 days of the date of the MDO
 - 10.75.
 - deadline
- To appeal a PMTA RTA/RTF or an NSE order, may seek supervisory review

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• US Court of Appeals for DC or in the circuit in which the applicant resides or has its principal place of business • Seek "supervisory review" of the MDO under 21 C.F.R. §

• There is no deadline for requesting supervisory review; however, seeking 10.75 review does not toll the 30-day

• If FDA denies the supervisory review request, the applicant may: (i) appeal the decision to the FDA Commissioner's Office or (ii) challenge the decision in federal district court







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