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FDA Application Pitfalls

Stacy L. Ehrlich
Partner
Kleinfeld Kaplan & Becker LLP

PMTAs

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
- Does not include the most recent, and final, versions of FDA Forms 4057 and 4057b
- 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 files)
- 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

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

- In late 2021, in order to expedite review of the over one million still-pending PMTAs for ENDS products filed by 9/9/20, FDA established its so-called "fatal flaw" approach
  - First applicable only to non-tobacco, non-menthol ENDS but then expanded to cover menthol ENDS as well
- If a PMTA for a non-tobacco flavored ENDS does not appear to include
  - A randomized controlled trial or a longitudinal cohort study (or other "reliable and robust evidence")
  - 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 a product includes effective access technology)
- This policy has been the subject of extensive litigation, but FDA has not yet authorized any non-tobacco flavored ENDS products

SE Reports

Acceptance Criteria

- FDA will refuse to accept an SE report that was filed after the effective date of the SE rule (November 4, 2021) if, for example:
  - It does not include the required forms
  - It does not include a statement of compliance with applicable tobacco product standards
  - It does not include a health information summary or statement that information will be available upon request
  - It does not meet the formatting requirements
  - It does not include the name and contact information for the authorized representative or US agent

Predicate Eligibility Review

- 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)

Predicate Eligibility Review

- Any perceived “discrepancy” will trigger a request for additional information sent via email from ctp-preexisting@fda.hhs.gov
- OCE will request a response within an extremely short timeframe (e.g., 3-5 business days)
- Respond with a letter submitted to the Document Control Center or CTP Portal (with an emailed courtesy copy)

Predicate Eligibility Review

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

Predicate Eligibility Review

- When the applicant differs from the entity that made any GF/PX submission for the predicate product, FDA now seeks information and documentation to “explain the business relationship” between the entities
- When the applicant didn’t manufacture the predicate product, FDA now requires explanation of the applicant’s “authority” to make a test marketing statement

Deficiency Letters

- In general, FDA will now issue only one 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 calendar 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

- Comparing flavored NTPs to unflavored predicates still results in automatic NSE orders, but some recent deficiency letters curiously have not addressed sensory/appeal impacts of changes in characterizing flavors
- FDA now consistently takes a stepwise approach to stability data requests, requiring no further testing when the NTP does not have increased water activity relative to the predicate product

Appeal Options

- Appeal of a PMTA MDO:
  - US Court of Appeals for DC or in the circuit in which the applicant resides or has its principal place of business
    - Within 30 days of the date of the MDO
  - Seek “supervisory review” of the MDO under 21 C.F.R. § 10.75.
    - There is no deadline for requesting supervisory review; however, seeking 10.75 review does not toll the 30-day deadline
- To appeal a PMTA RTA/RTF or an NSE order, may seek supervisory review
  - 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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