# FDA Marketing Authorization Requirements for Nicotine Dissolving Strips

## 1. Regulatory Classification and Legal Basis

### 1.1 Definition as Tobacco Products

**1.1.1 FDA Authority Over Nicotine-Containing Products** The **Family Smoking Prevention and Tobacco Control Act (TCA) of 2009** established the foundational framework for FDA regulation of tobacco products, granting the agency comprehensive authority over the manufacture, marketing, and distribution of products meeting the statutory definition (Counter Tobacco) . This landmark legislation initially covered cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco, but its scope has expanded dramatically through subsequent regulatory and legislative actions to encompass virtually all nicotine-containing products regardless of source or delivery mechanism.

The **2016 FDA Deeming Rule** represented the first major expansion, explicitly extending FDA oversight to **electronic nicotine delivery systems (ENDS), all cigars, hookah tobacco, pipe tobacco, nicotine gels, and dissolvables**—a category that directly encompasses nicotine strips and films (Counter Tobacco) . This rule's inclusion of "dissolvables" was deliberate and forward-looking, capturing products that dissolve in the oral cavity to deliver nicotine without requiring spitting, including formats resembling "mints, mouthwash strips, and toothpicks" (Counter Tobacco) . The deeming regulation's explicit coverage of "any novel and future tobacco products" ensured that innovative delivery mechanisms could not escape regulatory scrutiny through claims of technological novelty.

The regulatory landscape underwent its most consequential transformation in **April 2022**, when Congress amended the TCA to close the **"synthetic nicotine loophole"** (Counter Tobacco) (Counter Tobacco) . Prior to this amendment, some manufacturers had marketed products containing laboratory-synthesized nicotine as "tobacco-free" to argue they fell outside FDA jurisdiction. The 2022 amendment explicitly expanded the statutory definition to include products containing nicotine **"from any source"**—eliminating any ambiguity and ensuring comprehensive coverage (accortoreg.com) (Counter Tobacco) . As regulatory authorities have emphasized, **"all such products, including new oral nicotine products containing nicotine from any source, are subject to premarket tobacco product application requirements"** (Counter Tobacco) , and **"all such products that are marketed without FDA marketing authorizations are, in fact, being marketed illegally"** (Counter Tobacco) .

This expanded authority means that nicotine dissolving strips—whether containing tobacco-extracted nicotine, synthetic nicotine, or any other source—are **unambiguously classified as tobacco products** subject to full FDA regulation. The delivery mechanism (dissolving film), marketing claims ("tobacco-free," "clean"), and physical form (pharmaceutical-like strip) do not affect this fundamental classification.

**1.1.2 Specific Inclusion of Dissolving Strips** The classification of nicotine dissolving strips as regulated tobacco products is **explicitly established in FDA guidance, public health documentation, and industry practice**. The Minnesota Department of Health specifically identifies "nicotine strips" as an emerging product category of concern, noting that "these flavored strips dissolve quickly in the mouth, delivering nicotine discreetly" and that "their youth appeal and misuse potential have raised concerns among researchers and clinicians" (MN Dept. of Health) (MN Dept. of Health) . This official recognition underscores that regulatory and public health authorities treat these products as within FDA's jurisdictional purview regardless of branding or positioning.

The **FDA's NicScreen project**, initiated to develop scientific tools for tobacco product regulation,

explicitly included "tobacco sticks, pellets and strips that dissolve in your mouth" within the scope of deemed products requiring regulatory oversight (Charles River Laboratories) . This early scientific attention demonstrated the agency's recognition that dissolving strips, despite their consumer-product appearance, function as nicotine delivery systems with public health implications comparable to other tobacco products.

**Industry practice confirms this regulatory understanding.** SENO, a manufacturer of nicotine film products, announced in January 2025 that it had obtained **"first-round FDA Premarket Tobacco Application (PMTA) approvals"** with assigned application numbers **PM0010199, PM0010173, and PM0010176** (PRWeb) . The company explicitly described its products as **"FDA-compliant nicotine film"** developed, produced, and sold **"in full compliance with FDA regulations"** (PRWeb) . Similarly, Zolv, a U.S. startup preparing to market dissolvable nicotine strips, announced its intention to **"file a premarket tobacco product application (PMTA) with the U.S. Food and Drug Administration within the next year"** as a prerequisite for U.S. market entry (Nicotine Insider) . These corporate strategies demonstrate unambiguous industry recognition that PMTA authorization is mandatory for this product category.

The **"tobacco-free" marketing claim provides no regulatory exemption**. Products marketed as "tobacco-free," "clean nicotine," or "alternative" remain subject to full FDA tobacco product regulation if they contain nicotine intended for human consumption. The statutory and regulatory framework treats marketing terminology as irrelevant to jurisdictional determination; what matters is the **presence of nicotine as an active pharmacological agent**.

### 1.2 Premarket Review Requirement

**1.2.1 Mandatory PMTA Submission** The **Premarket Tobacco Product Application (PMTA)** pathway represents the **exclusive lawful mechanism** for introducing nicotine dissolving strips into U.S. commerce. Under **Section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)**, any "new tobacco product"—defined as one not commercially marketed in the United States as of **February 15, 2007**, or any modification to a tobacco product commercially marketed after that date—must obtain FDA marketing authorization before introduction or delivery for introduction into interstate commerce (HHS.gov) .

This requirement applies **without exception** to dissolving strips. The February 15, 2007 predicate date for "new tobacco product" classification effectively eliminates any grandfathering protection, as dissolving strip technology emerged as a commercial product category substantially after this cutoff. The **Substantial Equivalence (SE)** pathway—an alternative authorization mechanism for products demonstrably similar to predicate products legally marketed in 2007—is **unavailable for novel formats like dissolving strips**, as no appropriate predicate products existed at that time (HHS.gov) . As FDA has noted, "the expected difficulty in identifying valid ENDS predicate products" for substantial equivalence determinations extends equally to dissolving strips (HHS.gov) .

The **PMTA submission must satisfy comprehensive statutory requirements** specified in Section 910(b)(1) of the FD&C Act. FDA guidance recommends that submissions include: a detailed cover letter identifying the applicant, authorized U.S. agent, specific product identification, prior submission history, and explicit mapping of how PMTA sections satisfy each statutory requirement (HHS.gov) . The submission must provide **"specific information pertaining to different topic areas and scientific disciplines"** to enable FDA's APPH determination (HHS.gov) .

| PMTA Core Content Areas | Specific Requirements |
|---|---|
| Product identification | Complete description, brand/sub-brand, intended use |
| Manufacturing information | Facilities, processes, quality controls, batch records |
| Ingredient listing | All constituents, additives, HPHCs with quantities |
| Health risk investigations | Toxicology, clinical studies, abuse liability assessment |
| Marketing plan | Target audience, channels, proposed restrictions |
| Environmental impact | Assessment under NEPA requirements |

*Table 1: Essential components of PMTA submission for nicotine dissolving strips*

**1.2.2 Consequences of Non-Compliance** Marketing nicotine dissolving strips **without FDA authorization carries severe legal and operational consequences**. Under **FFDCA Section 902**, unauthorized tobacco products are deemed **adulterated**, rendering their sale illegal and exposing all supply chain participants to enforcement action (Congress.gov) (EveryCRSReport.com) . The FDA has deployed a **multi-tiered enforcement strategy** that has intensified significantly since 2022.

| Enforcement Mechanism | Description | Typical Application |
|---|---|---|
| Warning letters | Formal notice of violation with opportunity to correct | Initial detection of unauthorized marketing |
| Import alerts | Detention without physical examination at ports of entry | Foreign-manufactured products |
| Product seizure | Physical removal from commerce through judicial process | Domestic distribution of violative products |
| Injunction actions | Court-ordered cessation of manufacturing/sales | Systematic or repeated violations |
| Civil monetary penalties | Financial penalties per violation | Calculated based on violation scope and duration |
| Criminal prosecution | Felony or misdemeanor charges | Knowing and willful violations |

*Table 2: FDA enforcement mechanisms for unauthorized nicotine products*

The FDA has **actively exercised these authorities** against unauthorized nicotine products. The agency has issued **hundreds of warning letters** to firms marketing products without required PMTAs and, through the Department of Justice, filed **complaints for permanent injunctions** against manufacturers failing to submit required applications (Office of Inspector General) . In 2022, the FDA filed its **first complaints for permanent injunctions against e-cigarette manufacturers**, establishing precedent for judicial enforcement (Office of Inspector General) .

**Operational consequences of non-compliance** extend beyond direct legal exposure. Unauthorized products face: **inability to secure product liability insurance**; **exclusion from legitimate distribution channels** (major retailers increasingly require PMTA verification); **vulnerability to competitor challenge**; **reputational damage** affecting investor and consumer confidence; and **payment processing and banking restrictions** as financial institutions implement tobacco product compliance screening. The 2023 HHS Office of Inspector General audit found that despite extensive PMTA decisions, **"few participants in 2023 were using FDA-approved devices or liquids"**—yet these unauthorized products operate in persistent regulatory jeopardy (nih.gov) .

## 2. The PMTA Process: Core Components

### 2.1 Public Health Standard (APPH)

**2.1.1 "Appropriate for the Protection of Public Health" Determination** The **"Appropriate for the Protection of Public Health" (APPH)** standard constitutes the **central evaluative criterion** for all PMTA submissions, including nicotine dissolving strips. This standard, codified in **Section 910(c)(4) of the FD&C Act**, requires FDA to conduct a **comprehensive, population-level assessment** that weighs potential benefits and risks across the entire U.S. population—not merely individual user effects (HHS.gov) .

The APPH determination is **distinct from conventional product safety assessments**. Unlike drug approval, which evaluates safety and efficacy for individual patients under medical supervision, or device clearance, which assesses substantial equivalence to predicate products, the APPH standard **explicitly incorporates behavioral dynamics and population-level trajectories**. FDA must evaluate how product availability will affect: **initiation** among non-users (particularly youth); **cessation** among current users; **switching** between product categories; and **long-term epidemiological outcomes** across diverse demographic segments.

For nicotine dissolving strips, the APPH analysis presents **distinctive tensions**. The product format offers **potential benefits** as an alternative to combustible cigarettes for adult smokers unable or unwilling to quit nicotine entirely: elimination of combustion and its associated toxicants; discrete use enabling social acceptability; and potentially reduced secondhand exposure. However, these same characteristics —**rapid onset, flavor variety, concealability**—may **increase youth appeal and initiation risk**, potentially offsetting adult benefits through expanded nicotine dependence among adolescents.

The FDA's **evolving APPH jurisprudence** has become increasingly demanding. Through early 2023, the agency had resolved **over 99% of more than 6.5 million timely PMTA applications**, yet granted marketing authorization to **only 23 products**—an authorization rate below 0.001% (nih.gov) . This extraordinary selectivity reflects both the stringency of APPH requirements and FDA's prioritization of **youth protection** in authorization decisions. Marketing denial orders have consistently cited **"well-documented, alarming levels of youth use"** as determinative where evidence of youth appeal outweighed demonstrated adult smoker benefits (Congress.gov) (nih.gov) .

Manufacturers may **propose specific restrictions** to support favorable APPH determination. These may include: **flavor limitations** (tobacco/menthol only, or restricted flavor portfolio); **nicotine concentration caps**; **packaging specifications** (child-resistant, plain, or warning-enhanced); **marketing channel restrictions** (prohibition on social media, influencer, or event marketing); and **retail access limitations** (age-verified online sales only, or restricted distribution networks) (HHS.gov) . FDA may incorporate proposed restrictions as **mandatory conditions in marketing orders**, adding to baseline regulatory requirements.

**2.1.2 Population-Level Impact Assessment** The **population-level impact assessment** required for APPH determination demands **sophisticated modeling and empirical evidence** that projects behavioral and health outcomes across diverse population segments. This assessment extends far beyond product-specific toxicology to encompass **complex substitution dynamics and long-term epidemiological trajectories**.

| **Critical Modeling Parameters** | **Description** | **Evidence Requirements** |
|---|---|---|
| Adult smoker switching rate | Proportion of cigarette smokers transitioning to exclusive strip use | Longitudinal cohort studies, consumer panels, purchase data |
| Dual use prevalence | Proportion using strips concurrently with combustible products | Use-pattern studies, biomarker verification of continued smoking |
| Youth initiation rate | Proportion of nicotine-naïve youth initiating with strips | National surveillance, school-based surveys, retail audit data |
| Progression/regression dynamics | Movement between product categories and to/from abstinence | Longitudinal tracking, state-transition models |
| Net population mortality/morbidity | Projected disease burden changes over 20–50 year horizons | Comparative risk modeling, Monte Carlo simulation |

*Table 3: Population-level impact assessment parameters for dissolving strip PMTA*

For dissolving strips, **critical behavioral questions** include: Will cigarette smokers who would otherwise continue smoking switch completely to strips, reducing toxicant exposure? Or will strips primarily attract smokers who would otherwise quit nicotine entirely, extending dependence? Will dual use predominate, maintaining or even increasing total toxicant exposure? Will youth initiation with strips increase subsequent progression to combustible cigarettes, or will strips divert youth from more harmful products?

The **temporal dimension** of population health assessment introduces substantial uncertainty. FDA must evaluate not merely immediate effects but **long-term trajectories**, including the possibility that product introduction might **delay smoking cessation** at critical life stages or **re-normalize nicotine use** in social contexts where it had become stigmatized. These dynamic considerations require applicants to present **quantified projections with sensitivity analyses** addressing parameter uncertainty and model structural assumptions.

### 2.2 Scientific Evidence Requirements

**2.2.1 Product Chemistry and Characterization** **Comprehensive product chemistry and characterization** forms the evidentiary foundation of PMTA submissions for nicotine dissolving strips. This characterization must enable FDA scientists to **reconstruct the product composition**, assess potential interactions, and establish quality control benchmarks for regulatory surveillance.

**Nicotine documentation** requires particular rigor. Applicants must specify: **source** (tobacco-derived, synthetic, or biosynthetic) with manufacturing process description; **purity specifications** including impurity profiles and stereochemical composition; **stability data** demonstrating maintenance of specifications throughout shelf life; **batch-to-batch consistency** in nicotine content and delivery; and **pharmacokinetic behavior** following oral dissolution (HHS.gov) . For synthetic nicotine, additional documentation of **starting materials, synthetic route, and chiral purity** may be required given the pharmacological significance of nicotine enantiomer composition.

**Excipient characterization** addresses the film matrix and functional ingredients. Dissolving strips typically employ **hydrophilic film-forming polymers** (alginate, hydroxypropyl methylcellulose, pullulan, polyvinyl alcohol), **plasticizers** (glycerin, propylene glycol), **sweeteners**, **flavoring agents**, and **coloring compounds** (Nicotine Insider) . Each excipient requires: **chemical identification** with CAS number and structural information; **functional role** in the formulation; **safety profile** in intended use context; and **specifications** for quality control. The use of **food-approved or pharmaceutical-grade ingredients**, while providing baseline safety reference, does not automatically establish safety in the specific formulation, concentration, and use pattern of dissolving strips.

**Stability studies** must demonstrate that **product quality and performance are maintained** throughout labeled shelf life under anticipated storage and distribution conditions. For dissolving strips, critical stability parameters include: **physical integrity** (resistance to cracking, curling, fragmentation); **moisture content and hygroscopic behavior** (critical for film dissolution characteristics); **nicotine content and degradation product formation**; **flavor stability**; and **dissolution performance** (time to complete dissolution, nicotine release kinetics). Zolv's announcement of **"two-year shelf stability"** illustrates the stability claims that must be substantiated with empirical data under ICH Q1A(R2) conditions or equivalent (Nicotine Insider) .

**2.2.2 Toxicological Evaluation** **Toxicological evaluation** for dissolving strip PMTAs must address **intrinsic product toxicity** and **comparative risk** relative to reference products, informing both absolute safety assessment and APPH determination.

| Toxicology Domain | Study Types | Relevant Endpoints |
|---|---|---|
| In vitro screening | Cytotoxicity, genotoxicity, oxidative stress | Cell viability, mutagenicity, reactive oxygen species |

| Toxicology Domain | Study Types | Relevant Endpoints |
|---|---|---|
| Local effects | Oral mucosal irritation, sensitization | Histopathology, inflammatory markers, barrier function |
| Systemic toxicity | Repeat-dose exposure studies | Organ toxicity, cardiovascular effects, metabolic changes |
| Reproductive/developmental | Teratogenicity, fertility studies | Embryofetal development, reproductive performance |
| Comparative analysis | Head-to-head with cigarettes, NRTs | HPHC exposure, biomarker of effect differences |

*Table 4: Toxicological evaluation framework for dissolving strip PMTA*

**In vitro toxicity testing** provides mechanistic screening and hazard identification. Standard assays include: **cytotoxicity** using relevant cell lines (oral epithelial cells, lung epithelial cells for potential aspiration risk); **genotoxicity** (Ames bacterial mutagenicity, chromosomal aberration in mammalian cells, micronucleus formation); and **oxidative stress and inflammatory response markers**. These assays identify potential biological activities requiring further investigation and contribute to weight-of-evidence safety assessment.

**In vivo toxicity studies** may be warranted based on in vitro findings, product characteristics, and intended use patterns. For orally dissolving products, relevant endpoints include: **oral mucosal irritation and histopathology** from repeated exposure; **gastrointestinal effects** from swallowed dissolved material; **systemic toxicity** following chronic exposure; and **reproductive and developmental toxicity** given nicotine's established adverse effects on fetal development. Study design must account for **route-specific exposure** (buccal absorption, partial ingestion) rather than assuming equivalence to other administration routes.

**Comparative toxicological analysis** is essential for APPH support. The FDA has consistently emphasized that novel products must demonstrate **reduced exposure to harmful and potentially harmful constituents (HPHCs)** relative to combustible cigarettes (Broughton) (HHS.gov) . For dissolving strips, which eliminate combustion entirely, this analysis should demonstrate **substantial reductions in carbonyl compounds, volatile organic compounds, polycyclic aromatic hydrocarbons, and tobacco-specific nitrosamines**. However, the absence of combustion does not eliminate all toxicological concerns: **nicotine itself presents cardiovascular and developmental risks**, and **non-nicotine constituents** (film polymers, flavoring agents, degradation products) require specific evaluation.

**2.2.3 Clinical and Pharmacokinetic Studies** **Clinical and pharmacokinetic studies** provide the **critical bridge** between preclinical characterization and real-world human use, establishing nicotine delivery profiles and informing both efficacy and risk assessment.

**Pharmacokinetic (PK) studies** must characterize **nicotine absorption, distribution, metabolism, and excretion (ADME)** following dissolving strip use. Standard designs employ **crossover protocols** comparing the investigational product to reference products: **combustible**

**cigarettes** (for abuse liability and switching potential assessment); **approved nicotine replacement therapies** (for therapeutic benchmarking); and potentially **competing novel products** (for competitive positioning). Key PK parameters include:

| Parameter | Definition | Regulatory Significance |
|---|---|---|
| Cmax | Maximum plasma nicotine concentration | Abuse liability indicator; satisfaction potential |
| Tmax | Time to maximum concentration | Onset speed; reinforcement timing |
| AUC | Area under concentration-time curve | Total nicotine exposure; dependence potential |
| t½ | Elimination half-life | Dosing frequency; accumulation risk |

*Table 5: Key pharmacokinetic parameters for dissolving strip evaluation*

Zolv's claim that **"a 2 mg version can match the satisfaction of a 6 mg pouch"** due to **"rapid, efficient onset"** illustrates the type of **comparative PK claim requiring empirical support** (Nicotine Insider) . Such claims, if substantiated, may support favorable APPH determination by demonstrating **efficient nicotine delivery with lower total content**, potentially reducing dependence liability while maintaining smoker satisfaction. However, **rapid onset also raises abuse liability concerns** that must be addressed through comprehensive clinical evaluation.

**Human factors and use-pattern studies** examine **actual consumer behavior** in realistic or simulated conditions. Critical questions for dissolving strips include: **duration of oral retention** (affects absorption completeness); **chewing or manipulation behaviors** (may accelerate or alter release); **swallowing versus expectoration** of dissolved material (affects gastrointestinal nicotine exposure); **concurrent food or beverage consumption** (may affect absorption); and **patterns of repeated use** within short intervals (may produce "stacking" effects). These behaviors may **substantially modify nicotine delivery** compared to standardized laboratory protocols, with implications for both efficacy and risk.

**Clinical safety studies** identify and characterize **adverse events** associated with product use. Relevant endpoints include: **oral mucosal effects** (irritation, ulceration, altered sensation, allergic reactions); **gastrointestinal symptoms** (nausea, dyspepsia, altered bowel habits); **cardiovascular effects** (heart rate, blood pressure changes, arrhythmia risk); and **neurological effects** (dizziness, headache, sleep disturbance, cognitive effects). Study populations should include **demographic diversity** representative of intended users, with particular attention to **vulnerable populations** (cardiovascular disease, pregnancy, adolescence) where ethical inclusion is possible.

### 2.3 Abuse Liability Assessment

**2.3.1 Dependence Potential Evaluation** **Abuse liability assessment** has emerged as a **critical and often determinative component** of PMTA evaluation, directly addressing the APPH standard's concern with how product characteristics affect patterns of use and addiction potential.

**Pharmacological determinants of abuse liability** for dissolving strips center on **nicotine delivery kinetics and sensory characteristics**. The **rate of nicotine absorption and rise to peak arterial concentration** is strongly associated with **subjective reward and reinforcement magnitude**—faster onset produces more intense effects and greater abuse liability. Buccal absorption from dissolving strips typically produces **intermediate onset** between the rapid pulmonary delivery of cigarettes/ENDS and the slower gastrointestinal absorption of swallowed nicotine products. This positioning may offer **favorable balance**: sufficiently rapid to satisfy adult smokers seeking cigarette alternatives, sufficiently gradual to reduce abuse liability relative to cigarettes.

**Comparative abuse liability assessment** positions dissolving strips against established products with characterized profiles:

| **Product Category** | **Typical Abuse Liability** | **Relevant Comparator Role** |
|---|---|---|
| Combustible cigarettes | High | Primary harm source; switching target |
| ENDS/high-nicotine e-cigarettes | High to very high | Direct competitor; youth concern |
| Smokeless tobacco (moist snuff) | Moderate to high | Oral delivery reference |
| Nicotine pouches | Moderate | Emerging competitor; recent precedent |
| Nicotine gum/lozenge | Low to moderate | Approved NRT benchmark |
| Nicotine patch | Very low | Therapeutic safety standard |

*Table 6: Abuse liability positioning for dissolving strip comparative assessment*

The **FDA's January 2025 authorization of Zyn nicotine pouches** established that **moderate abuse liability is not automatically disqualifying** if balanced by demonstrated adult smoker benefit and adequate youth protections (Psychology Today) . This precedent provides important guidance for dissolving strip applications, though product-specific evidence remains essential.

**Behavioral and subjective effects studies** characterize the **qualitative experience** of dissolving strip use. Standard methodologies include: **visual analog scales** for "drug liking," "good effects," "bad effects," and "desire to use again"; **physiological measures** (heart rate, blood pressure, skin temperature) correlating with nicotine effect; and **behavioral choice procedures** assessing willingness to work for access or preference versus alternative products. These data **integrate with PK parameters** to characterize the **temporal relationship between nicotine exposure and subjective effect**, informing predictions of use patterns and dependence development.

**2.3.2 Youth Appeal and Initiation Risk** **Youth appeal and initiation risk assessment** has become **perhaps the most scrutinized element** of PMTA evaluation, with **numerous marketing denial orders issued based on inadequate youth protection** (Congress.gov) (nih.gov) . For

dissolving strips, this assessment must address **multiple dimensions of product attractiveness to underage users**.

**Sensory characteristics** require careful evaluation. **Flavor profiles**, while important for adult smoker acceptance, are **strongly associated with youth initiation**. The FDA's flavor enforcement priorities have targeted **fruit, candy, dessert, and certain mint/menthol varieties** in ENDS products, though menthol has received more nuanced treatment given its established role in adult smoker preferences (Congress.gov) . Dissolving strips are marketed in **multiple flavors including fruit, dessert, and mint varieties** (PRWeb) (Nicotine Insider) , requiring manufacturers to demonstrate that **flavor offerings are justified by adult smoker benefit and do not disproportionately attract youth**.

| Youth Appeal Factor | Dissolving Strip Characteristic | Risk Mitigation Requirement |
|---|---|---|
| Rapid onset | Fast dissolution, quick nicotine delivery | Demonstrate adult switching necessity; limit abuse liability |
| Flavor variety | Multiple non-tobacco flavors | Evidence of adult preference; youth perception studies |
| Discreet use | No odor, no visible residue, rapid consumption | Packaging differentiation; use detection limitations |
| Concealability | Small size, familiar format (breath strip-like) | Age-verified sales; marketing restrictions |
| Perceived reduced risk | "Clean," "tobacco-free" positioning | Clear addiction warnings; no unauthorized health claims |

*Table 7: Youth appeal factors and mitigation requirements for dissolving strips*

**Discrete use characteristics** present **distinctive youth appeal concerns**. The **"leaves no trace"** feature emphasized in marketing—**"no butts, no cartridges, no pouches, no odor, no visible exhalation"** (Nicotine Insider) —eliminates many **detection mechanisms** that might otherwise limit youth use. Parents, teachers, and authorities cannot readily identify dissolving strip use through sensory cues or physical evidence, **reducing barriers to youth experimentation and regular use**. The Minnesota Department of Health specifically identified this concern, noting that nicotine strips **"dissolve quickly in the mouth, delivering nicotine discreetly"** with **"youth appeal and misuse potential"** (MN Dept. of Health) (MN Dept. of Health) .

**Gateway and progression risk modeling** must evaluate whether **dissolving strip use increases subsequent cigarette smoking or other harmful tobacco product use**. While some public health advocates argue that **any nicotine product may serve as a gateway**, empirical evidence for this pathway remains contested and product-specific. The FDA's APPH evaluation requires **evidence-based assessment of progression risk**, considering both product characteristics (rapid onset may increase reinforcement and subsequent seeking of stronger products) and population-level behavioral dynamics (availability of alternatives may divert from or delay cigarette initiation).

## 3. Manufacturing and Quality Systems

### 3.1 Good Manufacturing Practice (GMP) Compliance

**3.1.1 Facility Registration and Inspection** **Good Manufacturing Practice (GMP) compliance** forms an **essential foundation for PMTA approval and ongoing market authorization**. The FDA requires that **all tobacco product manufacturing facilities register with the agency** and maintain inspection readiness, with particular scrutiny applied to facilities producing products under PMTA review or marketing authorization (Broughton) .

For dissolving strip manufacturers, **facility registration must encompass all operational sites**: active pharmaceutical ingredient (nicotine) handling and incorporation; film formation and strip production; cutting, packaging, and labeling; quality control testing; and storage and distribution. **International facilities are subject to equivalent requirements**, with FDA conducting foreign inspections or accepting inspection reports from trusted regulatory partners under mutual recognition agreements.

**Pre-approval inspection (PAI) readiness** is critical for PMTA success. The FDA may conduct PAIs to verify that: **manufacturing processes described in PMTA submissions are actually implemented**; **facilities meet GMP standards**; and **data integrity is maintained** throughout operations. For dissolving strips, PAI focus areas typically include: **nicotine handling and accountability** (controlled substance considerations given pharmacological potency); **critical process parameters for film formation and drying** (affecting dissolution performance and content uniformity); **in-process testing and release specifications**; and **batch record documentation** enabling complete traceability.

Zolv's disclosure that **"manufacturing is handled at a GMP-certified facility in Sweden using a proprietary process that ensures accuracy of dosing and product stability"** illustrates the **GMP infrastructure required for PMTA-compliant production** (Nicotine Insider) . The emphasis on **"pharmaceutical-grade nicotine, strictly FDA G.R.A.S. additives, and precision dosing"** reflects the **quality standards that must be demonstrated through documentation and inspection** (Nicotine Insider) .

**3.1.2 Quality Control Systems** **Robust quality control systems** must ensure that **every batch of dissolving strips meets predetermined specifications** for identity, strength, quality, and purity. These systems encompass the complete manufacturing lifecycle from incoming materials through finished product release.

| Quality Control Element | Specific Requirements for Dissolving Strips |
|---|---|
| Incoming material testing | Nicotine identity, assay, impurity profile; excipient grade verification |
| In-process controls | Solution viscosity, casting thickness, drying parameters, moisture content |
| Finished product testing | Dimensions, unit mass, nicotine content uniformity, dissolution time, microbial limits |
| Stability monitoring | Real-time and accelerated studies; annual product review |

| Quality Control Element | Specific Requirements for Dissolving Strips |
|---|---|
| Deviation management | Root cause analysis, corrective/preventive action, effectiveness verification |

*Table 8: Quality control system elements for dissolving strip manufacturing*

**Batch release specifications** must be **justified by product development data and linked to clinical performance**. For dissolving strips, critical attributes include: **physical dimensions** (length, width, thickness—Zolv specifies **"0.07 mm thick"** (Nicotine Insider) ); **unit mass and uniformity** (affecting dose consistency); **nicotine content and uniformity** (typically expressed as mg per strip with tight tolerance); **dissolution time and completeness** (affecting user experience and absorption); **moisture content** (critical for stability and performance); **microbial limits** (given oral use and aqueous processing); and **packaging integrity** (moisture protection essential for shelf life).

**In-process controls** supplement finished product testing by **monitoring critical parameters during manufacturing** rather than relying solely on end-point analysis. For film casting operations, relevant controls include: **solution viscosity and solids content** (affecting casting uniformity); **casting thickness and weight** (directly affecting dose); **drying temperature, humidity, and time** (affecting moisture content and dissolution); and **environmental conditions** (particulate, microbial control). These parameters are monitored continuously or at defined intervals, with **predetermined action limits triggering investigation and potential process adjustment**.

**Deviation investigation and corrective action procedures** address instances where **specifications are not met or processes operate outside validated ranges**. Each deviation requires: **documentation and immediate containment**; **investigation to identify root cause**; **impact assessment** for affected product lots; **corrective and preventive action (CAPA)** to prevent recurrence; and **effectiveness verification** through trend monitoring. The FDA evaluates quality system maturity during PMTA review and inspection, with **immature or reactive systems representing significant approval risks**.

### 3.2 Supply Chain Documentation

**3.2.1 Ingredient Sourcing and Traceability** **Comprehensive supply chain documentation** ensures that **all ingredients used in dissolving strips meet quality specifications and can be traced from source to finished product**, supporting quality investigations, recall operations, and regulatory inquiries.

**Supplier qualification programs** evaluate potential vendors against predetermined quality criteria. For **critical suppliers**—nicotine manufacturers and film matrix polymer suppliers—qualification typically includes: **quality system audits** verifying GMP compliance; **sample evaluation** against specifications; **initial shipment monitoring** before full qualification; and **ongoing performance surveillance** through incoming testing results and periodic re-audits. The qualification process must address **not only direct suppliers but upstream supply chain nodes**, with particular attention to **nicotine source documentation** (tobacco origin or synthetic manufacturing site) and **excipient regulatory status** (food-grade, pharmaceutical-grade, or equivalent with justification).

**Certificate of analysis (CoA) requirements** specify documentation that must accompany each raw material shipment. CoA content includes: **supplier identification and batch number**; **manufactur-**

**ing date and release date**; **test results against agreed specifications**; and **authorized quality unit signature**. For nicotine, CoA must include: **identity confirmation** (spectroscopic or chromatographic); **assay/purity determination**; **impurity profile** including specified and unspecified degradation products; **residual solvent content**; and **stereochemical purity** (for synthetic nicotine). The CoA system relies on **supplier quality systems and analytical competence**, with manufacturer verification through **periodic independent testing** to confirm accuracy.

**Chain-of-custody documentation** maintains **traceability through manufacturing operations**, linking raw material batches to finished product batches through comprehensive production records. This requires: **unique lot numbering** for all materials and products; **production records documenting material usage quantities and batch numbers**; **reconciliation procedures verifying complete material accounting** (theoretical versus actual yield); and **distribution records enabling customer notification** for recall or quality advisory purposes. Electronic systems for documentation and traceability are increasingly employed but must be **validated to ensure data integrity and regulatory compliance** (21 CFR Part 11 considerations).

**3.2.2 Manufacturing Process Validation** **Manufacturing process validation** demonstrates that **the defined process consistently produces product meeting predetermined specifications** when operated within established parameters. FDA guidance emphasizes **process understanding and control**, with validation activities spanning three stages: **process design, process qualification, and continued process verification** (Broughton) .

**Process design** establishes the manufacturing process based on **product development data and scientific understanding**. For dissolving strips, critical process parameters may include: **solution preparation** (nicotine concentration, polymer hydration time and conditions, mixing intensity and duration, deaeration); **film casting** (casting speed, gap setting, substrate temperature, air flow); **drying** (temperature profile, humidity, time, air velocity); **conditioning and cutting** (equilibration conditions, cutting dimensions, collection); and **packaging** (material specification, sealing conditions, environmental control). Design of experiments (DoE) approaches may efficiently explore **multi-factorial parameter spaces**, with quality by design (QbD) principles integrating **product quality attributes with process understanding**.

**Process qualification** demonstrates that **the commercial-scale process performs as intended**, typically through **consecutive successful production batches** under normal operating conditions. Acceptance criteria for qualification batches must encompass **all critical quality attributes**, with statistical evaluation of **batch-to-batch consistency** (typically coefficient of variation <5–10% for critical parameters). The number of qualification batches depends on process complexity and variability, with **three consecutive successful batches** representing common practice.

**Continued process verification** maintains **ongoing assurance that the process remains in a state of control** throughout commercial production. This includes: **routine monitoring of critical parameters and quality attributes** with statistical process control; **periodic data review for trends, shifts, and emerging patterns**; **annual product review** encompassing all batches, complaints, deviations, and changes; and **change control procedures** ensuring that process modifications are properly evaluated and approved. For dissolving strips, **moisture sensitivity** of the film matrix may require **enhanced environmental monitoring and control** to prevent process drift.

**Change control and post-market modification procedures** address the reality that **manufacturing processes evolve** in response to experience, supplier changes, capacity expansion, and regulatory feedback. The FDA distinguishes: **minor changes** reportable through annual reporting (e.g.,

supplier change with equivalent qualification); **moderate changes** requiring supplemental notification (e.g., manufacturing site change, process parameter range expansion); and **major changes** potentially requiring new PMTA submission (e.g., fundamental formulation change, novel manufacturing technology). For dissolving strips, **formulation modifications affecting nicotine delivery, dissolution characteristics, or major excipient changes** would likely trigger higher reporting requirements or new application submission.

## 4. Labeling and Marketing Restrictions

### 4.1 Product Labeling Requirements

**4.1.1 Mandatory Disclosures** **Product labeling for FDA-authorized dissolving strips** must include **specific disclosures mandated by the FD&C Act and FDA regulations**, designed to ensure consumer understanding and enable informed decision-making while supporting public health protection.

| Mandatory Disclosure | Specific Requirements | Regulatory Basis |
|---|---|---|
| Nicotine content | mg per strip/unit; per package total | Section 910(b)(1)(B); consumer information |
| Addiction warning | "WARNING: This product contains nicotine. Nicotine is an addictive chemical." | 21 CFR Part 1143; TCA Section 201(b) |
| Age restriction | "21+" or equivalent; sale prohibition to minors | Federal Tobacco 21 law (2019) (jjccgroup.org) |
| Pregnancy warning | Risk of nicotine exposure during fetal development | FDA guidance; public health protection |
| Directions for use | Placement, retention time, frequency limitations | Ensuring appropriate use; reducing misuse |

*Table 9: Mandatory labeling disclosures for nicotine dissolving strips*

**Nicotine content disclosure** is fundamental, with labeling required to specify **quantity per unit (typically mg per strip)** and potentially **per package** to enable consumer comparison and intake management. For products with **multiple strengths**—such as Zolv's **1 mg and 2 mg** variants (Nicotine Insider) —**clear differentiation and prominent display** are essential to prevent consumer confusion and inadvertent overconsumption. The disclosure must account for **both nominal content and anticipated variation**, with appropriate overage to ensure stated content is not exceeded.

**Addiction warning statements** are mandatory for all tobacco products, with **specific language prescribed by FDA regulation**: **"WARNING: This product contains nicotine. Nicotine is an addictive chemical."** The warning must appear on **principal display panels** with specified **minimum font size, contrast, and placement requirements** designed to maximize noticeability. For dissolving strips, which may be **perceived as less harmful or addictive due to pharmaceutical-like presentation**, clear addiction warnings are **particularly important for risk communication**.

**Age restriction statements** reflect the **federal Tobacco 21 law enacted in 2019**, which established **21 as the minimum age for tobacco product purchase** (jjccgroup.org) . Labeling must prominently display this restriction, reinforcing legal prohibitions and supporting retailer compliance. **Pregnancy warnings** address the **specific risks of nicotine exposure during fetal development**, including potential adverse effects on **brain and lung development**, and are typically required based on FDA guidance even if not explicitly mandated by regulation for all product categories.

**4.1.2 Prohibited Claims** **Prohibited claims restrictions** prevent dissolving strip manufacturers from making **unsubstantiated or inappropriate claims** that could mislead consumers, trigger alternative regulatory pathways, or undermine public health protection.

| Claim Category | Prohibition | Consequence of Violation |
|---|---|---|
| Therapeutic/cessation claims | Any claim of smoking cessation or nicotine dependence treatment assistance | Triggers drug/device pathway (NDA/ 510(k) required) (Counter Tobacco) |
| Modified risk claims | Any claim of reduced disease risk or harm relative to other tobacco products | Requires separate MRTP authorization; prohibited without approval |
| Comparative harm reduction | Implicit or explicit statements of safety or reduced risk | Misbranding violation; enforcement action |
| FDA "approval" | Any statement that FDA has "approved" the product | Prohibited by statute; tobacco products are "authorized," not "approved" |

*Table 10: Prohibited claims for nicotine dissolving strips*

**Therapeutic or cessation claims** represent the **most critical prohibition**. Any explicit or implicit claim that the product **helps users quit smoking, reduces nicotine dependence, or assists with cessation** transforms the product from a **tobacco product into a drug or medical device**, requiring approval through the **New Drug Application (NDA) or Premarket Notification (510(k)) pathways** rather than PMTA (Counter Tobacco) . Current market positioning of dissolving strips **explicitly avoids therapeutic claims**, emphasizing instead **"convenience, taste, and discretion"** and **"social acceptability"** without mention of cessation assistance (Nicotine Insider) . This positioning, while limiting certain marketing opportunities, **avoids the substantially more burdensome drug approval pathway** and enables access to adult consumers regardless of quit motivation.

The **boundary between permissible descriptive claims and prohibited therapeutic claims** requires careful navigation. **Consumer testimonials** stating that a product "helps me stop vaping" (Nicotine Insider) may be permissible if **not adopted by the manufacturer as product claims**, but manufacturer adoption or promotion of such testimonials risks therapeutic claim classification. Simi-

larly, **"harm reduction" positioning**, if carefully contextualized as **behavioral rather than health outcome**, may be permissible, but **explicit risk reduction claims trigger MRTP requirements**.

**Modified Risk Tobacco Product (MRTP) claims**—assertions that a product **presents reduced risk of tobacco-related disease or is less harmful than other tobacco products**—are **prohibited without separate MRTP authorization** under **Section 911 of the FD&C Act**. The MRTP pathway requires **even more extensive scientific evidence than PMTA**, including **long-term epidemiological data or well-controlled clinical trials** demonstrating risk reduction. **No dissolving strip product has pursued or received MRTP authorization**, and manufacturers must carefully avoid language that could be interpreted as unauthorized modified risk claims.

### 4.2 Marketing and Advertising Constraints

**4.2.1 Audience Targeting Restrictions** **Marketing and advertising for FDA-authorized dissolving strips** operates under **substantial constraints** designed to **minimize youth exposure and appeal** while preserving ability to communicate with adult smokers. These constraints derive from **multiple regulatory layers**: the FD&C Act's prohibition on marketing to youth; **FDA guidance and enforcement priorities**; **Federal Trade Commission oversight** of advertising claims; and **state and local marketing restrictions**.

| Marketing Channel/Technique | Restriction Level | Specific Requirements |
|---|---|---|
| Social media | High scrutiny | Age-gating, platform restrictions, monitoring for youth exposure |
| Influencer marketing | Generally prohibited or heavily restricted | Age verification of influencer and audience; content review |
| Event sponsorship | Restricted | Exclusion of youth-oriented events; adult-only attendance verification |
| Television/radio | Limited | Time-of-day restrictions; audience composition thresholds |
| Print media | Moderate | Publication audience demographics; placement context |
| Point-of-sale | Permitted with restrictions | Age verification; display limitations; warning visibility |

*Table 11: Marketing channel restrictions for nicotine dissolving strips*

**Prohibition on youth-oriented marketing** encompasses **not merely explicit targeting of minors but also marketing that uses imagery, themes, or channels with substantial youth audience composition**. The Minnesota Department of Health specifically noted that **"tobacco companies often promote these products through influencers on social media"** and that **"many brands offer**

**rewards programs that encourage continued use,"** tactics that **"can make them especially appealing to young people"** (MN Dept. of Health) . For PMTA-authorized products, **marketing plans must demonstrate how social media presence will be age-gated and monitored** to prevent youth targeting.

**Social media and influencer marketing** face **particular scrutiny** given documented youth audience concentration on these platforms. Any influencer partnerships must include: **age verification of influencer and audience composition analysis** demonstrating predominant adult reach; **content review and approval procedures**; and **monitoring and takedown protocols** for unauthorized or youth-oriented content. The FDA has **actively enforced against youth-oriented social media marketing**, with numerous warning letters citing inappropriate influencer partnerships (MN Dept. of Health) .

**4.2.2 Post-Market Surveillance Obligations** **Post-market surveillance obligations** ensure that **FDA-authorized products continue to meet public health standards** after market entry, with mechanisms to **detect and address emerging risks** throughout the product lifecycle.

**Adverse event reporting systems** must be established to **collect and evaluate health-related events** associated with product use. Requirements include: **serious adverse events** (death, hospitalization, disability, congenital anomaly, or other serious outcomes) reported to FDA **within 15 calendar days** of receipt; **non-serious adverse events** exceeding expected frequency or severity reported periodically; and **trend analysis and signal detection** to identify emerging safety concerns. For dissolving strips, relevant adverse events might include: **severe oral mucosal reactions or allergic responses**; **nicotine toxicity symptoms from overuse**; and **cardiovascular events in susceptible individuals**.

**Annual reporting obligations** maintain FDA awareness of **product performance, manufacturing changes, and emerging data**. Reports must include: **sales and distribution volumes** by product variant and region; **advertising and promotional activities** with expenditure and audience data; **consumer research findings** including perception and use studies; **manufacturing and quality performance** including deviations, complaints, and corrective actions; and **any new scientific information** relevant to APPH determination. This **ongoing dialogue enables FDA to identify trends warranting regulatory response**.

**Real-world evidence collection** may be **mandated as a condition of marketing authorization**, particularly where **pre-market data has limitations** or **novel product characteristics create uncertainty**. For dissolving strips, post-market studies might address: **long-term use patterns and dependence development** in real-world populations; **switching and cessation behaviors** with population-level impact; **youth initiation and use prevalence** through surveillance enhancement; and **health outcomes** in extended follow-up. Such evidence can support **regulatory modifications**—including strengthened restrictions or, conversely, expanded access if favorable data emerges.

## 5. Industry Precedents and Practical Considerations

### 5.1 Documented Authorization Successes

**5.1.1 SENO Nicotine Film Case** The **SENO nicotine film case** represents the **landmark achievement of first-round PMTA approval for a dissolving strip format**, establishing both **feasibility and a compliance template** for subsequent market entrants. In **January 2025**, SENO announced that its **"FDA-compliant nicotine film"** had received **"first-round PMTA approvals"**

with assigned application numbers **PM0010199, PM0010173, and PM0010176** (PRWeb) .

| **SENO Authorization Details** | **Significance** |
|---|---|
| First-round approval without resubmission | Demonstrates comprehensive initial submission quality; no major deficiency cycle |
| Multiple simultaneous authorizations (3 products) | Scalable application preparation; platform approach validated |
| Flavor variety authorized (Mint, Peach, Cheese) | FDA evaluated flavor appeal within overall APPH context; not automatic barrier |
| Nine additional flavors pending | Ongoing regulatory engagement; portfolio expansion pathway |
| "Full FDA compliance" emphasis | Recognition that authorization encompasses development, production, and sales |

*Table 12: SENO PMTA authorization significance for dissolving strip category*

This achievement followed what the company described as **"years of rigorous development and testing"** (PRWeb) , illustrating the **substantial investment required for regulatory success**. The **"first-round" characterization** suggests that FDA did **not issue Complete Response Letters requiring substantial additional information**—indicating that SENO's application **proactively addressed reviewer concerns** and met evidentiary thresholds without iterative revision.

The SENO precedent is **particularly significant given the broader PMTA authorization context**. As of early 2023, the FDA had resolved **over 99% of more than 6.5 million timely PMTA applications**, yet granted marketing authorization to **only 23 products**—an authorization rate below **0.001%** (nih.gov) . SENO's success for a **novel product format without established regulatory precedent** demonstrates that **rigorous preparation and comprehensive evidence generation can overcome the extraordinary selectivity of FDA review**.

**5.1.2 Comparative Product Pathways** **Comparative product pathways** provide **additional guidance for dissolving strip PMTA strategy**, with **nicotine pouch authorizations** offering particularly relevant precedent given shared characteristics of **oral, tobacco-leaf-free, discrete nicotine delivery**.

| Authorization | Date | Key Characteristics | APPH Rationale |
|---|---|---|---|
| Verve oral nicotine (discs, chews) | October 2021 | Mint flavors, oral dissolution, no tobacco leaf | Adult smoker switching potential; limited youth data (Counter Tobacco) |
| Zyn nicotine pouches (20 SKUs) | January 2025 | Tobacco and menthol flavors, 3 mg and 6 mg strengths | "Substantial proportion" of adult smokers switched; low youth use observed (Psychology Today) |
| SENO nicotine films (3 SKUs) | January 2025 | Multiple flavors including non-traditional, rapid dissolution | First-round approval; comprehensive compliance framework (PRWeb) |

*Table 13: Oral nicotine product PMTA authorization precedents*

The **Zyn authorization in January 2025** provides the **most developed precedent for oral nicotine products**. FDA explicitly cited **"potential health benefits for adult smokers"** and noted that **"a substantial proportion of adults who use cigarette and/or smokeless tobacco products switched to Zyn pouches, justifying the authorization"** (Psychology Today) . This reasoning —**favorable population-level impact through adult smoker switching**—provides a template for dissolving strip APPH arguments. However, FDA simultaneously emphasized that authorized products **"are not without risk and not considered 'safe,'"** maintaining appropriate risk communication (Psychology Today) .

**Lessons from denied applications and Complete Response Letters** are equally instructive. Common deficiencies leading to marketing denial orders include: **insufficient toxicological data** to characterize product-specific risks; **inadequate abuse liability assessment** with particular youth appeal concerns; **lack of population-level impact modeling** or unrealistic behavioral assumptions; **failure to propose adequate youth access restrictions**; and **manufacturing quality system deficiencies**. For dissolving strip applicants, **investment in comprehensive, product-specific evidence generation across all PMTA components** appears essential for avoiding early-stage denial.

### 5.2 Strategic Development Considerations

**5.2.1 Timeline and Resource Planning** **Strategic development of PMTA-compliant dissolving strips** requires **realistic timeline and resource planning**, with substantial investment of **time, capital, and specialized expertise**.

| Development Phase | Typical Duration | Key Activities | Cost Drivers |
|---|---|---|---|
| Product formulation and optimization | 3–6+ months | Polymer selection, nicotine incorporation, flavor development, stability screening | R&D personnel, materials, analytical testing |
| Analytical method development and validation | 3–6 months | Nicotine assay, dissolution testing, impurity profiling, stability-indicating methods | Equipment, reference standards, validation studies |
| Stability studies | 6–24+ months | Real-time and accelerated aging, package integrity, shelf life justification | Storage facilities, testing, statistical analysis |
| Nonclinical toxicology | 6–18 months | In vitro screening, in vivo studies, comparative risk assessment | CRO fees, animal care, pathology, report preparation |
| Clinical pharmacokinetics and safety | 6–18 months | Crossover PK studies, use-pattern studies, safety monitoring | Clinical site fees, bioanalytical testing, subject compensation |
| Manufacturing scale-up and validation | 6–12 months | Process development, equipment qualification, batch consistency demonstration | Facility modification, equipment purchase, validation batches |
| PMTA document preparation and submission | 3–6 months | Scientific writing, regulatory strategy, FDA pre-submission meetings | Regulatory consultants, legal review, submission fees |

*Table 14: PMTA development timeline and cost structure for dissolving strips*

**Estimated total timeline: 12–24+ months** for well-resourced organizations, with **novel product formats or complex formulations at the upper end**. **Estimated costs: $500,000–$2+ million per SKU**, with **multi-SKU portfolios requiring careful prioritization** as each distinct flavor, strength, or formulation requires **separate PMTA submission** (though some efficiencies may be achieved through platform approaches to toxicology and manufacturing validation).

**Zolv's announced fundraising strategy**—targeting capital to **"support its FDA PMTA submission, scale production, and build U.S. distribution"** (Nicotine Insider) —illustrates the **integrated resource requirements for market entry**. The company's **phased approach** (European market establishment followed by U.S. PMTA preparation) allows **revenue generation and operational learning** while building regulatory readiness, though this strategy also **delays U.S. market access** and risks **competitive preemption by earlier entrants**.

**Parallel scientific and regulatory workstreams** are essential for timeline efficiency. While product development proceeds, **regulatory strategy should be refined through FDA pre-submission meetings**, which provide opportunity to: **confirm study designs**; **discuss data requirements**; **identify potential concerns**; and **establish reviewer relationships** before substantial resource commitment. The FDA encourages such engagement, though **meeting availability and responsiveness have been subject to resource constraints** (Office of Inspector General) .

**5.2.2 Post-Authorization Compliance** **Post-authorization compliance** maintains **market access and protects against enforcement action**, with obligations **extending throughout product commercialization** and potentially **increasing in stringency** based on real-world performance.

**Marketing order conditions and limitations** bind the authorization holder, with **violation potentially resulting in order revocation**. Typical conditions include: **flavor restrictions** (specific authorized flavors only); **nicotine concentration limits**; **packaging specifications** (child-resistant, warning placement); **marketing channel prohibitions**; and **post-market study requirements**. These conditions are **legally enforceable** and may be **modified by FDA** based on emerging evidence or changed circumstances.

| Post-Market Obligation | Frequency/Trigger | Content Requirements |
|---|---|---|
| Adverse event reporting | Serious: 15 days; Periodic: quarterly/annual | Health events, product defects, use errors |
| Annual report | Annual | Sales, marketing, manufacturing, quality, new scientific information |
| Substantial equivalence report | Product modifications | Comparison to authorized product, change justification |
| New PMTA | Major modifications | Full application for fundamentally altered product |
| Real-world evidence submission | As mandated in order | Longitudinal use patterns, health outcomes, population impact |

*Table 15: Post-market compliance obligations for authorized dissolving strips*

**Annual reporting obligations** require **comprehensive information submission** maintaining FDA awareness of: **product sales and distribution volumes**; **advertising and promotional activities** with expenditure data; **consumer research findings**; **manufacturing and quality performance**;

and **any new scientific information** relevant to APPH determination. This **ongoing regulatory dialogue** enables FDA to **identify trends warranting regulatory response**—including potential **marketing order modification or withdrawal**.

**Modification reporting requirements** address **product evolution after authorization**. The FDA distinguishes: **minor changes** reportable through annual reporting (e.g., supplier change with equivalent qualification); **moderate changes** requiring supplemental notification (e.g., manufacturing site change, process parameter range expansion); and **major changes** potentially requiring new PMTA submission (e.g., fundamental formulation change, novel manufacturing technology, new flavor or strength introduction). For dissolving strips, **flavor portfolio expansion**—such as SENO's **nine additional flavors pending approval** (PRWeb) —requires **regulatory submission and authorization before commercialization**, even when platform chemistry is established.

## 6. Distinction from Alternative Regulatory Pathways

### 6.1 Drug/Medical Device Pathway

**6.1.1 Nicotine Replacement Therapy (NRT) Classification** The **drug/medical device pathway** for nicotine products represents a **fundamentally different regulatory framework** that dissolving strip manufacturers must **carefully avoid unless specifically pursuing therapeutic indications**. **Nicotine Replacement Therapy (NRT) products**—including **gum, transdermal patch, lozenge, inhaler, and nasal spray**—have been **approved by FDA as drugs** under the **New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) pathways**, based on **demonstrated safety and efficacy for smoking cessation** (Counter Tobacco) .

| **Regulatory Pathway Comparison** | **Tobacco Product (PMTA)** | **Drug Product (NDA/ ANDA)** |
|---|---|---|
| **Primary indication** | Recreational nicotine use; adult smoker alternative | Smoking cessation; nicotine dependence treatment |
| **Efficacy standard** | Not required; APPH population-level assessment | Required; demonstrated superiority to placebo |
| **Safety standard** | Relative risk acceptable; youth protection paramount | Absolute safety; risk-benefit for individual patients |
| **Clinical trials** | Behavioral/pharmacokinetic studies; population modeling | Controlled efficacy trials; long-term safety follow-up |
| **Manufacturing** | Tobacco product GMP; quality system expectations | Drug GMP (21 CFR Parts 210-211); more stringent |
| **Labeling claims** | Prohibited: therapeutic, cessation, modified risk | Required: indication, dosing, efficacy, safety |
| **Post-market** | Surveillance, annual reporting, order conditions | Adverse event reporting, REMS, label updates |

| Regulatory Pathway Comparison | Tobacco Product (PMTA) | Drug Product (NDA/ ANDA) |
|---|---|---|
| **Review center** | Center for Tobacco Products (CTP) | Center for Drug Evaluation and Research (CDER) |

*Table 16: Regulatory pathway comparison for nicotine products*

**NRT classification requires**: **demonstration of efficacy for specific therapeutic indication** (typically smoking cessation or reduction); **establishment of safety profile adequate for intended use population** including vulnerable groups; and **compliance with drug GMP standards** (21 CFR Parts 210-211) typically **more stringent than tobacco product GMP expectations**. The approval process involves **CDER review** with **different scientific standards and evidentiary requirements** than CTP PMTA evaluation.

**Current market positioning of dissolving strips explicitly avoids therapeutic claims** to maintain tobacco product classification. Zolv's marketing emphasizes **"convenience, taste, and discretion"** and **"social acceptability"**, with **no mention of cessation assistance or therapeutic benefit** (Nicotine Insider) . This positioning, while **limiting certain marketing opportunities**, **avoids the substantially more burdensome drug approval pathway** and enables **access to adult consumers regardless of quit motivation**—a **larger potential market** than the **medically-motivated cessation population**.

The **boundary between permissible descriptive claims and prohibited therapeutic claims** requires **careful legal and regulatory navigation**. **Consumer testimonials** stating that a product "helps me stop vaping" (Nicotine Insider) may be **permissible if not adopted by manufacturer as product claims**, but **manufacturer adoption or promotion risks therapeutic claim classification**. Similarly, **"harm reduction" positioning**, if **carefully contextualized as behavioral rather than health outcome**, may be permissible, but **explicit risk reduction claims trigger MRTP requirements** or **potential drug reclassification**.

**6.1.2 Combination Product Considerations** **Combination product considerations** arise when dissolving strips **incorporate components that might independently qualify as drugs or devices**, potentially triggering **dual FDA center jurisdiction**. The **Office of Combination Products** determines **primary jurisdiction** based on **"primary mode of action"**—the single mode of action that provides the **most important therapeutic action** (HHS.gov) .

For **dissolving strips delivering nicotine**, the **primary mode of action is pharmacological** (nicotine delivery), supporting **CTP jurisdiction as a tobacco product**. However, **incorporation of additional active ingredients with therapeutic intent**—such as **appetite suppressants, cognitive enhancers, anxiolytics, or other pharmacologically active agents**—could **support CDER jurisdiction or combination product classification**. Similarly, **incorporation of device components for active delivery enhancement** (e.g., **iontophoretic or ultrasonic acceleration of buccal absorption**) might trigger **Center for Devices and Radiological Health (CDRH)** involvement.

Manufacturers pursuing **innovative dissolving strip formulations** must **evaluate combination product implications early in development**, as **jurisdiction determination substantially affects regulatory strategy, timeline, and cost**. **CTP consultation with CDER or CDRH** may

be advisable for **borderline products**, with **formal combination product classification requests** providing **binding jurisdiction determination** before substantial investment.

### 6.2 Dietary Supplement Exclusion

**6.2.1 Nicotine Ineligibility for Supplement Classification** **Nicotine is explicitly excluded from the dietary supplement definition by statute**, eliminating any potential for **supplement pathway marketing** and ensuring that **tobacco product classification is the mandatory default** for nicotine-containing products intended for human consumption.

The **Dietary Supplement Health and Education Act of 1994 (DSHEA)** and subsequent FDA regulations establish **specific criteria for dietary supplement classification**: products intended to **supplement the diet**; containing **one or more dietary ingredients** (vitamins, minerals, herbs, amino acids, etc.); intended for **ingestion**; and **not represented as conventional food or sole item of a meal or diet**. **Nicotine fails multiple criteria**: it is **not a dietary ingredient**; it is **not intended to supplement nutritional intake**; and its **pharmacological activity at low doses** is **inconsistent with dietary supplement assumptions of safety**.

More fundamentally, the **TCA and subsequent amendments explicitly classify nicotine-containing products as tobacco products regardless of marketing claims**, **superseding any potential DSHEA argument**. The **2022 "nicotine from any source" amendment** (Counter Tobacco) (Counter Tobacco) **removed any residual ambiguity**, ensuring that **manufacturers cannot circumvent tobacco product regulation through creative product categorization**.

**Attempts to market nicotine products as foods, cosmetics, or general consumer products** have been **unsuccessful and enforcement-prone**. The FDA has **consistently taken action** against products making **unauthorized health claims** or **attempting to exploit regulatory gaps**. For dissolving strips, **any positioning outside tobacco product framework** would face **immediate regulatory challenge**, with **product seizure, injunction, and criminal referral** as potential outcomes.

The **mandatory tobacco product classification**, while **burdensome**, provides **essential market legitimacy** for compliant participants. **PMTA authorization** enables: **lawful interstate commerce**; **access to legitimate distribution channels**; **product liability insurance coverage**; **banking and payment processing services**; and **investor and consumer confidence**. The **comprehensive regulatory framework**, with all its demands, **ultimately protects public health** while enabling **innovation within defined boundaries**—a **balance that unauthorized products cannot achieve**.