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FDA Pathways for AI SaMD: 510(k), De Novo & PMA Guide

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Executive Summary

The regulatory framework for Software as a Medical Device (SaMD) in the United States offers three primary premarket pathways: **510(k), De Novo, and Pre-market Approval (PMA)**. Each path has distinct requirements and is chosen based on device risk, novelty, and the existence of a marketed predicate. For AI/ML-driven SaMD, these decisions must carefully weigh the device's **risk classification** and **technological maturity**. Historically, the FDA's **510(k) pathway** has dominated, clearing the vast majority of moderate-risk devices as "substantially equivalent" to existing predicates (www.nature.com) (www.mdpi.com). By contrast, **De Novo** provides a pathway to Class I or II classification when no legally marketed predicate exists and the relevant controls provide reasonable assurance of safety and effectiveness (FDA). Joshi et al.'s historical cohort comprised 691 AI/ML-enabled medical devices listed through October 19, 2023: about 2.9% used De Novo and 0.4% PMA (Joshi et al.). All pathway percentages cited from that study describe this broader device cohort, rather than standalone SaMD alone. **PMA** generally applies to Class III devices (FDA).

Selecting the appropriate path has major implications. The 510(k) route requires substantial equivalence to a legally marketed predicate; supporting performance evidence can include clinical data (FDA). De Novo filings take longer (typically ~9–12 months on average (www.nature.com)) but establish new device types for future predicates. PMA is FDA's safety-and-effectiveness review for Class III devices, supported by clinical evidence and non-clinical data (FDA).

Recently, FDA's digital health regulations have evolved to address AI-specific concerns. The FDA has introduced new guidance on **AI-enabled lifecycle management**, including a mechanism for authorizing specified future modifications (FDA) (Predetermined Change Control Plans) (www.fda.gov) and detailed **Good Machine Learning Practices (GMLP)**. The FDA now requires structured electronic submissions (eSTAR templates) for 510(k) and De Novo filings (www.fda.gov) and has begun enforcing the updated Quality Management System Regulation (QMSR) in 2026 (www.fda.gov).

In sum, while accelerated innovation in AI/ML medical devices continues, manufacturers must align with longstanding FDA statutes and emerging AI-specific policies. This report synthesizes historical context, current practices, and future trends to guide stakeholders in choosing and preparing the appropriate regulatory pathway for AI/ML-driven SaMD. We examine each pathway in detail, analyze clearance data and case examples (e.g. IDx-DR, Viz.ai, Arterys, HeartFlow), and discuss evolving FDA expectations (e.g. draft AI guidance, IMDRF frameworks, EU AI Act) that will shape AI SaMD regulation going forward.

Introduction and Background

Software as a Medical Device (SaMD) – standalone software intended for medical purposes without being part of a hardware product – has grown rapidly with advances in artificial intelligence (AI) and machine learning (ML) (www.fda.gov). AI/ML technologies now empower diagnostics, decision-support, and therapy guidance across specialties. For example, autonomous AI can screen diabetic retinopathy (www.retinalphysician.com), interpret radiology scans (innolitics.com) (www.biospace.com), and monitor vital signs via wearable sensors (cardiovascularbusiness.com). The FDA has recognized that SaMD uniquely straddles software innovation and medical performance, prompting both new guidance and adaptation of existing device laws.

Globally, regulators have sought harmonization on SaMD. The International Medical Device Regulators Forum (IMDRF) defined SaMD and developed risk-categorization frameworks, emphasizing the software's **clinical context and intended use** (www.fda.gov). For instance, an IMDRF matrix classifies SaMD by (1) the **significance of information** the software provides (inform, drive, diagnose/treat) and (2) the **state of the healthcare situation** (critical, serious, non-serious) (www.fda.gov). Category IV (highest risk) arises when software is used to "treat or diagnose" *critical* conditions, while Category I (lowest risk) aligns with informational outputs for non-serious conditions (www.fda.gov). Although the FDA does not formally assign IMDRF categories, such models inform risk assessment: a diagnostic image-analysis tool, for example, typically falls into a higher-risk category than a scheduling aid.

Under U.S. law, medical devices are categorized into **Class I, II, or III** by statutory risk (Box 1). Class I devices are low-risk (often exempt), Class II moderate-risk (requiring general and special controls), and Class III high-risk (require full PMA review) (www.accessdata.fda.gov) (www.mdpi.com). Most AI/ML SaMD reviewed so far have been classified as **Class II**. For example, FDA classified IDx-DR as Class II under DEN180001 for automatic detection of more than mild diabetic retinopathy in adults diagnosed with diabetes who have not previously been diagnosed with diabetic retinopathy, for use with the Topcon NW400 (FDA order). The classification drives which regulatory pathway applies (described below).

Box 1. *U.S. Medical Device Classes and Pathways.* Devices are classified by risk: Class I (general controls, often exempt), Class II (general + special controls), Class III (life-supporting/high-risk, requires PMA). *Premarket pathways:* 510(k) for demonstrating "substantial equivalence" to a predicate; De Novo for novel moderate-risk without a predicate; PMA for novel high-risk devices. A 510(k) submission shows that the new device is as safe and effective as an existing legally marketed device (www.nature.com). By contrast, the De Novo pathway (established by law in 1997) enables a new device to be classified as Class I or II and creates a new product code when no predicate exists (www.nature.com). The PMA process is the most stringent, requiring comprehensive clinical evidence of safety/effectiveness for Class III devices (www.mdpi.com).

New legislative and guidance changes are shaping SaMD regulation. The FDA's Quality Management System Regulation (QMSR) – aligning FDA QSR with ISO 13485 – became enforceable Feb 2, 2026 (www.fda.gov). Unless exempted, 510(k) submissions must use eSTAR from October 1, 2023, and De Novo requests from October 1, 2025 (FDA 510(k); FDA De Novo) (www.fda.gov). The Cures Act's non-device CDS exclusion requires all four criteria in section 520(o)(1)(E), including limits on medical-image/signal processing and enabling clinicians to independently review the basis for recommendations rather than relying primarily on them (FDA).

This report assumes devices are regulated by the FDA (U.S. market) and focuses on FDA pathways, but where helpful we note international context. Understanding the choice among 510(k), De Novo, and PMA is crucial for AI/ML SaMD sponsors: it determines evidentiary needs, review timelines, and market strategy. Subsequent sections detail each path, contrast them, and supply data-driven insight and examples. We then discuss AI-specific lifecycle issues (e.g. algorithm changes, "good ML practices", demographic fairness) and future regulatory trends.

The 510(k) Pathway for AI/ML SaMD

Overview: The **510(k) Premarket Notification** is the FDA's most commonly used pathway for moderate-risk devices (www.nature.com). A 510(k) submission must show that the new device is **"substantially equivalent"** (SE) to a predicate device on the market. Mathematically, sponsors demonstrate equivalence in intended use and either technological characteristics or performance data (www.nature.com). The process assumes the predicate has been proven safe and effective; the agency then ensures the new device does not raise new safety or efficacy questions.

When It's Used: For AI/ML SaMD, 510(k) is appropriate if:

- A legally marketed **predicate device** has the same intended use. Technological characteristics may differ if they raise no different safety or effectiveness questions and supporting data demonstrate substantial equivalence (FDA). For example, a new AI algorithm for chest X-ray nodule detection could use a cleared algorithm in the same category (e.g. other radiographic CAD tools) as a predicate.
- The **risk level is moderate** (Class II) or lower. In practice, most AI/ML SaMD cleared via 510(k) have been classified Class II. (Notably, Class I "reserved" devices can only use 510(k) if specifically listed as requiring it.)
- The new software's differences from the predicate are not substantial enough to alter mode of action or risk profile. In other words, the core clinical function remains essentially the same.

The 510(k) pathway is **much faster** and less burdensome than De Novo or PMA, making it attractive for software updates or incremental innovations. According to regulatory reviews, the median 510(k) clearance time for AI/ML devices is on the order of 142 days, i.e. about 4.5 months (innolitics.com). In 2025, 24% of AI/ML 510(k)s were cleared in <90 days and only 22% took >200 days (innolitics.com), reflecting efficiency. By comparison, De Novo reviews average nearer 10–11 months (www.nature.com).

Evidence Requirements: A 510(k) file typically includes a detailed software description, performance bench testing, and often some clinical or retrospective test data. The FDA has clarified that for AI/ML SaMD, performance should be evaluated on representative datasets covering the intended patient population. Since many FDA-cleared AI tools target imaging analysis, companies often provide accuracy/sensitivity/specificity metrics from retrospective image sets. Notably, the FDA now expects robust subgroup analyses; reviewers will flag submissions lacking demographic performance breakdowns as a bias risk (see Implications) (www.fda.gov). Discussing real-world performance during premarket review aligns with FDA's emphasis on transparency for AI outputs.

Risk Controls: FDA's DEN180001 order classified IDx-DR as Class II and requires clinical performance testing under anticipated conditions of use (FDA classification order). FDA's January 2025 draft AI lifecycle guidance proposes recommendations for risk management throughout the total product lifecycle; it is not for implementation and contains non-binding recommendations (FDA draft guidance).

Case Examples – 510(k): Many recent AI/ML SaMD cleared via 510(k) illustrate common scenarios:

- **Apple Watch HTN Notification (Cardiovascular ML Software)** – In 2025, Apple gained FDA clearance for an AI algorithm on its Watch that non-invasively flags possible hypertension (cardiovascularbusiness.com). Apple's Hypertension Notification Feature received 510(k) clearance on September 11, 2025 (FDA K250507).
- **Viz.ai ICH Plus (Intracerebral Hemorrhage Quantification)** – Viz.ai's 2024 clearance of "Viz ICH Plus" is another example FDA K232363. The FDA cleared a 510(k) for this deep-learning algorithm that measures hemorrhage volume on CT scans. (As a Class II tool, it justified 510(k).)
- **Arterys Cardio DL (Cardiac MRI Segmentation)** – Arterys received a 510(k) in 2017 for its cloud-based Cardio DL application FDA K163253. It automates ventricular segmentation on cardiac MRI. Since predicate MRI segmentation tools existed, Arterys could show substantial equivalence and avoid PMA.

In Joshi et al.'s historical AI/ML-enabled medical-device cohort through October 2023, 96.7% used 510(k) (study). **Table 1** summarizes the pathways.

The De Novo Pathway for AI/ML SaMD

Overview: The **De Novo pathway** is intended for novel, low-to-moderate risk devices that have no marketed predicate. It was established by the FDA Modernization Act of 1997 to **"foster innovative devices by providing an intermediate pathway between 510(k) and PMA"** (www.nature.com). After FDASIA (2012), de novo can be requested directly, without first failing a 510(k) (www.nature.com). A granted De Novo request results in: (1) the device being classified as **Class I or II** (never Class III), (2) creation of a new FDA product code (special controls defined in regulations), and (3) the device becoming a first-of-kind predicate for future 510(k) submissions (www.nature.com).

When It's Used: De Novo is appropriate if the device is **eligible for Class I or II classification**, **has no legally marketed predicate**, and **can be adequately controlled by general controls alone or general and special controls** (FDA). In practice, AI/ML SaMD sponsors consider De Novo if their algorithm is first-in-class

for a particular use. For example, the autonomous IDx-DR retinopathy scanner was granted a De Novo in 2018 (DEN180001) because no prior automated diabetic retinopathy device existed (www.accessdata.fda.gov) (www.nature.com). The De Novo path is also chosen for novel functions in cardiology, AI-based pathology tools, and other arenas without existing claims.

Eligibility depends on whether the relevant controls provide reasonable assurance of safety and effectiveness for the intended use, rather than on a critical clinical context alone. (Table 2 presents real-world examples.)

Evidence Requirements: A De Novo submission requires substantial evidence of safety and effectiveness – essentially like a mini-PMA. This typically means bench and clinical data demonstrating performance. FDA's 2017 De Novo guidance specifies that sponsors should provide "comprehensive information" including test data, risk analysis, and proposed special controls (www.nature.com). In practice, AI/ML De Novo applications often include human clinical validation. For instance, IDx-DR's FDA summary reported a pivotal clinical study of 900 patients (www.retinalphysician.com). DermaSensor's FDA De Novo review describes testing of device-output sensitivity and specificity against biopsy-based ground truth (FDA DEN230008). As noted by Aboy et al., De Novo applicants now prepare dossiers akin to PMA applicants, because no predicate exists to rely on (www.nature.com).

Special Considerations: A successful De Novo yields a *new predicate*. Future entrants can pursue 510(k) by demonstrating substantial equivalence: the intended use must be the same, while technological differences must raise no different safety or effectiveness questions and be supported by appropriate data (FDA). This "predicate-ifying" effect is a major benefit. However, innovators must be prepared for longer review times and potentially tougher review standards. On average, De Novo reviews have been around 338 days (median 309 days) in recent years (www.nature.com) – roughly 2–3 times the duration of a typical 510(k). Also, because De Novo devices often create new categories, FDA may require creating novel special controls (e.g. labeling requirements, performance standards) tailored to the AI risk. White papers stress that including post-market monitoring plans (like Performance Goals) and engaging early with FDA (Q-Submissions) can smooth the process.

Case Examples – De Novo: Notable AI-driven De Novo products include:

- **IDx-DR** (Digital Diagnostics) – An autonomous diabetic retinopathy screener. DEN180001 was granted April 2018 (www.accessdata.fda.gov) after a pivotal clinical trial (87.4% sensitivity) (www.retinalphysician.com). Subsequently, IDx-DR became the predicate for future retina-AI 510(k)s.
- **Notal Vision Home OCT System** – A prescription home imaging system for eyes already diagnosed with neovascular AMD, used between scheduled clinic assessments. Its results must not be used for diagnosis, detecting dry-to-wet AMD conversion, making treatment decisions, or replacing scheduled examinations (FDA De Novo summary, DEN230043).
- **HeartFlow FFR-CT** – Class II De Novo classification, DEN130045, granted November 26, 2014 (FDA order).
- **DentalMonitoring** – Prescription software authorized through De Novo (DEN230035) to assist healthcare professionals in remotely monitoring orthodontic treatment and progress. Its results are an aid to diagnosis and monitoring, not a stand-alone basis for clinical decisions (FDA De Novo review).

- **DermaSensor** – An adjunct to clinical assessment by physicians who are not dermatologists, assisting referral decisions for patients aged 40 and above with lesions already suspicious for skin cancer. It is not a screening tool or a sole diagnostic criterion (FDA De Novo summary, DEN230008).

The historical De Novo share reported by Joshi et al. concerns the broader AI/ML-enabled medical-device cohort, rather than standalone SaMD alone (study). Table 1 and Table 2 describe the pathways and examples.

The PMA Pathway for AI/ML SaMD

Overview: Premarket Approval (PMA) is the FDA's most stringent review for Class III devices (www.accessdata.fda.gov) (www.mdpi.com). Statutorily, Class III includes devices that *"support or sustain life"* or *"present a potential unreasonable risk"* (www.accessdata.fda.gov). To proceed under PMA, an AI/ML SaMD would typically involve high-risk diagnoses or direct therapy decisioning. PMA requires a full application of clinical (and non-clinical) data establishing safety and effectiveness.

When It's Used: PMA generally applies to Class III devices for which general and special controls alone are insufficient to assure safety and effectiveness. FDA notes that some Class III preamendment devices may instead require a Class III 510(k) (FDA).

Evidence Requirements: The PMA bar is extremely high. Clinical trials are the norm, often randomized controlled trials. AI-specific extra evidence (like learning curve or user training) might be scrutinized. A PMA submission for an AI algorithm must justify not only algorithmic performance but also that any risk (e.g. false-negative results) is acceptably low. The requirements are outlined in CFR 21 Part 814 and typically require "valid scientific evidence" (clinical and bench data) (www.mdpi.com). In practice, any AI/ML software that truly requires a PMA would face PMA expectations akin to drugs – something most developers avoid unless needed.

In summary, PMA generally applies to Class III devices for which general and special controls alone are insufficient to assure safety and effectiveness (FDA). IMDRF categories do not determine FDA classification or the premarket pathway (IMDRF framework).

Regulatory Pathway Comparison

Basis of Pathway Selection: Choice among 510(k), De Novo, and PMA depends on *three key dimensions*: (1) **Risk Level** of the device (advantaged by FDA Class / IMDRF category), (2) **Novelty/Predicate** (whether a legally marketed predicate exists), and (3) **Intended Use** (e.g. diagnosis vs inform). Table 1 below (adapted from industry guidance (www.complizen.ai)) summarizes these considerations:

Pathway	When It Applies	FDA Classification	Market Effect
510(k) Clearance	Substantial equivalence to a legally marketed predicate: same intended use; technological differences may be acceptable if they raise no different safety/effectiveness questions and supporting data establish equivalence (FDA).	Commonly Class II; some Class I and Class III devices also use 510(k).	FDA issues a substantial-equivalence determination permitting marketing.

Pathway	When It Applies	FDA Classification	Market Effect
De Novo Classification	No legally marketed predicate; general controls alone or general and special controls provide reasonable assurance of safety and effectiveness (FDA).	Class I or II	Establishes a new classification and may provide a predicate for subsequent 510(k) submissions.
Premarket Approval (PMA)	Generally applies where Class III general and special controls are insufficient; some preamendment Class III devices instead require 510(k) (FDA).	Class III; IMDRF categories are not FDA regulatory classes (IMDRF).	Approval requires sufficient valid scientific evidence of safety and effectiveness.

Table 1. Summary of FDA regulatory pathways for SaMD. 510(k) is used when substantial equivalence to an existing device can be shown (www.complizen.ai); De Novo when no predicate exists but risk is low/moderate (www.nature.com); PMA for high-risk (Class III) devices (www.mdpi.com).

Table 1 distinguishes the pathways by FDA classification, predicate availability, and the relevant controls (FDA). Historical pathway shares for AI/ML-enabled medical devices should not be treated as standalone-SaMD shares.

Evidence and Burden: As reflected in Table 1, the evidence burden escalates from 510(k) → De Novo → PMA. For 510(k), demonstrating equivalence often means bench testing and moderate clinical validation. De Novo requires standalone demonstrations of safety/effectiveness (often with substantial clinical data since no predicate exists). PMA typically mandates large clinical trials. The **FDA's risk-based guidance** now also ties evidence level to risk impact: devices that "drive" important clinical decisions need stronger clinical evidence than mere informative tools (qualysec.com) (www.nature.com). In short, an AI that only *informs* a clinician (low risk) may clear via 510(k), whereas an AI that *treats/diagnoses* major conditions may need De Novo or PMA and robust trials.

Data on AI/ML SaMD Clearances

Empirical analyses underscore these trends. Joshi et al. reviewed **691 AI/ML-enabled medical devices** listed by FDA through October 19, 2023; this broader cohort includes more than standalone SaMD (study) (www.mdpi.com). Key findings were:

- **Dominance of 510(k):** By far the most common pathway. ~97% of AI/ML devices were cleared via 510(k) (www.mdpi.com). Only ~2.9% used De Novo and ~0.4% used PMA (www.mdpi.com).
- **Specialty Focus:** Radiology accounted for the majority. The 2025 data showed ~71.5% of new AI clearances in radiology (innolitics.com), reflecting ample image data availability. Cardiology and neurology trailed.
- **Rise over Time:** AI/ML SaMD approvals surged post-2018 (www.mdpi.com), reflecting technological advances. In 2025 alone, one analysis found 295 AI/ML 510(k) clearances (innolitics.com) — nearly one per weekday. This rapid growth emphasizes why streamlined pathways (510/k) are crucial for timely innovation.

Figure 1 describes the historical AI/ML-enabled medical-device cohort, rather than standalone SaMD alone.

Figure 1. FDA pathway distribution in Joshi et al.'s AI/ML-enabled medical-device cohort through October 19, 2023 (study). The 510(k) share was 96.7%.

In Aboy et al.'s historical analysis of De Novo requests from 1997 to August 2023, the mean decision time was 338 days and the median was 309 days (study). The study covered medical devices broadly, including hardware, software, and in vitro diagnostics; these figures are not a current AI-specific benchmark. In 2025, the **median 510(k)** review for AI devices was ~142 days (innolitics.com). Regulatory experts note that while FDA has goals (e.g. 90-day review for 510(k)), actual reviews can vary based on complexity and completeness. FDA still uses virus scanning and technical screening for eSTAR submissions (FDA eSTAR program). Data also show that about 10% of 2025 AI clearances included *predetermined change control plans* (PCCPs) for future algorithm updates (innolitics.com), reflecting FDA's encouragement of such planning for adaptive AI.

AI/ML Lifecycle and Regulatory Considerations

Beyond the initial pathway, AI/ML SaMD raise unique issues across the product lifecycle. The FDA has published several guidance documents relevant to AI SaMD (Table 3) and is actively shaping policy (e.g. with the Digital Health Center of Excellence). Key points include:

- **Algorithm Modifications and PCCP:** AI models may be updated post-market (as new data accrue). The joint FDA, Health Canada, and MHRA guiding principles address predetermined change control plans (PCCPs) for machine learning-enabled medical devices (joint guiding principles). For example, a PCCP would detail what kinds of retraining or performance drift mitigation a device will undergo, and how these changes will be tested and documented. Changes outside an authorized PCCP must be assessed under applicable device-change requirements and guidance to determine whether a new submission is needed. If a planned change deviates from the authorized Modification Protocol, FDA says a new submission will likely be required before implementation (FDA). FDA's 5 guiding principles emphasize that PCCPs should be **focused/limited**, **risk-based**, and **evidence-driven** (www.fda.gov). FDA provides recommendations for PCCPs tailored to AI-enabled devices (FDA PCCP guidance).
- **Good Machine Learning Practices (GMLP):** FDA and international bodies emphasize development controls. This includes high-quality, well-curated training datasets; transparent model documentation; robust validation plans; and provisions for human oversight (www.fda.gov). The FDA's draft 2025 guidance on "AI-Enabled Device Software Functions" stresses a **total product lifecycle (TPLC)** approach to risk management (www.fda.gov). Submissions now commonly include a description of how data were collected, how bias was assessed, and how performance is monitored over time. The January 2025 AI lifecycle document remains draft guidance, marked "Not for implementation" and containing non-binding recommendations; it should not be presented as an enforceable demographic-analysis mandate (FDA).

- **Cybersecurity and Software Supply Chain:** Section 524B(b)(3) of the FD&C Act requires an SBOM in applicable premarket submissions for devices meeting the statutory cyber-device definition. That definition includes sponsor-authorized software, the ability to connect to the internet, and technological characteristics that could be vulnerable to cybersecurity threats (FDA). FDA's updated QMSR (2026) also requires documented processes for software design, maintenance, and change control which apply to AI development life-cycles (www.fda.gov). These frameworks are technology-neutral but are vigorously enforced, given the interconnected nature of modern AI platforms.
- **Post-Market Surveillance and Real-World Performance:** FDA's RWE guidance contains nonbinding recommendations (FDA RWE guidance). If a manufacturer receives a section 522 order, it must submit a postmarket surveillance plan within 30 calendar days (FDA section 522 guidance).
- **International Regulatory Interplay:** U.S. sponsors should also be aware of global trends. In the **European Union**, the AI Act (in force since August 2024) classifies AI/ML-based medical software that requires notified-body conformity assessment under the MDR or IVDR as "high-risk AI" under Article 6(1), with those obligations applying from August 2, 2028 after the 2026 Digital Omnibus on AI (EUR-Lex) (mdxcro.com). High-risk AI systems face stringent obligations on data governance, transparency, and human oversight (on top of existing MDR requirements) (mdxcro.com). For Article 6(1)/Annex I high-risk systems, Chapter III, Sections 1–3 of the AI Act apply from August 2, 2028 (EUR-Lex). Similarly, the FDA and other agencies are discussing international harmonization (IMDRF, IEC standards, etc.) of SaMD quality systems.

Table 3. *Select recent FDA guidance relevant to AI/ML SaMD.* Key topics include AI lifecycle management, data transparency, and quality systems. (FDA guidances are non-binding; compliance ensures 'least risk' submissions.)

Guidance Title	Issued	Relevance
Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles	October 24, 2023 (FDA/Health Canada/MHRA)	Joint guiding principles for planning and controlling changes to ML-enabled medical devices (MHRA publication).
AI-Enabled Device Software Functions: Lifecycle Mgmt… (Draft)	Jan 2025 (FDA Draft)	Recommends what to include in AI/ML device marketing submissions, focusing on risk management over the **total product lifecycle** (www.fda.gov).
Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act	September 27, 2019	Addresses section 520(o)(1)(A)–(D) of the FD&C Act (FDA guidance).
Quality Management System Regulation (QMSR)	Final rule published February 2, 2024; effective February 2, 2026	Regulation updating 21 CFR Part 820 to align device quality-system requirements with ISO 13485:2016 (FDA QMSR; FDA publication and effective dates).

These guidance updates (and others) make clear that the FDA expects AI/ML developers to adopt rigorous software engineering and transparency practices from design through post-market. Manufacturers should monitor FDA communications (e.g. CDRH's **AI-enabled devices list** (www.fda.gov)) and engage with FDA

early (through Pre-Submissions) to clarify expectations for their specific device function.

Case Studies and Real-World Examples

To illustrate these pathways, consider the following representative AI/ML medical devices and their regulatory routes:

Device	Company	Function (Indication)	Regulatory Class	FDA Pathway (Year)	References
IDx-DR	Digital Diagnostics	Autonomous diabetic retinopathy screening (retinal images)	II (software)	De Novo (DEN180001, 2018)	(www.accessdata.fda.gov) (www.law.cornell.edu)
Viz ICH+ (Viz HDS)	Viz.ai	Quantifies intracranial hyperdensities, lateral ventricles and midline shift on non-contrast head CT at a single time point; physician review alongside original images	II (software)	510(k) (K232363, 2024)	FDA clearance and indications
Apple Hypertension AI	Apple Inc.	AI-based hypertension risk detection on smartwatch	II (software)	510(k) (2025)	FDA K250507
Arterys Cardio DL™	Arterys	MRI data visualization and quantification using manual and semi-automatic border detection	II (software)	510(k) (K163253, 2017)	FDA clearance and indications
DermaSensor	DermaSensor, Inc.	Assists non-dermatologist referral decisions for already suspicious skin lesions in patients aged 40 and above; does not confirm skin cancer	II (AI-enabled hardware/software system)	De Novo (DEN230008, 2024)	FDA De Novo summary
Notal Vision Home OCT	Notal Vision, Inc.	Home imaging between clinic assessments of eyes already diagnosed with neovascular AMD; not for diagnosis or treatment decisions	II (AI-enabled imaging hardware/software system)	De Novo (DEN230043, 2024)	FDA De Novo summary
HeartFlow FFR-CT	HeartFlow, Inc.	Coronary physiologic simulation software	II (software)	De Novo (DEN130045, November 26, 2014)	FDA order

Table 2. Selected AI/ML-enabled medical devices and their FDA premarket pathways; the table includes hardware/software systems. IDx-DR received Class II De Novo classification in 2018 for automatic detection of more than mild diabetic retinopathy in adults with diabetes without a previous diabetic-retinopathy diagnosis, using the Topcon NW400 (FDA order). Arterys Cardio DL received 510(k) clearance in 2017 (FDA K163253); Viz ICH+ is specifically named with Viz HDS and Viz Volume Plus in the 2024 clearance record (FDA K232363). HeartFlow FFR-CT illustrates Class II De Novo classification (FDA). Apple's Hypertension Notification Feature received 510(k) clearance on September 11, 2025 (FDA K250507).

These case studies highlight that when the use-case overlaps existing devices and the risk is moderate, sponsors successfully used 510(k). When a first-of-its-kind clinical function is introduced (as with IDx-DR or Home OCT), De Novo has been appropriate. De Novo classification is a risk-based classification process (FDA De Novo overview).

Discussion and Future Directions

Implications for Stakeholders: For AI/ML SaMD developers, pathway choice is pivotal. A 510(k) strategy demands finding a predicate and focusing on equivalence data; this can expedite clearance but locks in labeling and predicate limitations. De Novo requires investing in more upfront evidence and analysis but can yield category leadership. PMA selection depends on the applicable FDA classification and whether general and special controls are sufficient (FDA). Sponsors planning future AI device modifications can seek authorization of a PCCP to cover specified changes (FDA); it is not a universal submission requirement. Moreover, the regulatory trend is moving toward greater scrutiny of AI performance in diverse populations; manufacturers should accumulate validation data on subgroups and be prepared to monitor bias post-market.

Regulators too balance innovation with safety. The surge in AI devices (hundreds per year) strains review capacity, prompting new tools (like eSTAR) and policies to focus reviewer attention on device-specific concerns (demographics, cybersecurity, training set validity). The FDA's transparent AI-enabled devices list helps clinicians and patients identify which FDA-authorized devices use AI, but also signals spotlight to quality and adherence to guidance. Internationally, convergence (IMDRF, IEC, EU AI Act) is shaping a more uniform landscape; a U.S. grant or clearance may facilitate approvals in Europe or Asia, though differences remain (e.g., EU's Notified Body scrutiny of Software Life Cycle under MDR).

Trends and Emerging Issues: AI/ML SaMD will continue to evolve. Key future directions include:

- **Adaptive and Continuous Learning:** Regulators are actively exploring how to oversee algorithms that change after commercialization. The innovations in physician-aided learning and cloud updates will likely lead to more robust post-market requirements. We may see FDA require periodic submissions when models drift, or mandate AI "Algorithmic Change Protocols" as outlined in the Cures Act amendments. **Real-world Performance Monitoring** will become formalized through databases or registries for AI devices.
- **Large Language Models (LLMs) and Generative AI:** The FDA has recognized that future SaMD may incorporate foundation models (e.g. GPT-style systems) (www.fda.gov). While current AI/ML in diagnostics is largely feature-based (images, signals), new devices may use generative models for clinical text analysis or patient interaction. This raises new questions, but the FDA and IMDRF are beginning to extend their frameworks to address LLM safety and transparency.
- **Societal & Ethical Oversight:** As AI SaMD proliferates, public concerns (equity, privacy, algorithmic bias) are driving legislative attention. As noted, the FDA may soon demand demographic performance reports as a regulatory requirement (www.fda.gov). Future legislative acts or FDA guidance might impose requirements for reporting on outcomes (e.g. does an AI tool actually improve patient care?) in post-market. These "living matters" go beyond traditional premarket review.

- **Regulatory Innovation:** Given the fast pace of AI, FDA is experimenting with novel approaches. For example, the (now-terminated) Digital Health Precertification program aimed to rate companies' quality systems to expedite their products. Although the original Pre-Cert pilot ended, its spirit lives on in accelerated programs (Breakthrough Devices, Safer Technologies Program) and in the FDA's collaboration forums (IMDRF for Software and AI). We may see new pathways or exemptions for well-controlled AI diagnostics in the future, but none have been codified yet.

In conclusion, choosing 510(k) vs. De Novo vs. PMA for an AI/ML SaMD is not merely a legal box-check: it reflects a holistic risk management decision. Stakeholders must match device capabilities to FDA categories and shape development practices accordingly. The insights in this report, drawn from regulatory history, data analyses, and real devices, aim to guide developers in navigating the complex FDA ecosystem in 2026. As AI/ML in healthcare matures, industry and regulators alike will need to balance innovation with robust oversight, ensuring patients benefit from AI's promise in a safe, equitable, and transparent manner.

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