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The Role of the FDA and Regulatory Approval of New Devices for Diabetes Care

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Abstract
Purpose of Review The Food and Drug Administration (FDA) is responsible for assuring the safety, effectiveness, and quality of medical devices in the USA. Extensive review times coupled with the demand for necessary treatments have prompted the policymakers to implement measures to speed medical devices to market.The purpose of this review is to summarize the evolution of the regulatory pathways through which medical devices utilized in diabetes care gain market access.
Recent Findings Regulatory pathways, ranging from premarket notification to premarket approval, require distinct, yet necessary ("least burdensome") evidence demonstrating a device's safety and effectiveness. Collaboration between manufacturers, regulators, and patients has resulted in the development and approval of novel diabetes care devices, including the first hybrid closed-loop artificial pancreas.
Summary Policy provisions, ranging from the least burdensome approach to the "breakthrough device" expedited pathway, aim to balance innovation, access, and safety. Clinicians must be aware of the evolving regulatory landscape and play an active role in enhancing patient safety.

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Introduction

The Food and Drug Administration (FDA) is responsible for assuring the security and quality of pharmaceuticals and medical devices in the USA [1]. The agency's Center for Devices and Radiological Health (CDRH) protects the public's health by ensuring medical devices not only perform reliably and consistently, but also are safe and effective [2, 3]. Regulators, through established review procedures, make certain each medical device is adequately categorized and labeled, thus allowing for appropriate use by clinicians and patients [3]. The need to balance safety, efficacy, and innovation has only grown since the 1970s, when the Medical Device Amendments of 1976 expanded the agency's authority [4].

As the scientific landscape has evolved, so too has the technological acumen required to review and approve medical devices [3]. Increased complexity has led to prolonged regulatory reviews and subsequent delayed access to some medical treatments [5•]. Policymakers have focused on amending the process to speed products to market, with the introduction of the "least burdensome" provisions in the Food and Drug Administration Modernization Act (FDAMA) of 1997 to the establishment of a "breakthrough device" expedited review pathway in the 21st Century Cures Act [6, 7]. However, questions remain regarding the potential trade-offs between improved access and device safety.

Clinicians play an integral role in the prescribing and use of medical devices. Despite, this active position, few are aware of the regulatory pathways through which products gain market access [8•]. Healthcare professionals must understand the

changing regulations and participate in the development, evaluation, and monitoring of medical devices [5•]. Knowledge is especially critical in the field of diabetes care, which has witnessed innovative progress in device design and mechanics, from the simplistic syringe to the infusion pump to the continuous glucose monitor to the hybrid closed-loop (HCL) artificial pancreas. The purpose of this review is to provide an overview of medical device review procedures and to detail regulations in practice for diabetes care.

Medical Device Classification and Regulatory Control

The Medical Device Amendments of 1976 established three classes of devices based on the risk posed to patients and required level of regulatory control [2, 8•, 9]. Class I, or low-risk, devices are subject only to "general controls." Such controls, which include manufacturing facility registration, device listing, and good manufacturing practices, are sufficient to assure the device's safety and effectiveness [2, 10•]. Due to a demonstrated history of safe use, class I devices (e.g., lancets) are often exempt from premarket review [2]. Manufacturers ("sponsors") must notify the FDA regarding the commercial distribution of the device [11].

Class II devices are subject to additional information requirements—mandatory performance standards, guidance documentation, or additional labeling—known as "special controls" [2, 9, 10•]. Together, general and special controls mitigate the moderate risk posed by the device. Class II devices (e.g., blood glucose meters, infusion pumps) are typically reviewed and cleared via the premarket notification pathway (this and other pathways are described in more detail under section "Regulatory Pathways") [5•, 12, 13]. Sponsors are required to demonstrate that their device is as safe and effective and thus, substantially equivalent to an existing, cleared device [9, 14].

Class III devices support or sustain life, prevent impairment of health, or present a potential, unreasonable risk of injury [15]. The general and special controls are insufficient to assure the safety and efficacy of high-risk devices; therefore, the agency's review and approval is required [15]. Class III devices (e.g., continuous glucose monitors, hybrid closed-loop artificial pancreas) are often approved through the premarket approval (PMA) pathway, which requires the submission of preclinical and clinical studies [2, 8•, 16]. However, high-risk devices that aid in the diagnosis or treatment of rare diseases may qualify for the Humanitarian Device Exemption (HDE) [5•, 14, 17].

Regulatory Pathways

Due to the significant risks posed by class II and class III devices, the FDA conducts premarket reviews prior to determining device clearance or approval [5•, 14]. Only when "reasonable assurance of the safety and effectiveness of the device" has been demonstrated will the agency clear or approve a medical device [5•, 14]. Devices gain market access through one of three primary mechanisms—one regulatory pathway for device clearance (premarket notification) and two regulatory channels for device approval (PMA and HDE) [2, 5•, 10•, 14]. Figure 1 provides an overview of the key steps and milestones associated with each pathway; the details and nuances of which are described in this section.

Premarket Notification

Premarket notification, generally referred to as the 510(k) pathway, requires manufacturers to demonstrate that their *new* device is substantially equivalent to a pre-existing or *predicate* device [2, 9]. A predicate device is one that was legally marketed prior to May 1976, previously cleared via a 510(k) submission or has been reclassified via the De Novo pathway [2]. To be deemed substantially equivalent, the *new* device, when compared to the predicate, must have similar intended use, fundamental technology, or performance characteristics [2, 10•]. To aid in this determination, the sponsor must submit device specifications (e.g., design components, biocompatibility, operational principles) and preclinical evidence or modeling studies, as appropriate [5•, 14, 18]. The primary purpose of the 510(k) process is to speed the clearance of devices that have undergone slight modifications, resulting in incremental improvements in innovation and effectiveness [19, 20].

Despite this pathway's relatively brief review times (90 days), "The New 510(k) Paradigm" was established to further streamline regulatory review, introducing two alternative methods to demonstrate substantial equivalence—the Special 510(k) and Abbreviated 510(k) [21, 22]. The former pathway is utilized for changes that either do not impact the intended use or alter the fundamental technology of the device [21]. The latter process is used under three specific circumstances, including the existence of guidance documentation or establishment of special controls or consensus standards [23]. The Special 510(k) permits the sponsor to declare conformance to design controls, often without requiring accompanying data [21]. The Abbreviated 510(k) allows manufacturers to submit summary reports or declarations of conformity [23]. While both submission methods expedite review, Special 510(k) devices are usually cleared for marketing within 30 days [21, 23].

A broad array of diabetes diagnostic and testing devices, ranging from blood glucose monitors and test strips (e.g., UniStrip Generic Blood Glucose Test Strips) to hemoglobin A1c assays and test systems (e.g., Diazyme Direct HbA1c Assay Control Set), have been cleared via the premarket notification pathway [24, 25]. A significant proportion of device manufacturers have utilized the Special 510(k)

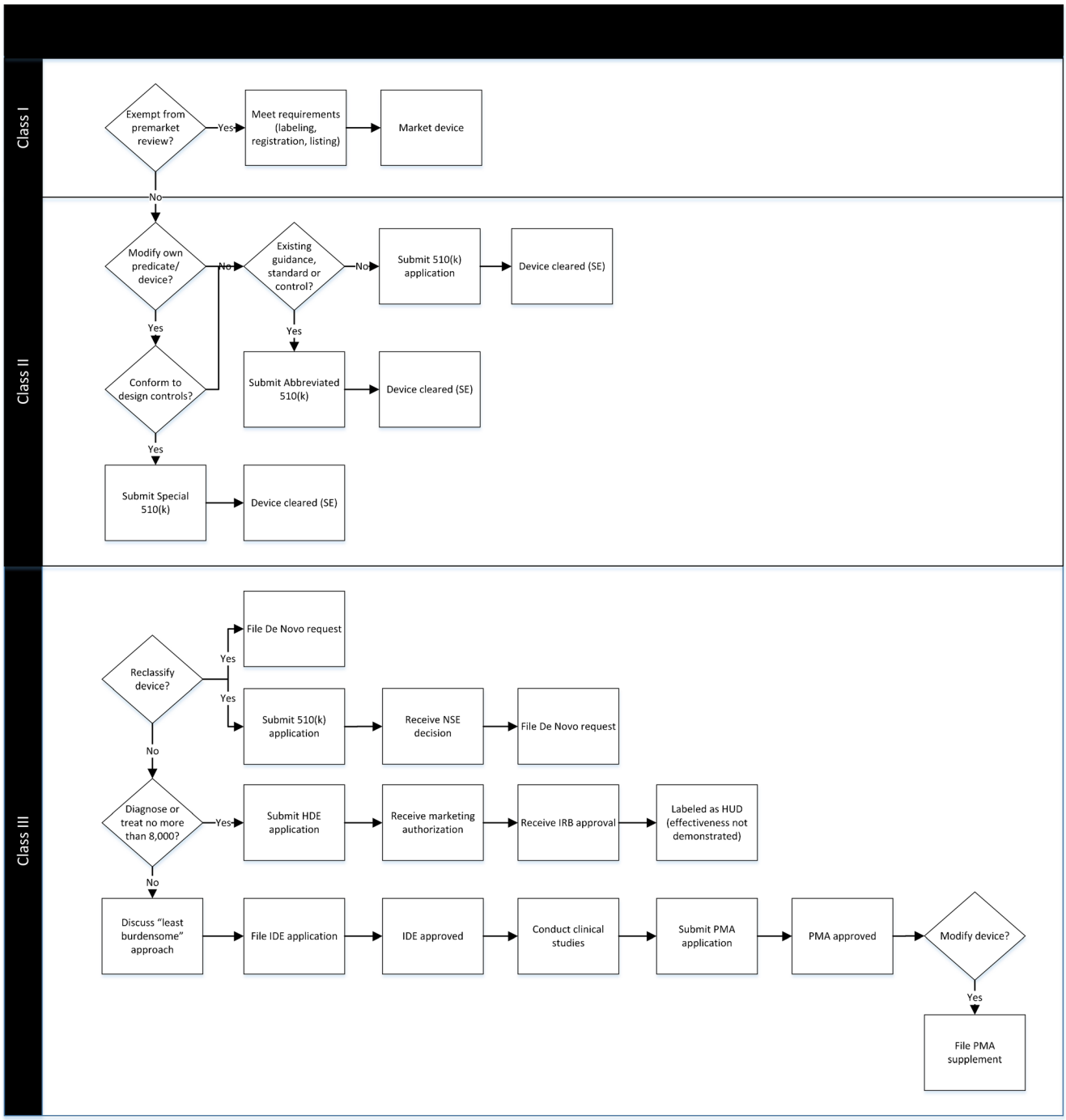

Fig. 1 Overview of device classifications and regulatory review. *SE* substantially equivalent, *NSE* not substantially equivalent, *HDE* Human Device Exemption, *IRB* institutional review board, *HUD*, Humanitarian Use Device, *IDE* investigational device exemption, *PMA* premarket approval
Source**:** Food and Drug Administration

submission, which entails modifications to the sponsors' own predicate device [26]. AgaMatrix, Inc. altered the name (One Drop Blood Glucose Monitoring System), weight, and length of its existing blood glucose meter, while SD Biosensor, Inc. modified the material and size of blood glucose test strips for its substantially equivalent device, the SD GlucoMentor™ [27–30].

De Novo 510(k)

In the absence of a comparable predicate, the Federal Food, Drug, and Cosmetic Act (FFDCA) automatically designates a novel device as class III [2, 10•]. The FDAMA of 1997 and the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 established and amended an expedited

mechanism for reclassifying such devices using a risk-based approach [2, 10•]. There are two paths to gain a De Novo classification. Following receipt of a *not substantially equivalent* decision, the sponsor submits a De Novo request for the FDA to reclassify the device as low or moderate risk [31]. Alternatively, a De Novo request may be submitted without first filing a 510(k) [10•, 31]. The FDA may decline the request if the device type has previously been classified according to risk, the risks and benefits of the device are poorly understood, or if the application of general and special controls is inadequate to mitigate potential risk [2, 10•].

Diabetes care devices, ranging from diagnostics (e.g., hemoglobin A1c test systems) to disease management (e.g., continuous glucose monitor data management systems), have been reclassified via the De Novo pathway [32, 33]. The impact of such classification decisions often extends beyond the scope of the sole device under review and applies broadly to the identified generic device type. In the case of the Dexcom Share Direct Secondary Displays, the establishment of special controls, related to data protection and adequate labeling, provided the basis of the FDA's classification decision [34]. Not only did the agency's order reclassify the designated class III diabetes monitoring device as class II, but also classified substantially equivalent devices of this generic type ("continuous glucose monitor secondary display") as moderate risk [34].

Humanitarian Device Exemption

A Humanitarian Use Device (HUD), which diagnoses or treats a disease or condition that affects no more than 8000 patients per year in the USA, gains marketing approval via the Humanitarian Device Exemption (HDE) [7, 17]. The regulatory pathway balances innovation and safety. The HDE encourages the development of devices for rare disorders and low prevalent conditions but does not require the rigors of clinical investigations demonstrating the product's effectiveness [10•, 14, 17]. Rather, the sponsor is required to establish sufficient evidence related to three key areas: (1) the potential benefits outweigh the probable risks; (2) no comparable devices are currently available to diagnosis or treat the condition; and (3) the device could not be approved through an alternative pathway [10•, 17, 19, 35]. Following marketing authorization, future use of the exemption is restricted. An HDE cannot be granted for a device that has the same intended use as a legally, marketed HUD [10•].

Due to the prevalence of diabetes mellitus (approximately 29 million Americans), approval of medical devices via the Humanitarian Device Exemption is atypical [36]. However, HUDs treating conditions related to or resulting from diabetes have been approved via the exemption. Medtronic's Enterra Therapy System (formerly named Gastric Electrical Simulation (GES) System), which is indicated to treat, "chronic, intractable nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology," was approved in March 2000 [37, 38].

Premarket Approval

The premarket approval (PMA) pathway is analogous to the drug approval process, in that it requires the submission of preclinical and clinical studies, as well as preliminary applications [8•]. Prior to filing an investigational device exemption (IDE), which is required to initiate clinical studies, the sponsor meets with the FDA to discuss available preclinical data and determine the least burdensome approach for collecting clinical evidence [3, 8•, 14, 39]. The goals of the least burdensome provision involve "appropriate investment of time, effort and resources" to allow for an evaluation "that would have reasonable likelihood of approval" [40]. Agency guidance grants the flexibility to submit non-clinical data (e.g., well-designed bench or animal testing), conduct alternatives to randomized controlled trials, or use valid surrogate endpoints to provide assurance of a device's safety and effectiveness [2, 8•, 40].

Filing of an IDE application prompts the formal review process. The goal of the review is two-fold: (1) the initial preclinical results ensure the device is appropriate for clinical investigations and (2) such studies will generate the data necessary to support a premarket approval submission [3, 5•, 14, 40]. The application is comprised of information related to prior research (e.g., preclinical evidence, outside the US (O-US) data), manufacturing processes (e.g., sterilization, packaging), and pivotal clinical study protocol (e.g., risk analysis, monitoring procedures, consent materials) [3, 5•, 14, 41, 42]. Upon approval of the IDE application, the sponsor is permitted to study the device in accordance with the proposed clinical trial plan [5•, 14].

Following completion of clinical trials and data collection, the sponsor prepares the PMA submission, which is considered "the most stringent type of device marketing application required by the FDA" [15]. The key components of the submission are similar in form and content to the IDE application, such as additional preclinical studies, proposed labeling, and intended use [5•, 14]. However, the focus of the application is the clinical research demonstrating the safety and effectiveness of the device [5•]. Subsets of PMA submissions, primarily those related to first-of-a-kind devices, are often reviewed by an advisory panel [3, 5•, 43]. The panel is tasked with reviewing specific aspects of the application and providing recommendations, which the FDA considers in its final determination [3, 43].

Recent PMA approvals highlight the technological advances in diabetes monitoring and treatment. Continuous glucose monitors, such as the FreeStyle Libre Pro Flash Glucose Monitoring System, and insulin pumps with sensor technology, including the Paradigm REAL-Time Revel System, represent progress in diabetes maintenance [44, 45]. Together, these

device types comprise the foundation of a novel breakthrough—Medtronic's MiniMed 670G System, the first hybrid closed-loop artificial pancreas [46].

Premarket Approval Supplements

To update or modify an FDA approved high-risk device, the manufacturer must submit a PMA supplement. The supplements are required for changes that affect the safety or effectiveness of the device, including but not limited to, significant modifications to design or components and minor alterations to labeling or packaging [8•, 47, 48]. Such incremental innovations are considered an "accepted part of a device's life cycle" [8•]. As shown in Table 1, the device manufacturer may choose from five supplement pathways, each of which entails a distinct purpose, data submission, and review time [8•, 47]. However, the FDA maintains the authority to reject or alter the selection, as necessary [8•, 47].

Device modifications requiring a panel-track supplement include new indications for use, ranging from expansion of the intended patient population to changes involving duration of use [49]. Significant labeling updates are often required, such as the addition of intended use or the removal of a contraindication [49]. In terms of the former, the FDA recently expanded the use of the Dexcom G5 Mobile Continuous Glucose Monitoring System to include "replacement of fingerstick blood glucose testing for diabetes treatment decisions" [50]. Similar to the traditional PMA submission, the panel-track supplement requires clinical evidence demonstrating the altered device's safety and effectiveness and may require review by an advisory committee [8•, 49].

Major changes to a device's design, materials, or components (e.g., altering the transmitter of a continuous glucose monitor) are approved via the 180-day review supplement [49, 51]. Preclinical studies are often sufficient to support such modifications, although "confirmatory clinical data" may be required [8•, 48, 49]. Submitted 180-day supplements may be eligible for real-time review. Real-time review supplements are often used for minor or expected changes to a device's design or software, such as adding an alternative screen to the quick bolus feature of the T: Slim G4 Insulin Pump [49, 52, 53]. Although clinical studies are not required, sponsors often submit risk analyses prior to meeting with the FDA [48, 53]. Following joint review of the proposed changes, the FDA often provides a same-day determination [8•, 53].

A manufacturer must submit supplements related to labeling changes and manufacturing processes. Alterations to a device's label that address new safety concerns, including the addition of a warning or strengthening of a contraindication (e.g., emphasizing alerts regarding the potential for Dexcom Seven and Seven Plus System's sensors to malfunction), are submitted via the special supplement pathway [47–49, 54]. Manufacturing procedural changes that do not impact the device's designs or components (e.g., automation, sterilization, quality control testing) are often implemented 30 days after a notice is filed with the agency [37, 48, 49].

Table 1 Description and use of premarket approval supplements

Supplement type	Purpose	Data	Example device	Example device modification
Panel-track	New indications; significant changes to design	Clinical studies	Medtronic's MiniMed 530G Insulin Pump	Included intended and non-intended uses (not intended to directly prevent or treat hypoglycemia; not intended for directly making therapy adjustments)
180-day review	Changes to design and materials	Preclinical studies; clinical data may be requested	Dexcom G5 Continuous Glucose Monitoring System	Modified device transmitter and receiver; added mobile app
Real-time review	Changes to device design or software	Preclinical testing; risk analysis	T: Slim G4 Insulin Pump with Dexcom G4 Platinum Continuous Glucose Monitoring System	Implemented an alternative screen on quick bolus button
Special	Update to label	No specified requirements	Medtronic's Paradigm Real-time Pump; Paradigm Real-time Revel Insulin Pump	Labeling change to the user guide and two package inserts
30-day notice	Changes to manufacturing processes	No specified requirements	Medtronic's MiniMed 630G System with Smartguard	Altered process parameters for device sensors
135-day review	Changes to manufacturing processes	Additional data requested by the FDA	Medtronic's MiniMed 530G Insulin Pump	Added an operating system for partial manual assembly of device sensors

Source: Food and Drug Administration; Premarket Approval (PMA) Database

The 30-day notice may be converted to a 135-day supplement if additional information is requested by the FDA [8•, 55].

Postmarketing Surveillance

The FDA employs multiple strategies for surveillance, ranging from voluntary reporting of adverse events to authorized post-approval studies that ascertain a device's long-term risk-benefit profile [56, 57]. The extent and type of postmarketing surveillance is dependent upon device classification. Due to the least burdensome provisions, premarket approval may be contingent upon the collection of postmarketing data [40, 56, 57]. Post-approval studies further assess the safety, efficacy, and reliability of high-risk devices, but in *real-world* settings [57]. The FDA may authorize manufacturers of class II or III devices to conduct postmarket surveillance studies ("522 studies") [10, 57]. The manufacturers utilize a variety of study designs and data sources—observational studies, randomized controlled trials, patient registries—to understand the nature, severity, or frequency of unexplained adverse outcomes [56–58].

In response to limitations of current surveillance procedures, such as disparate data sources and incomplete or inaccurate reports, the FDA has proposed and begun to implement *modern* methodologies [10•, 56]. The unique device identifier (UDI) system, which aims to adequately identify devices through distribution and use, will allow for studying individual patient experiences and prompt recalls of malfunctioning devices [8•, 59, 60, 61]. The label of each device, unless exempt, must contain a device identifier (DI) that identifies the device model and a production identifier (PI) that identifies additional information (e.g., expiration date, serial number) [59]. Unique identifiers will not only integrate the incongruent postmarketing surveillance platforms and electronic health records (EHRs), but will also lead to enhanced accuracy in the analysis of adverse events [10•, 56, 58].

The Premarket Approval Process in Current Practice: The Case of Medtronic's Hybrid Closed-Loop Artificial Pancreas

Through collaboration with patient advocates, healthcare providers, and industry, the FDA facilitated the development and approval of the first hybrid closed-loop artificial pancreas device system on September 28, 2016 [62]. Medtronic's MiniMed 670G System, which automatically monitors blood glucose levels and adjusts basal insulin doses, was granted priority review on July 13, 2016 [62, 63]. To be eligible for priority review, a medical device must treat a life-threatening or irreversible debilitating condition and address an unmet medical need (e.g., breakthrough technology, no approved alternative, significant clinical advantage) [64]. In the case of the artificial pancreas, the novel technology's availability was "in patients' best interest" [63].

As part of the expedited PMA application, the sponsor was required to complete and submit preclinical studies and clinical trials. In regards to the former, system functionality and environmental tests, ranging from chemical compatibility tests to X-ray immunity studies, were performed on the device and each component [63]. Results not only demonstrated the reliability and safety of the MiniMed 670G System, but also confirmed appropriateness for clinical investigation [63]. Following approval of distinct IDE applications, one for each proposed pivotal study, the manufacturer enrolled patients in multicenter clinical studies that evaluated the safety, effectiveness, and accuracy of the artificial pancreas in type I and type II diabetes patients [63, 65, 66].

The artificial pancreas was not referred to the Clinical Chemistry and Clinical Toxicology Devices Panel (advisory committee); rather, the PMA application demonstrated reasonable assurance of the device's safety and effectiveness and thus, was approved by the CDRH [63, 64]. The MiniMed 670G System's approval was conditional, in that the manufacturer must conduct a post-approval study in adult and pediatric type I diabetics. The study, which was approved on December 22, 2016 and has yet to commence, will determine the long-term safety (e.g., incidence of severe hypoglycemia, diabetic ketoacidosis, and serious adverse events) and effectiveness of the device in the home setting [63, 67, 68].

Prior to market entry in mid-2017, the manufacturing of Medtronic's MiniMed 670G System has undergone several modifications requiring the submission of PMA supplements [69]. Five 30-day notices were filed in October and November of 2016, each related to the changes in the manufacturing of device components [70–74]. Two notices entailed the relocation of the injection molding process and sensor substrate fabrication to new facilities, while the remaining three notices pertained to adding alternative equipment, altering sensor hardware, and changing parameters to component processes [70–74]. Submitted information, such as the description of and evidence supporting each modification, was adequate for the notices were not converted to 135-day supplements [55].

The Future of Regulatory Review: The Impact of the 21st Century Cures Act

While the passage of the 21st Century Cures Act has promised to usher in a new era of innovation in and access to medical technology, the law does not explicitly modify device review and approval processes. The legislation does introduce new mechanisms to expedite product development and review, but many of the provisions focus on altering or enhancing

established definitions and procedures, including the application of the least burdensome approach and the use of a *panel of experts* to make recommendations with respect to device classifications [7]. The key areas of the 21st Century Cures Act are outlined in Table 2, the most important of which will be described.

Expedited Review

The legislation introduces a breakthrough device pathway, which is based on definitions and procedures associated with existing priority review processes. To qualify as a breakthrough technology, the device must diagnose or treat a life-threatening disease or debilitating condition and meet one of the following criteria: (1) represent a technology with no existing alternatives; (2) offer advantages over current alternatives; or (3) be in the patient's best interest [7]. If the FDA reviewers agree with a sponsor's request, then the device is designated for priority development and review [7]. Similar to current priority review mechanisms, the sponsor may be assigned a subject matter expert to facilitate the expedited development and review of the device [7, 64]. While the goal is to accelerate innovation, devices granted priority review are not assured timely approval [64]. Effective collaboration between the agency and manufacturer will be critical in guaranteeing improved access to novel diabetes devices.

Multicenter Clinical Trials

It is worth noting that the MiniMed 670G System's sponsor was required to obtain approval from each clinical trial site's institutional review board (IRB); however, the 21st Century Cures Act removes this barrier to efficiency and promotes, for the first time, the use of centralized models [7]. A centralized

Table 2 The future of medical device regulatory reviews

Topic	21st Century Cures Legislation
Breakthrough devices	Establishes a "breakthrough device" expedited review pathway, which builds upon existing definitions and procedures. Devices qualifying as a "breakthrough device" are eligible for priority development and review. Guidance regarding the designation and regulatory process is expected within the year.
Humanitarian Device Exemption	Amends the Federal Food, Drug, and Cosmetic Act requirements regarding the use of the Humanitarian Device Exemption. The exemption may be applied to devices that diagnose or treat conditions affecting not more than 8000 patients. The cap was originally 4000 patients.
Recognition of standards	Amends the Federal Food, Drug, and Cosmetic Act requirements related to the submission and establishment of a national or internationally recognized performance standard ("special control"). Following the submission of a request, within 60 days the secretary shall determine to recognize all, part, or none of the standard. In addition, the secretary of Health and Human Services shall provide training to FDA reviewers on the use of recognized standards.
Classification panels	Amends the Federal Food, Drug, and Cosmetic Act requirements regarding the composition and use of classification panels. If a manufacturer's device is required to be reviewed by a panel, then the sponsor may recommend the expertise necessary, as well as appoint a representative to present and address the panel (e.g., correct misstatements, answer posed questions). Panel members must consider the manufacturer's presentation and responses in panel review.
Institutional Review Board Flexibility	Amends the Federal Food, Drug, and Cosmetic Act requirements for clinical trial approval by local IRBs. The change will allow for the use of centralized models.
Informed consent waiver or alteration for clinical investigations	Amends the Federal Food, Drug, and Cosmetic Act requirements related to informed consent. The secretary of Health and Human Services may waive consent under the following circumstances: (1) the proposed clinical test poses minimal risk and (2) the proposed clinical test protects the rights, safety, and welfare of the subject.
Least burdensome device review	Amends the Federal Food, Drug, and Cosmetic Act requirements regarding premarket approval applications and requests for additional information that is necessary to demonstrate the safety and efficacy of the device. "Necessary" is defined as the minimum required information that provides a reasonable assurance of a device's safety and effectiveness and promotes the use of postmarketing surveillance to fulfill the "necessary" means.
Cleaning instructions and validation data requirement	The secretary of Health and Human Services shall publish a list of reusable device types and determine which validation data (e.g., cleaning, disinfection, sterilization) will be used for substantial equivalence determinations. Guidance regarding premarket notification requirements is expected within the year.
Combination product innovation	Amends the Federal Food, Drug, and Cosmetic Act requirements related to premarket review. Combination products (e.g., drug or biologic and device) will be reviewed under a single application, which is determined by the primary mode of action or greatest expected contribution to intended therapeutic benefit. If the primary mode of action is that of a medical device, then the appropriate center (e.g., CDRH) will have authority over the product's regulation.

Source: Pub L No. 114-255 (2016)

IRB process involves agreement under which participating study sites rely, partially or wholly, on the review of a qualified IRB ("single IRB of record") [75, 76]. Although centralized IRBs have been available to pharmaceutical manufacturers prior to the passage of the 21st Century Cures Act, lack of familiarity with the model has impeded adoption [76]. To benefit from the process (e.g., reduce duplicative efforts, time and monetary investments), medical device sponsors must learn from the mistakes of their pharmaceutical counterparts [75].

Least Burdensome Provisions

The 21st Century Cures Act further clarifies the definition and application of the least burdensome provisions. When requesting additional data in relation to a PMA submission, the agency must consider the *necessary* or *minimum required information* to support "reasonable assurance of the safety and effectiveness of the device" [7]. Similar to current practice, the use of postmarketing surveillance will most often fulfill the necessary means. To ensure consistent use of the least burdensome provisions, the legislation requires the FDA to train medical device reviewers and supervisors, as well as conduct an audit on the implementation of the said requirements [7]. The key components of the audit that may influence future revisions to or application of the least burdensome approach are sponsor interviews, which highlight experiences with review processes [7].

Conclusion

Medical device regulatory review procedures have continually evolved to balance safety, effectiveness, and innovation. Clinicians who utilize diabetes devices should be aware of the nuances of the regulatory processes through which such products gain market entry. Each review pathway requires distinct preclinical or clinical evidence, with an increasing reliance on postmarketing surveillance to assure a device's safety and efficacy. Healthcare professionals should play an active role in monitoring the safety of prescribed devices, as well as articulate the risks and benefits of such devices when making treatment decisions with patients. Enhancing patient safety is critical, as researchers assess the impacts of the latest policy provisions aimed at accelerating access and innovation.

Compliance with Ethics Standards

Conflict of Interest Shelley A. Jazowski and Aaron N. Winn declare that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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