



Navigating the Regulatory Pathway for Medical Devices—a Conversation with the FDA, Clinicians, Researchers, and Industry Experts

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Abstract

Successful translation of new and innovative medical products from concept to clinical use is a complex endeavor that requires understanding and overcoming a variety of challenges. In particular, regulatory pathways and processes are often unfamiliar to academic researchers and start-ups, and even larger companies. Growing evidence suggests that the successful translation of ideas to products requires collaboration and cooperation between clinicians, researchers, industry, and regulators. A multi-stakeholder group developed this review to enhance regulatory knowledge and thereby improve translational success for medical devices. Communication between and among stakeholders is identified as a critical factor. Current regulatory programs and processes to facilitate communication and translation of innovative devices are described and discussed. Case studies are used to highlight the importance of flexibility when considering evidence requirements. We provide a review of emerging strategies, opportunities, and best practices to increase the regulatory knowledge base and facilitate medical device translation by all stakeholders.

Keywords Medical device regulation · Translational science · Regulatory science

Abbreviations

AI	Artificial intelligence	FDA	United States Food and Drug Administration
CDRH	Center for Devices and Radiological Health	HBD	Harmonization By Doing
CMS	Centers for Medicare & Medicaid Services	HDE	Humanitarian Device Exemption
CTSI	Clinical and Translational Science Institutes	HUD	Humanitarian Use Device
DICE	Division of Industry and Consumer Education	IDE	Investigational Device Exemption
ECG	Electrocardiogram	IMDRF	International Medical Device Regulators Forum
EFS	Early Feasibility Study	ISCTR	International Society of Cardiovascular and Translational Research
		IVD	In Vitro Diagnostics
		ML	Machine learning
		MDIC	Medical Device Innovation Consortium
		MDUFA	Medical Device User Fee Amendments
		NEST	National Evaluation System for health Technology
		OSEL	Office of Science and Engineering Laboratories
		PMA	Pre-market approval
		PMDA	Pharmaceuticals and Medical Devices Agency
		RWE	Real-world evidence
		STeP	Safer Technologies Program

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Introduction

The translation of novel medical devices from discovery through development, testing, and regulatory review, and finally to clinical use, is well known to contain a metaphorical “valley of death” in which products fail to advance from the development and testing phases to successful clinical use [1]. To bring new and innovative medical devices to market efficiently and effectively, a greater understanding of challenges faced and how to overcome those challenges is needed. One area, for academic researchers, start-ups, and small companies in particular, is understanding the various regulatory processes that must be navigated before most products can be used in patients or commercially marketed [2–4]. A multi-stakeholder group representing a cross-section of the medical device field, including clinicians, academic researchers, industry professionals, and regulators from the United States Food and Drug Administration (FDA), all of whom play critical roles in maintaining a vibrant and productive network for the development of medical devices, prepared this review of salient points and best practices toward a goal of increasing knowledge and advancing medical device translation through the regulatory process from concept to clinic [5].

Role of FDA Center for Devices and Radiological Health (CDRH)

As the FDA center responsible for the regulatory oversight of medical devices, CDRH plays a crucial role in facilitating device development by interacting with all stakeholder groups in the medical device ecosystem. CDRH activities relevant to improving translational processes include engaging with patients and the community to bring a product to market, the work of the FDA Office of Science and Engineering Laboratories (OSEL), special considerations related to pediatric populations, the Breakthrough Devices Program, Early Feasibility Studies (EFS), Q-submissions, current initiatives related to National Evaluation System for health Technology (NEST) and real-world evidence (RWE), evolution of regulatory pathways, global harmonization, and training.

Early engagement with key stakeholders including patients, clinicians, and payers is critical for regulatory and commercial success given the many pitfalls on the path from product concept to marketing, adoption, and reimbursement. In particular, patients are at the heart of CDRH activities and patient input, preference, and benefit-risk decisions are important parts of product development

and regulatory decision-making. Involvement of patient advocacy groups and FDA as part of a patient-caregiver collaborative community can provide expert input from the patient perspective, bring together key stakeholder groups to solve shared problems, and provide community-driven solutions that may be accepted by FDA [6]. Systems and solutions identified and developed by collaborative communities are often designed not just for use by FDA, but also to meet the needs of industry and other stakeholders such as patients, caregivers, healthcare providers, and payers. Communicating with FDA, innovation hubs, and regional consortiums throughout the development process builds connections to stakeholders who can help address various scientific and regulatory issues to accelerate innovation.

As new technologies are rapidly developed, FDA expertise must also advance. To address this challenge, OSEL supports pre-market reviews and post-market surveillance requirements by engaging in practical research and problem solving, and developing tools to better assess and understand new and cross-cutting technologies. Research areas include *in silico* clinical trials that can be completed in days rather than years, identification of early biomarkers for age-related conditions, and additive manufacturing, among many others. Through OSEL, FDA can align common research interests and goals with academia and other partners and provide expertise and laboratory capabilities that can help enable optimal review of novel products.

The use of innovative regulatory pathways such as the Breakthrough Devices Program, Safer Technologies Program (STeP), and EFS Program has rapidly expanded over time [7]. These programs and other efforts to de-risk the product development process for innovative technologies help attract investment and continue to drive innovative product development efforts in the USA. The Breakthrough Devices Program is intended to improve timely access to novel and innovative technologies that provide more effective treatment or diagnosis of a life-threatening or irreversibly debilitating disease or condition, often in areas of unmet clinical need, whereas STeP is intended for devices that do not meet the breakthrough criteria but still provide important safety advantages over existing technologies [8]. Both programs offer opportunities to engage early and frequently with FDA. To consider the suitability of a device for the Breakthrough Program, the product design should be developed at least to the point of understanding specific risks and key performance characteristics. Additionally, the intended use, patient population to be treated, and existing treatment options should be known, along with information to support why the proposed treatment would be more effective than existing options. Demonstration of expected effectiveness could include clinical data, bench or animal data, or a scientifically supported theoretical argument, depending on the

technology. At that point, one approach may be to reach out to the assistant director for the relevant review team at FDA and have a brief informal conversation to help determine if there is enough information for a more formal discussion and/or breakthrough designation request.

The Q-Submission process is a helpful and popular pathway for communicating with FDA [9]. Gaining a clearer understanding of regulatory requirements early in the development process can help de-risk the business aspects of projects, which can be especially important for small innovators. A sponsor can share information and obtain FDA's feedback on a particular question(s) to keep a product moving forward on the translational pathway. Q-Submissions, including Informational Meetings and Pre-Submissions, can be especially helpful for complex products such as indwelling or implantable devices, new technology, or innovative non-clinical or clinical testing strategies. Very early in the development process, an Informational Meeting can help FDA gain a deeper understanding of new technology by providing an overview of the device and optionally demonstrating a prototype; having an opportunity for FDA personnel to interact with a device in a hands-on environment, or in a video-conference setting, can be extremely beneficial. Working with an expert who understands the Q-Submission process and can provide guidance may help optimize the benefit of the program.

In addition to allowing more concrete feedback from FDA, Pre-Submissions also provide an opportunity to engage with both FDA and payors, including CMS and private payors, together as part of the Early Payor Feedback Program [10]. A clinically successful device that makes it through the regulatory process can still fail to be integrated into medical practice if there is no or poor reimbursement. Therefore, it is often important to develop a reimbursement strategy early during product development and clinical planning. Including payors in a Pre-Submission meeting allows payors to consider and provide feedback on the type of clinical evidence that could support payment for a technology (e.g., reasonable and necessary criteria for CMS) along with FDA feedback on clinical evidence that can potentially demonstrate a reasonable assurance of safety and effectiveness.

Real-world evidence is an increasingly important concept to support device development and evaluation. Continuing improvements in infrastructure, data completeness, definitions, and harmonization may provide increased opportunities for RWE to support regulatory and clinical decision-making. FDA has identified numerous cases where RWE has been accepted to support pre-market authorizations and fulfill post-market requirements [11]. RWE can be leveraged not only to support regulatory decisions, but also to facilitate hypothesis generation or finding appropriate patients. When using RWE, it is important to understand not just the device and clinical space, but also the data source quality

and the relevance and reliability of the data. NEST is working to help advance the use of RWE to support regulatory decision-making and has drafted data quality and methods frameworks. Discussing RWE use in advance with FDA, again potentially as part of a Pre-Submission, is highly encouraged.

The role of post-market surveillance has evolved over time beyond merely serving as a regulatory requirement to also helping answer important clinical questions that may not have been fully addressed in pre-market studies. For example, post-market surveillance offers an opportunity to fill in evidence gaps in the patient population being treated or to collect information on how a device could be used in a real-world setting. This multi-purpose use provides a potential role for patient registries or coordinated registry networks that in a total product lifecycle environment can then be used as RWE to support expanding a device indication and identify unmet clinical needs.

The mission of CDRH is not just to protect the public health, but also to promote the public health. This includes facilitating medical device innovation by advancing regulatory science and providing efficient regulatory pathways. The vision and values supporting this mission include being a leader in regulatory science and medical device innovation by challenging the status quo and testing and adopting new approaches to foster positive change and more effectively and efficiently accomplish the CDRH mission. As a future consideration to support innovation, additional flexibility could be considered in regulations to allow a more agile regulatory process; for example, leveraging of individual building blocks as appropriate to meet requirements. A risk-based and least-burdensome approach would remain at the core, but regulatory processes may be tailored to a specific technology. This more agile approach could be particularly relevant for innovative, rapidly changing technologies, such as digital health, as well as small, underserved patient populations and rare diseases. As one example, the current ecosystem is not well-designed to support development of innovative products for small and complex patient populations, such as pediatrics, due to high risks and limited investment incentives. As a result, physicians often must attempt to leverage technology designed for adults for use in children. For devices designed to treat or diagnose a disease or condition that affects not more than 8000 individuals in the USA on an annual basis, the Humanitarian Device Exemption (HDE) program provides a regulatory pathway based on demonstration of safety and probable benefit, but there remain numerous additional requirements tied to the program such as institutional review board (IRB) reviews, profit limitations, and other challenges that have limited widespread use of this pathway [12]. For larger patient populations, the pre-market approval (PMA) pathway may still be too difficult for pediatric devices to be commercially viable. A hypothetical future

hybrid approach could envision a device coming to market with the HDE standard of safety and probable benefit, but without all of the currently associated requirements, and then developing additional evidence of a reasonable assurance of safety and effectiveness (PMA standard) in a streamlined manner. While this approach would require changes to US law, it may ultimately provide a more effective pathway to market along with greater confidence in the technology.

Similarly, efforts are ongoing within the International Medical Device Regulators Forum (IMDRF) to develop globally harmonized essential principles for pre-market review, which could potentially be used as building blocks to support a multi-national single review program [13]. A number of challenges remain, including differences in the current US regulatory framework compared to many other regions and the need to ensure confidence in whichever entities would conduct pre-market review for a new technology. The Medical Device Single Audit Program provides one example of success for international harmonization [14]. An effective single review program that allows for near-simultaneous entry of technology to multiple marketplaces could better drive innovation and boost global health.

Providing regulatory training to new scientists and engineers is an important facet for maintaining a robust innovation ecosystem for translation. Programs around medical device development provide an opportunity to walk trainees through the entire life cycle of a product, including regulatory components such as practical applications of regulatory science to develop and evaluate innovative technologies. Use cases, including those developed by FDA, can provide examples of how regulatory principles integrate into the medical device development process. Having students engaged in regulatory science working in the field with developers, FDA, and other stakeholders such as patients, providers, and payers would be a robust opportunity to develop skills and provide an investment for the future. Recent reports indicate a large gap is expected between the supply and demand for

skilled regulatory professionals, highlighting the need for expanding educational opportunities and pathways [15]. It is hoped that ongoing discussions will serve to motivate further development of regulatory-focused training programs for scientists, engineers, and other stakeholders.

Translational Pathways

Medical Device Development—from Academic Discovery to Regulatory Review to Patient Access

One starting point for device development is to consider the question: “How do we start with a breakthrough idea from an inventor’s mind and translate that idea to a product that actually reaches patients?” Three critical pieces are necessary to be successful in medical device translation: people, processes, and product selection. Additionally, one of the biggest current challenges to success is the increasing cost of medical device development due to regulatory burdens, dilution of capital by project failures and inefficient management, and falling product prices and reimbursement. Together, these factors result in decreased margins for innovation and drive the need to further optimize the pathway.

The first critical piece for success is people. Stakeholders that understand the medical device ecosystem and with the experience to provide leadership and knowledge on where to focus limited resources must be included. These leaders can assemble the right team of scientific experts, financial experts, clinicians, and supply chain necessary to guide development and source capital. Examples of collaborative efforts to develop this leadership within the translational ecosystem include the CTSIs, International Society of Cardiovascular and Translational Research (ISCTR), standards organizations, and international harmonization efforts such as Harmonization By Doing (HBD).

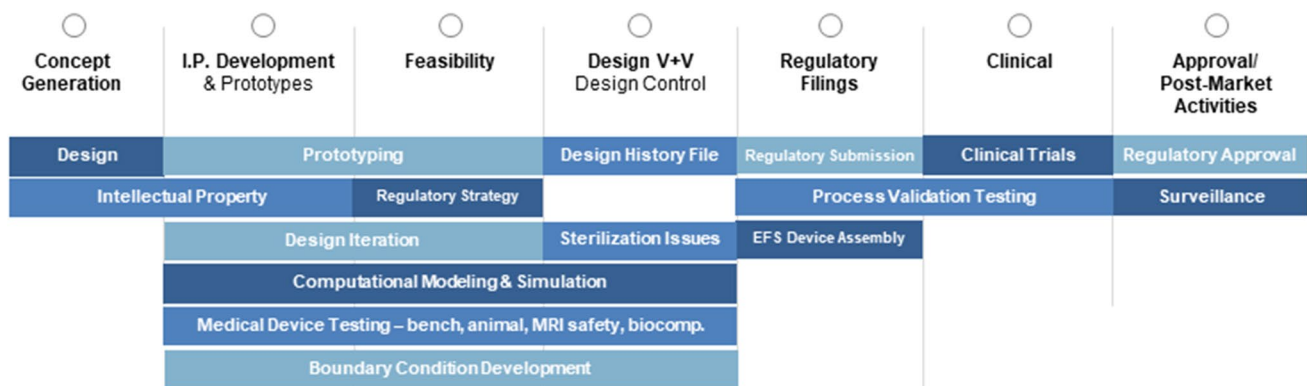


Fig. 1 Components of an accelerated product development sequence; careful coordination can identify efficiencies and maximize parallel development processes to achieve the most efficient path to market; figure used with permission from MED Institute, Inc

The next piece is having the right processes in place to accelerate the product development stages (Fig. 1). A good process will eliminate wasted effort from inexperience and mistakes, carefully coordinate to identify efficiencies and avoid pitfalls, and accelerate development by maximizing parallel processes to achieve the most efficient project plan. Combining the right people with the right process leads to development of successful engineering, testing, clinical, and regulatory strategies. This includes developing strategies around user needs, test models, simulations, and acceptance criteria, and planning and performing bench and animal testing. Developing a clinical and regulatory plan early, simultaneous with product development, allows feeding requirements and findings back into the development process to create a more efficient overall path.

The third piece for success is the product itself. The patient/clinical need comes first, and the best product is the one that best meets this need. Many great ideas do not pass this initial test, and trying to force a product to fit a need often ends in failure, regardless of how interesting or innovative the technology. Adapting the intended use and claims for a product to best fit the available data and clinical results is one approach to consider. In addition to being scientifically feasible, a successful product must also be economically feasible and commercially viable. Product ideas and the pros and cons of different strategies (e.g., regulatory path, intellectual property arrangements, development costs, reimbursement and payor strategies) should be considered from this perspective. Products that meet these initial requirements still require long-term dedication to succeed from an idea to patient use.

Early Feasibility Studies—a First Step Into Clinical Studies

The EFS process provides opportunities for rapid and efficient data collection to guide further product development activities [16]. These early studies can be integral to the device development process by obtaining insights into proof of concept related to various factors, including safety, performance, usability, or identification of the optimal patient population, and may form the basis for further device iteration and improvement. One benefit of EFS is the opportunity to enhance collaborations among all stakeholders, including developers, industry, investigators, and regulators.

Appropriate devices for EFS are those still in the development stage where the design has not yet been finalized and further development or evaluation is not available or adequate via non-clinical testing. The EFS pathway may reduce delays to device access for patients with limited alternatives and help device developers better understand the underlying clinical condition and unmet clinical need. Devices may be used in a few patients followed by making

modifications to the device and enrolling a few additional patients in an iterative process that can help refine device design. The EFS process is uniquely beneficial to first-in-class therapies where innovators may have no choice but to extrapolate from animal studies to predict design requirements for human devices. Clinical data either allow confirmation of boundary conditions used during development or provide tangible data to guide iteration. Outcomes during the EFS phase also aid in designing a subsequent pivotal study. EFS are expected to incorporate risk mitigation strategies, monitoring, and informed consent that includes general and specific information for early feasibility studies.

A Pre-Submission to discuss strategy for an EFS can help ensure the EFS submission is complete and has the best chance of being approved in the first 30-day review as well as allowing FDA an opportunity to provide feedback on progressing toward an Investigational Device Exemption (IDE) pivotal study. Depending on the device and intended use, there may be flexibility in the level and timing of information necessary to support an EFS. In some cases, a leaner testing approach may be adequate to initiate an EFS depending on the potential benefits and risks associated with the device and indications, but that could mean that more comprehensive studies may still need to be completed later (e.g., in parallel with or prior to initiating the pivotal study). The sponsor can consider if a staged approach is more efficient or if it may be preferred to perform a more rigorous study to start with.

Medical devices are often continually modified over time. As a result, the EFS process provides for facilitated review and approval of device or procedure modifications during the study. A concept of “contingent approval” can allow FDA to be interactive and work with sponsors to incorporate iterative changes into the clinical environment more quickly. For example, this approach may allow a sponsor to implement a device design or manufacturing change without prior FDA approval and with additional data provided later in the process, provided FDA prospectively concurs with the evaluation methods and acceptance criteria. A “just in time” testing approach focuses on completing the right test at the right time, which may include deferring some testing until after the device design is finalized.

The EFS process also provides the opportunity to involve regulators earlier so they can gain experience with a device during the development phase. Ideally, this leads to reaching a consensus with sponsors about what data are needed to proceed through the clinical study phase, from a first-in-human experience to a larger feasibility study to a pivotal trial leading to FDA approval. These discussions typically involve long-term strategic planning supported by initial safety and effectiveness evidence supporting clinical use of the device, and can entail frequent interactions during the IDE review itself. These issues may be intimidating for less

experienced device developers with academic backgrounds, and in addition to preliminary discussions with FDA it may be helpful to take advantage of industry-wide resources to facilitate these projects. For example, the Medical Device Innovation Consortium (MDIC) has an EFS initiative to achieve a 60/60/60 goal: FDA and IRB approval in the first 60 days, site contract executed in the next 60 days, and patient enrollment within the next 60 days. As of 2021, the approval and enrollment goals are close, but there remain challenges with site contracting and budgeting [17]. There are also efforts to begin engaging more directly with patient advocacy groups and industry trade organizations to encourage the use of EFS in more disease and device areas.

The EFS process has become increasingly popular, with a doubling of IDEs for EFS over the last 7 years. There are now more than 200 EFS IDEs approved with more than 2500 patients enrolled. As FDA has gained more experience, approximately 80% of EFS IDEs are now approved in the first review cycle. Future efforts include facilitating transitions from EFS to pivotal studies, working closer with the Centers for Medicare & Medicaid Services (CMS) on EFS coverage decisions, continuing to advance synergies between the EFS and Breakthrough Device programs, and enhancing collaboration with all stakeholders to drive sustainable growth in EFS.

EFS-type programs are also being considered outside the USA, for example, in Japan, through initiatives such as Harmonization By Doing [18]. Although Japan does not have a formal EFS program, there are opportunities to have consultations with the Japan Pharmaceuticals and Medical Devices Agency (PMDA) to discuss early phase clinical research opportunities. While the start-up culture is different in Japan compared to the USA, there are many opportunities for development of novel products through academic centers and openness within PMDA to discuss regulatory and clinical pathways for initiating clinical studies, particularly for clinical strategies that include a non-Japanese component.

Medical Device Development—Building a Productive Innovation Ecosystem Through De-risking

A primary step toward building a productive innovation ecosystem is to enable de-risking the product development process to the extent possible. This applies not just to product technical factors, but just as importantly to non-technical factors such as regulatory pathway, reimbursement, intellectual property coverage, and existence of an addressable market. Continuing funding challenges due to regulatory requirements and market uncertainties threaten to stall a product's advancement from development to commercialization. Hence, regulatory de-risking is critical, and the regulatory path must be determined early; a great idea

without a good regulatory path will not succeed. Additional de-risking from a payer perspective is also a necessity for long-term success.

De-risking can also enhance the likelihood of success for a start-up engaging with a large company; differences in culture, standards, expertise, and risk tolerance may be a source of friction in partnerships when risk is often shared. Often, there is not a high level of interest in acquisition until the product is near or at the end of development, e.g., in a pivotal trial or even ready to go to market. Higher risk may be acceptable for truly novel technologies that can clearly differentiate and be considered superior to products available on the market; the greater potential benefit allows for a greater potential risk.

Another important aspect of de-risking is having adequate supporting resources available such as innovation communities and a start-up environment infrastructure that includes maker space, office space, mentorship, and a venture studio model. As one example, the Indiana CTSI, including Purdue University, Indiana University, and the University of Notre Dame, has established Think Tanks to provide feedback and advice to academic innovators at various stages of drug and device development to help further de-risk the development process and drive advancements [19].

Pediatric Medical Devices

Recommended best practices for development of pediatric devices, case studies describing clinical and regulatory pathways to support pediatric indications, and FDA programs to promote and encourage development and marketing of pediatric devices are discussed in this section. Pediatric patients are defined in the Federal Food, Drug, and Cosmetic (FD&C) Act (Sect. 520(m)(6)(E)(i)) as persons aged 21 or younger at the time of their diagnosis or treatment; pediatric subpopulations for medical devices are neonates (from birth through the first 28 days of life), infants (29 days to less than 2 years), children (2 years to less than 12 years), and adolescents (aged 12 through 21, up to but not including the 22nd birthday). The development of a pediatric medical device from conception through regulatory approval can be considered through four key phases of development, namely (1) understanding the relationship between pediatric and adult pathology, (2) analysis, (3) iteration, and (4) testing. Details for each phase are provided in Table 1.

Due to the small size of many pediatric disease populations, the Humanitarian Device Exemption (HDE) program is one regulatory pathway sometimes considered for pediatric devices as it requires that a device must exhibit safety and probable benefit, but is exempt from the effectiveness requirements of Sects. 514 and 515 of the FD&C Act, if certain criteria are met [20]. Table 2 provides a further

Table 1 Key phases of development for a pediatric medical device

Phase of pediatric device development	Consideration within each phase
Understand the relationship between pediatric and adult pathology	In some cases, the pediatric variant of a disease may be similar enough to the adult version that pursuing the adult market first can be the more effective path to initially bring the device to market and make it available for physician use
Analysis	Experience in adults can be leveraged to support pediatric use
	Study the problem in extraordinary detail to identify as many variables as possible that are contributing to the pathology
	Use this knowledge to develop design requirements and come up with a blueprint for the device; capture this information to help support intellectual property
Iteration	Consider how these different variables can cause different clinical hazards, considering the wide variability of pathology in children
	Start with prototype, test it, analyze failure, modify prototype to mitigate failure mode, continue the iterative process until design requirements are achieved
	Working through various failure modes, and coming up with new designs, can demonstrate the robustness of and rationale for the final design
Testing	Continuing to iterate the device design also helps define clinically relevant boundary conditions to apply when testing the device; this can be particularly difficult in pediatrics due to the variability from patient to patient
	Identifying when to freeze the design and move into testing is a critical step
	Testing involves bench testing, animal testing, and eventually clinical testing
	At some point, further development or evaluation via non-clinical testing is limited and clinical evidence is necessary to move forward; the EFS program can help quickly identify necessary design modifications that could not be identified from non-clinical testing

Table 2 Comparison of HDE, PMA, and De Novo Classification Request

	HDE	PMA or De Novo Classification Request ^d
Indication for use	Proposed by applicant but based on HUD designation ^a	Proposed by applicant
Safety	Will not expose patients to an unreasonable or significant risk of illness or injury	Reasonable assurance of safety
Effectiveness	Demonstration of probable benefit; exempt from demonstrating a reasonable assurance of effectiveness	Reasonable assurance of effectiveness
Patient population size	≤ 8000 per year in the USA	No limit
Comparable devices	Must be no comparable legally marketed 510(k), De Novo, or PMA device to treat or diagnose such disease or condition ^b	No limit for PMA; for De Novo, must be no legally marketed predicate device
User fee	No	Yes
FDA review time	75 days	180 days for PMA (if no panel meeting); 150 days for De Novo
IRB oversight for use	May only be used at facilities with IRB or appropriate local committee oversight and approval	No
Profit restrictions	Yes ^c	No
Eligible for breakthrough device program	No	Yes

^aPrior to submitting an HDE application, an applicant must first obtain Humanitarian Use Device (HUD) Designation for the device from the FDA's Office of Orphan Products Development

^bOther than another HUD approved under an HDE or a device under an approved IDE

^cOnly certain HDE-approved devices can be sold for a profit, as discussed in Sect. 520(m)(6)(A)(i) of the FD&C Act

^dThe De Novo Classification Process provides a path to market for novel devices for which general controls or general and special controls are adequate to provide a reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device. In addition to providing marketing authorization, this process classifies the device into Class I or II and creates a new classification regulation, and the device may be used as a predicate device for future 510(k) submissions as appropriate [21]

comparison of the HDE, Premarket Approval (PMA), and De Novo Classification Request programs. As mentioned previously, there are limitations with the HDE Program such as restrictions on patient population size, need for IRB approval, and other requirements. However, the HDE Program also includes monitoring of the benefit-risk profile of an approved device in the post-market setting with additional requirements such as oversight by an IRB or appropriate local committee, and annual review of safety signals with FDA's Pediatric Advisory Committee.

Leveraging or extrapolating adult data to support pediatric use may be a relevant strategy when the disease course or condition and the effects of the device are sufficiently similar in adults and pediatric patients, and the existing data are determined to be valid scientific evidence [22]. If there are different risks or adverse events expected for a pediatric population, FDA may request supplemental clinical data to support safety in the pediatric setting. Additionally, pediatric populations are heterogeneous and comprised of numerous sub-populations with many factors to consider (e.g., differences in disease presentation, severity, and impact across different life stages) to appropriately leverage data from adults to pediatrics or from one pediatric sub-population to another.

The concept of pre- and post-market balance considers shifting some of the evidence requirements to the post-market phase to accept a greater degree of pre-market uncertainty if this uncertainty is sufficiently balanced by other factors, including the probable benefits of the device and the extent of post-market controls. In some cases, the probable benefit of having earlier access to a particular device outweighs the associated risks because there may be no alternatives available. Both pre-market and post-market studies should be properly designed to be small enough to complete, yet impactful enough to collect the necessary information to support approval and clinical use.

Cases studies described in Table 3 illustrate some of the points discussed above, particularly the potential for leveraging data from one patient population to another.

Three case studies of pediatric orthopedic devices highlighted the importance of flexibility in the development and review of pediatric devices and the different marketing pathways available in the USA. These cases and the lessons learned are described in Table 4. One clear message is that it is important to maintain good communication with FDA throughout the device life cycle, from early development to post-market.

In some cases, FDA has encouraged companies to consider an HDE as a stepping stone while continuing to work toward a PMA or De Novo submission. As two examples, the Berlin Heart EXCOR® device and the Medtronic Melody™ Valve both started with small studies to support safety and probable benefit for an HDE. Additional studies were

then designed with input from FDA and data collected via post-approval requirements and other data collection pathways to support safety and effectiveness for a PMA [23, 24]. Similar efforts are underway in the orthopedic space. This more holistic milestone-based approach to establishing a reasonable assurance of safety and effectiveness can make these important devices available to patients sooner. In addition, there may be a more favorable reimbursement process for devices that continue down a more traditional regulatory pathway.

HDE devices require approval by an IRB or an appropriate local committee prior to use. This requirement is intended to provide additional oversight and ensure institutions are aware of what data are available since these devices, by definition, may not yet have established a reasonable assurance of effectiveness. One long-time IRB member shared that in their experience this function of the IRB does not add value and wondered if this HDE requirement should be eliminated as it may serve as a barrier to use of HDE devices. There has also often been confusion from the hospital side about the purpose and requirement of IRB oversight. The process can be particularly confusing for hospitals when there is also an FDA-mandated post-approval study required as a condition of HDE approval, resulting in separate IRB approvals—one simply to use the device and a second for the post-market clinical study. One option to consider is a central IRB rather than multiple local IRBs. Initiatives to further educate IRBs on HDEs and the purpose and process of their reviews could also be helpful. However, it was also noted that from a non-FDA perspective, the IRB review process for HDEs may not be fulfilling the original intent of the requirement and alternative approaches may be worth considering. The different stakeholders agreed this is an important issue and should be further examined, and could possibly be discussed as part of the next Medical Device User Fee Amendments (MDUFA) reauthorization process.

How to best leverage existing partnerships to generate innovation related to pediatric devices is an important consideration. Within Indiana there is a recent alliance focused on pediatrics between the Weldon School of Biomedical Engineering at Purdue, Riley Hospital for Children, and Cook Medical to leverage complementary expertise and build synergies. Also, the IU School of Medicine in collaboration with Purdue Biomedical Engineering has a robust MD/PhD program that is a strong resource to develop pediatric devices. In early medical school training, a student can identify a clinical need in collaboration with Riley, start working at Purdue on a technical solution during their PhD, and then continue collaborating with Cook to help mature the technology and consider what clinical data are necessary while completing their MD. Keeping momentum going and building on different expertise throughout the process will be important. A similar

Table 3 Pediatric indication case studies

Device	Abbott SJM™ Masters Series Mechanical Heart Valve	Abbott Amplatzer Piccolo™ Occluder	Neurological implantable device
Status	Approved for nearly 40 years for adults. Recent development of smaller sizes enabled pediatric use and led to the question of what data were necessary to obtain a pediatric indication	Device used for the treatment of patent ductus arteriosus	Adult active implantable device pursuing pediatric indication
Challenge	Pediatric population is both very small in number and also difficult to enroll and follow in clinical studies. A typical adult study for this type of device may require on the order of 800 patient-years of follow-up data prior to being considered for approval, which would not be feasible in the pediatric space	A typical clinical study for this type of device would be hundreds of patients, but the specific device design was intended for a very small patient population of premature or very young babies that would make this study very challenging	Pediatric sub-populations with differences in growth, development, physical activity, quality of life, etc. may require different therapies (e.g., rate, intensity, duration)
Path forward	Determined that 20 pediatric patients enrolled in a clinical study would be adequate in combination with extrapolating knowledge from the substantial experience already available in adults	Study design developed to enroll 50 patients, including leveraging results in the cohort of babies > 2 kg birth weight to support use in the smaller cohort of those < 2 kg birth weight	Leverage existing (off-label) data in the older pediatric population and combine with additional clinical data to more broadly support safety and specifically support effectiveness in specified age group sub-populations
Result	This additional data allowed a specific assessment of device safety for a pediatric indication. In addition to extrapolation of adult data, there was also a shift of some long-term clinical evidence collection to the post-market space, as well as use in alternative cardiac valve locations	Flexibility on study population size and patient sub-population allowed the device to come to market and be available to treat patients	Safety and effectiveness demonstrated and appropriate therapy for active implantable device determined for various pediatric sub-populations

Table 4 Pediatric orthopedic case studies for different regulatory pathways

	Case 1	Case 2	Case 3
Device	Posterior spinal systems that incorporate pedicle screws for treatment of pediatric spinal patients	Device to address unmet need for repair of a torn anterior cruciate ligament in young, active patient population in which current techniques were inadequate	Spinal devices intended to provide fusionless correction of pediatric idiopathic scoliosis as an alternative to the traditional technique of spinal instrumentation and fusion
Regulatory pathway	510(k)	De Novo Classification ^a	HUD/HDE
Challenge	Posterior spinal systems that incorporated use of pedicle screws were available for adult patients, but no specific regulatory clearances addressed pediatric indications. However, physicians used these devices off-label for treatment of pediatric patients. Although non-clinical performance data are often adequate to demonstrate substantial equivalence to a predicate device, in some cases clinical data may also be necessary	Novel device, no legally marketed predicate device available upon which to base a determination of substantial equivalence	Clinicians developed device strategies by modifying devices available for adult use for use in pediatric patients. Clinical research to support regulatory approval for pediatric use would require an investigational device exemption (IDE) and individual physicians considered this approach burdensome to pursue
Solution	Leverage existing published clinical data from post-market use	Pursue De Novo Classification Request	FDA worked with medical specialty societies, the scoliosis community, and physicians to address this challenge. Subsequently, one manufacturer sponsored an IDE study that led to Humanitarian Use Device (HUD) designation and subsequent submission of data in support of a Humanitarian Device Exemption (HDE) application. A single-center study with a 2-year follow-up provided clinical evidence to support safety and probable benefit
Outcome	Devices cleared for pediatric use	De Novo Classification Request granted; device authorized for marketing and available to serve as predicate for future 510(k) submissions of the same device type	HDE granted for first spinal device for fusionless correction of pediatric idiopathic scoliosis
Lessons learned	Demonstration of how existing regulations can accommodate pediatric extrapolation of clinical data, as explained in subsequent FDA guidance [22]. Programs related to pediatric device development and guidance around use of valid scientific evidence from multiple sources and multiple types of data now developed. Due to heterogeneity within the overall pediatric population, it remains very important to carefully define the target population for a pediatric medical device	Critical to maintain good communication and engagement between sponsor and FDA at key stages throughout device development process, which included an EFS and pivotal study	Although some uncertainty remained regarding long-term effectiveness due to the limited data available, it was in the best interest of patients not to delay availability of these devices; long-term data could be collected via robust post-approval registries as a way to appropriately balance pre- and post-market data collection

program is in place at the University of Minnesota as part of a local pediatric consortium and Earl Bakken fellows program [25]. A limited number of FDA-funded pediatric consortia also act as hubs located around pediatric medical centers of excellence to provide support and assistance for multiple pediatric device projects during all stages of development [26].

Incentives or mandates could be considered to help accelerate or encourage pediatric device development, similar to what occurs with drugs for pediatric use. However, one key difference out of many between drug and device development is that the active ingredient in a drug is the same for adults and children. On the device side, a total redesign may be needed for pediatric use, resulting in a very different device to treat adults compared to children, which would make any sort of mandate a difficult concept to consider. However, evaluating pediatric needs when starting to develop a device for adults remains a critical concept, and FDA encourages sponsors to consider this as part of a marketing submission. It is also important to remember there are multiple potential pathways by which clinical evidence can support a submission to FDA. Different programs and tools are available for pediatric drugs and devices and these should continue to be improved and better utilized to move the development of pediatric devices forward.

Diagnostic Devices, IVDs, and Disease Detection

Academic researchers and start-ups in the diagnostics space often have a lack of understanding around when and how to reach out to FDA. This was highlighted during the COVID-19 pandemic when numerous academic researchers and private start-ups with extremely limited regulatory background rapidly entered the diagnostics space. Good communication with FDA is key and there is no differentiation in FDA's willingness to work with small start-ups, academics, or large companies. Some FDA communication pathways and programs applicable to all devices, not just diagnostics, include the following:

- Q-submission Program that provides various mechanisms for interacting with FDA, including receiving feedback prior to an intended premarket submission
- Breakthrough Devices program to help encourage and speed novel device development
- FDA's Division of Industry and Consumer Education (DICE) can provide technical and regulatory assistance, help answer questions, and provide direction, particularly for small businesses and academic and research organizations

In addition to considering when and how to communicate with FDA, it is also important to have regulatory scientists involved very early in diagnostics development to help guide the intended use and indications for use. The intended use should be clearly defined and can strongly influence the regulatory path and consequently the design and development of the test or device. This decision drives what analytical testing needs to be performed and what clinical testing should be considered. Understanding how the result or outcome from the test will be used clinically is also a key factor in determining the appropriate intended use. One theoretical example considers a carcinoembryonic antigen (CEA) test with a very general use "to measure CEA" compared to a more specific use "to measure CEA to monitor and aid in the diagnosis of a potential metastasis"; these two uses could lead to different regulatory paths and test requirements. While the general use would only require evidence of accurate CEA measurement, the specific use would require more extensive evidence to support that this measure can also be used for diagnosis; the diagnosis component could result in a higher classification due to increased risk around misdiagnosis.

Of particular importance to the diagnostics industry is that there be rigorous and scientifically sound data, testing, and documentation to support a technology. Additionally, manufacturability and scale-up can be vital considerations that are sometimes overlooked. For example, molecular assays to detect COVID-19 were developed in parallel to the manufacturing process rather than sequentially, resulting in numerous manufacturing challenges and increased risk that was necessary due to the time-critical situation.

Another industry challenge is the development and evaluation of novel diagnostic tests that do not have a clear predicate to successfully use the 510(k) process. In this case, a sponsor could consider a Pre-Submission to initiate conversation with FDA. The submission typically provides details of the device and how it will be validated, followed by specific questions to FDA about the proposed testing. Particular development steps will depend on the device, what it does, and how it can be validated, but in general it is helpful to include some way to compare to a reference standard, reference device, or reference test. FDA remains very open and willing to work with test developers on advancing novel technologies.

The integration of smartphones and similar devices into the performance, interpretation, or reporting of a diagnostic test is a topic of high interest. Understanding the regulation of these products can be challenging and specific examples or questions can be discussed with FDA to obtain feedback on the topic, if not identified in a final guidance document. One hypothetical example provided in Fig. 2 considers some of the decision points for an ancillary device or app that

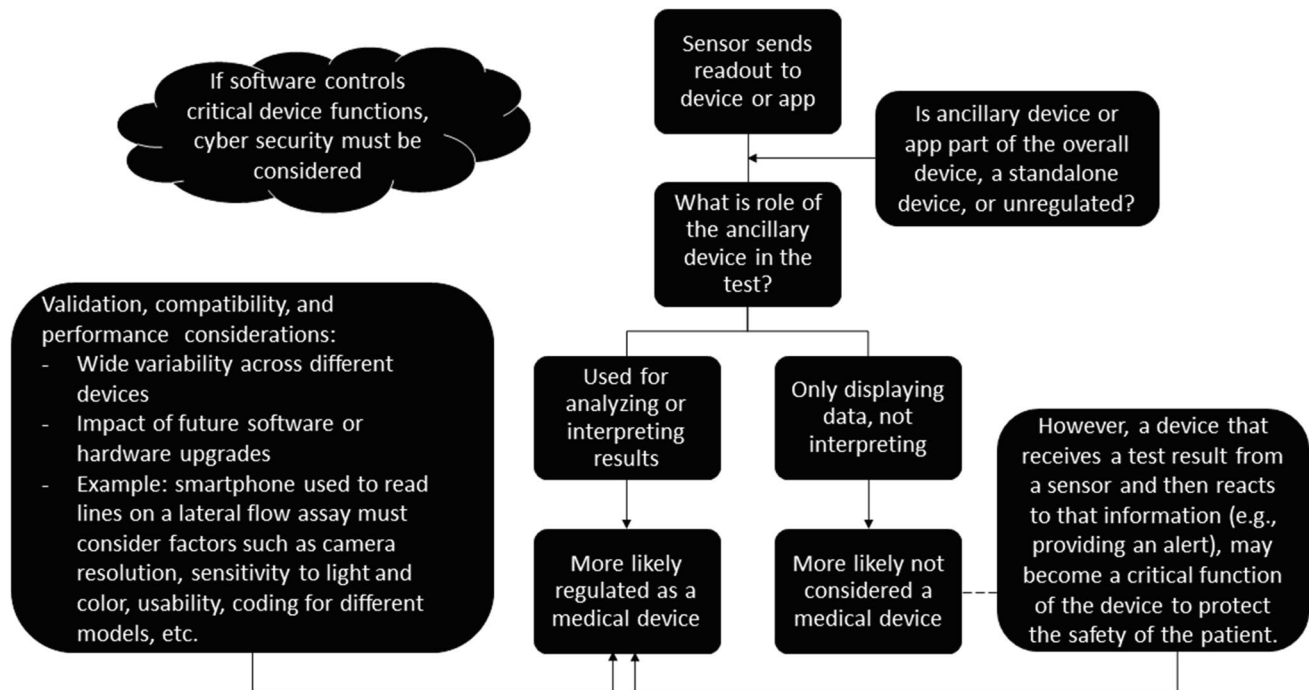


Fig. 2 Hypothetical regulation of ancillary device or app

receives readings from a sensor; additional examples are included in FDA guidance [27].

COVID-19 has catalyzed changes in development, regulatory, and clinical activities related to diagnostic devices, and some of these changes may be carried forward beyond the pandemic. For example, there is increased demand for testing in non-traditional settings, such as self-testing at home, and continuing innovation in this space may result in low-priced over-the-counter test kits for in-home testing for various diseases far beyond just COVID-19. This will provide new opportunities for improving patient care and disease management and promoting health. While the compressed pace of test development from years to just months is not expected to become standard, there are opportunities to improve efficiencies and accelerate the traditionally slower pace of development. These include an increased awareness to be proactive, considering alternative approaches throughout the development process, and potentially accepting a higher level of risk tolerance during development such as performing steps concurrently rather than sequentially.

Increased access to FDA's current thinking via guidance or Pre-Submission feedback has allowed industry to effectively develop new products and move products efficiently through the regulatory review process. Weekly open town-hall meetings offered by the Office of In Vitro Diagnostics and Radiological Health to discuss COVID-19 test development have been valuable and there is consideration to continue offering some sort of similar forum on a regular

basis (e.g., monthly). For new technologies that FDA realizes may be particularly important to public health, there is an effort to develop draft recommendations (e.g., rapid tests for COVID-19 diagnosis). Additionally, FDA submission templates for various technologies have helped clarify regulatory expectations, especially for new developers. FDA submission templates may continue to be developed, particularly for common technologies, to help democratize access.

Digital Health and Wearable Devices

The beginning of this section describes recent FDA initiatives involving digital health, shares recent FDA authorizations for digital health products including orthopedic products, and provides a look at the future of the digital health field. Digital health can be viewed as the convergence of connectivity, data, and computing power for healthcare and related uses across the life of an individual or a patient. Equally, digital technologies can help consumers make informed decisions, enable moving care from the traditional care setting such as a clinic to the patient, and facilitate better understanding of patient behavior and physiology to help prevent disease or change the course of disease via earlier and smaller interventions. FDA has expectations for different aspects of digital health technologies, including when used as a medical product, incorporated into a medical product, used to develop or study a medical product, and when used

as a companion or adjunct to a medical product. FDA's goal continues to be to enhance patients' access to high-quality, safe, and effective digital health products; this should be accomplished in a least burdensome manner while continuing to provide a reasonable assurance of safety and effectiveness in a field with a rapidly evolving pace of development. Within the FDA Digital Health Center of Excellence, the goal is to empower digital health stakeholders to advance healthcare by fostering responsible and high-quality digital health innovation. This is a broader focus on responsible innovation, not just regulations, and includes connecting and building partnerships to accelerate digital health advancements and sharing knowledge to increase awareness and advance best practices, in addition to pursuing innovative regulatory approaches. There are a number of focus areas within the Center that span the total product lifecycle. In particular, interoperability and cybersecurity are becoming increasingly important to consider.

Consumer technology has continued to move into the medical area as technology used in day-to-day life becomes part of healthcare, leading to the development of novel and innovative products. We should understand and have appropriate expectations for bringing these products to market when they are used for preventing, mitigating, diagnosing, or curing disease. One initial factor to evaluate when considering FDA regulation of a digital health technology is the benefit and risk profile. This assessment can help determine how or if the product will be regulated. Recent products include electronics that provide augmented reality as well as novel therapeutic technologies. Looking ahead to coming products, technologies such as energy harvesting are being connected with sensors to provide a holistic real-time view of an individual's physiology. Based on the evolution of these products, as a community of academia, government organizations, device manufacturers, small start-ups, regulatory affairs professionals, clinicians, patients, and the general public, we should think about how to prepare for a digital revolution in healthcare.

Digital health technologies undergo rapid development, iteration, and innovation compared to traditional medical devices, resulting in a potentially exponential increase in submission volume as a result. The current regulatory paradigm may not be fit for purpose in this space and a more holistic ongoing and continuous oversight approach that depends upon not just the product, but also the manufacturer/developer and how the product is performing in the marketplace, may be appropriate. At the core of this thinking are principles of patient safety, product quality, clinical responsibility, cybersecurity responsibility, and a proactive culture. A pre-certification concept of excellence appraisal, review pathway determination, streamlined pre-market review process, and real-world performance has been used to develop a working model with artificial

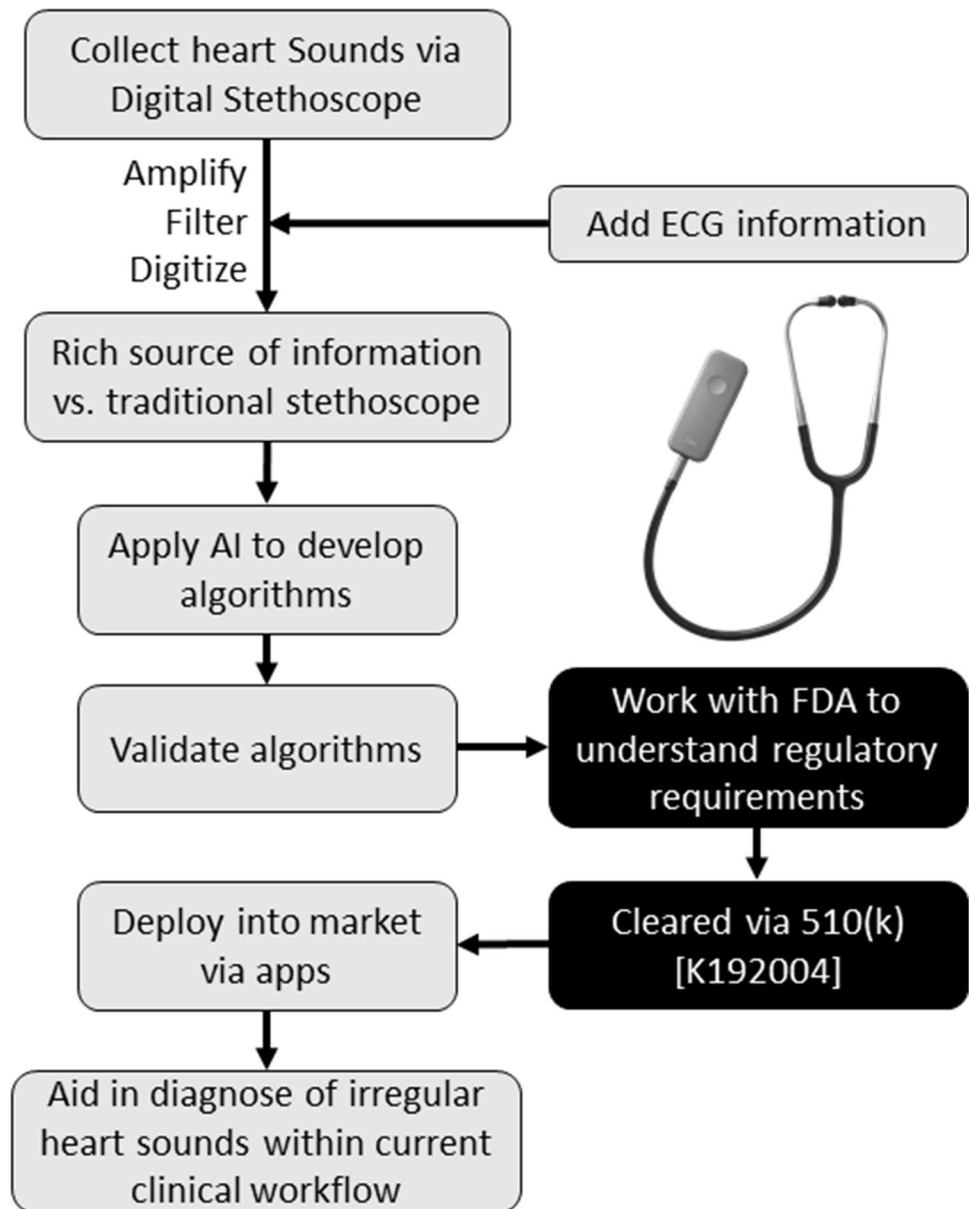
intelligence (AI) and machine learning (ML) as a use case to test this program. FDA received many comments and published a plan in January 2021 for moving forward in a total product lifecycle approach rather than an episodic manner [28]. The plan includes many aspects specifically intended to facilitate the appropriate development of devices incorporating AI/ML, including the potential for a "pre-determined change control plan" that would permit iterative changes to device algorithms after marketing. The plan also calls for additional public engagement and partnerships with stakeholders in this space, as recently evidenced by the joint development and publication of guiding principles for Good Machine Learning Practices (GMLP) by regulators in the USA, Canada, and the UK [29].

In many cases, digital health products may already be outdated as soon as they are approved or cleared because of iterative changes that continue to be developed. The concept of having a pre-determined change control plan could allow a company to work with FDA on discussing how a product or algorithm may evolve over time and what guardrails should be in place to allow a more agile regulatory framework that will continue to allow these products on the market for patients while also continuing to provide a reasonable assurance of safety and effectiveness. Within FDA there are ongoing conversations across offices (e.g., Digital Health Center of Excellence, Office of Science and Engineering Labs, Offices of Health Technology) to develop best practices and ensure consistency in reviews and feedback.

The following case study provides an example industry experience bringing a digital technology to market. Many digital products started as consumer wellness products and have transitioned over time into medical products. In many cases, the claims or intended use for the product determines if it is a general wellness product or a medical device, e.g., measuring heart rate for exercise feedback vs. to detect bradycardia. This case study, described in Fig. 3, reviewed the use of digital technologies to enhance the role of a stethoscope as a cardiac screening tool. As a result, algorithms to diagnose irregular heart sounds have been cleared through the 510(k) process and deployed via apps into the market [30]. The technology also enables remote examination and sharing of information with other healthcare providers.

Additional algorithms can be developed by leveraging the vast amount of information collected from digital devices. For example, low ejection fraction is currently measured and diagnosed by an echocardiogram and is undetectable by a traditional electrocardiogram (ECG). However, by analyzing a very large number of concurrent ECG and echocardiogram measurements, an algorithm can be built as a screening tool to allow a single lead ECG to predict who should undergo further testing for low ejection fraction [31]. This development of software as a medical device has received

Fig. 3 Example of digital health technology to enhance patient care



breakthrough designation with FDA to help bring the technology to market.

During clinical trials of digital health products, there are often questions around making and documenting changes to the technology being studied. Traditionally, the preferred approach in clinical trials has been to minimize any changes once a study has been initiated. However, this is not always possible for digital health; e.g., there may be software changes that occur over time. Starting with a risk-based assessment and considering the potential impact of a change on the study endpoints continues to be appropriate. Changes to critical aspects of a product, unless absolutely necessary, are not desirable, but changes that would not be expected to impact endpoints may be reasonable. Documentation is important to explain and justify how the change

will be managed and/or why the change will not affect the results of the study.

An important consideration when developing new technologies of any sort, and in particular digital technologies and artificial intelligence that often interact directly with the patient, is how users and/or patients will interact with and benefit from the product. Industry should focus on identifying and meeting user needs and considering usability and value of the product to the user throughout the development process. As one example, considering how a product fits within the current workflow to make transition to the technology as seamless, intuitive, and user-friendly as possible is an important consideration for digital stethoscope technology. Involving users throughout product development can help achieve this objective. Continuing to engage and

train physicians and patients on use of new technology is also important, and providing education around upcoming new developments in the digital health space will increase acceptance.

Having hands-on demonstrations and discussions of novel digital health technologies with FDA can also be very helpful. Bringing FDA experts together with product developers and end users may enable FDA to achieve a greater understanding of the technology and function of the device; how it fits in clinical practice, relevant patient-reported outcomes, and patient preferences; and what the benefits and risks may be when compared to only a paper-based review. This interactive process can lead to a more effective and efficient overall review process for a product, and the enhanced communication is beneficial for many novel products, not just those in digital health.

The Pressing Need for Enhanced Communication

Throughout this review, there is a consistent emphasis on the critical importance of communication with FDA. One initial barrier for many academics and small start-ups is simply knowing how and when to initiate contact. FDA encourages early communication through the Q-Submission process, both via Informational Meetings to start a general dialog with FDA regarding technology under development to ensure the technology is sufficiently well-understood, and via Pre-Submissions to obtain FDA feedback on specific regulatory and technical questions to guide device development and strategic planning. FDA feedback can also be obtained less formally via email, either from the relevant review team or from the Office of Communication and Education's Division of Industry and Consumer Education regarding general questions about medical device regulation. Within digital health specifically, many questions relate to if a technology falls under FDA regulation or not and the Digital Health Center of Excellence will try to provide feedback if similar technologies have or have not been regulated. In some Pre-Submission discussions, FDA may be able to provide feedback regarding potential predicates for the 510(k) pathway or discuss the appropriateness of the De Novo pathway to market for a particular device. FDA has internal discussions across offices around new and upcoming technologies to help identify best practices and provide consistent and effective feedback to innovators. In emerging fields, there will be a need for FDA, industry, and innovators to learn together, and clear communication from all parties is necessary.

The question of how early to engage with FDA was also considered. While there remains variability in preferred approaches, some potential prerequisites to consider for a productive Pre-Submission discussion include

understanding the device, the intended use, the patient population and clinical setting, and the relative benefits and risks, as well as having a basic strategy for evaluating the device. While some innovators may feel they are not ready for a full Pre-Submission early in the development stage, if a question is too complex for an informal email or query, it is important to consider that Pre-Submissions can be narrowly focused on a single topic.

For new start-ups and small companies in particular, there can be many unknowns around how and when to start interacting with FDA and, in some cases, a persistent fear of sharing information, especially information regarding early prototype failures. From FDA's perspective, it is often helpful to understand the history of development of a device, such as understanding previous failures, iterations, and improvements, which demonstrate the robustness of risk assessment and the current design. Similar to device developers, FDA is excited and interested to see novel devices brought forward to help patients and there is no need to fear sharing information.

By the same token, FDA also recognizes the value in broader proactive communication with the medical device ecosystem to demystify the regulatory process and gain further insight into device evaluation and access considerations. For example, FDA regularly convenes public advisory committee meetings to gain external expert recommendations on how to address new questions of safety and effectiveness as they arise, either as part of specific file reviews or to more generally inform the device evaluation landscape in a given topic area. FDA also convenes workshops during which FDA along with other stakeholders can discuss potential best practices in a given technical area, and routinely participates in scientific and clinical symposia to maintain currency in these fields. This multi-faceted approach to engagement supports FDA's mission to enhance the development of novel devices via collaboration and mutual learning.

In conclusion, collaboration and cooperation between clinicians, researchers, industry, and regulators is important for successful translation of laboratory and clinical observations and ideas into products and interventions that improve patient and public health. The criticality of good communication includes not only early and often communication with FDA, but also with patients, end-users, and other stakeholders. Numerous regulatory programs and processes are in place or being developed to help facilitate communication and translation of innovative products including the Pre-Submission, Breakthrough Devices, and Early Feasibility Study programs. Flexibility is an important consideration as evidence requirements may vary dependent upon technology, the benefit-risk ratio, and what is best for the patient. By sharing this review, we hope to highlight current strategies, opportunities, and best practices and thereby increase the

regulatory knowledge base for all stakeholders as one step toward improving medical product translation.

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Declarations

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