Research and Enlightenment of FDA's Digital Health Software Pre-Cert Program

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Abstract

Objective To study the supervision experiences of the US digital health software pre-cert program, and to provide reference for the scientific supervision of digital health in China. **Methods** By reviewing domestic and international databases from PubMed, Web of Science, CNKI, and Wanfang, as well as FDA's website, the innovative regulatory pathway of software pre-cert was investigated comprehensively. Then, This method was compared with the current regulatory actions in China so as to propose some suggestions for digital health regulation in line with our national conditions. **Results and Conclusion** FDA's software pre-cert program emphasizes assessment at the organizational level and product level first, streamlines the pre-market review process, and relies on post-market evidence generated from real-world data and elements of excellence appraisal to strengthen post-market regulation of software as a medical device (SaMD). However, post-marketing data in China are difficult to obtain, so this method cannot be copied totally. Currently, we can explore the elements that must be reviewed for registration of medical device according to enlightenment of the program, reduce the burden on enterprises and regulatory agency. At the same time, the post-marketing regulatory system should be improved gradually, and experience in the whole life cycle management of medical device should be accumulated, which can make preparations for enhancing the ability of regulatory innovation.

Keywords: digital health; software pre-cert; pre-marketing review

WHO released the "Global Strategy on Digital Health (2020–2024)", which defined the priority of digital health strategy in the development of global healthcare industry. As a cross-discipline of information, digital technology and innovative therapeutics, digital health has experienced the development of Internet medical and telehealth in the USA for many years, and the concept that digital health can improve national health has become a consensus. To accelerate the approval of digital health innovative therapeutics and utilize escalating regulatory tools to promote innovation, FDA believes that the traditional review pathway is no longer appropriate for regulating innovative therapeutics. Therefore, a new regulatory framework is urgently needed to accommodate the digital Health technology [1]. How to regulate such products and ensure the safety and efficacy of them while protecting the positive innovation of the manufacturers is what China's regulatory agency needs to consider. Since the United States has initially developed an innovative regulatory

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pathway for digital health products, we studied the U.S. digital health software pre-cert program to explore the establishment of a scientific regulatory pathway based on the characteristics of digital health software products. Then we can put forward some suggestions to enhance China's digital health industry.

1 Digital health innovation action plan

According to FDA's guidance of "Changes to Existing Medical Software Policies Resulting from Section 3 060 of the 21st Century Cures Act" which excluded certain classes of low-risk medical devices from FDA regulation [2], the FDA planned to create a risk-based regulatory approach for digital health.

On July 27, 2017, the FDA's Center for Devices and Radiological Health (CDRH) released the Digital Health Innovation Action Plan, which proposed a new regulatory approach to medical software. The plan aimed to advance digital health technology by building new relationships and fostering collaboration with digital health manufacturers, patients and providers. In addition, the plan was tasked with developing and implementing regulatory strategies, policies, and processes in this area and ensuring transparency and clarity of these policies and processes [3, 4].

This action plan worked to achieve several key goals: (1) Release guidance to modernize policies; (2) Increase the number and expertise of FDA's digital health staff; (3) Align FDA regulation of digital health technologies by reconceptualizing the regulatory pathway to software as a medical device (SaMD), such as developing a digital health software pre-cert program, and exploring how to leverage "AI/ML in SaMD".

2 Software pre-cert program

The current procedure of premarket reviews pathway for medical devices based on moderate- and high-risk hardware are lengthy and detailed, but such a pathway can impede or delay patient access to innovation therapeutics. Therefore, it is not suitable for digital health software products with faster iterative design, development, and validation types [5]. FDA initiated a "Software Pre-Cert Program" [6] in July 2017 to streamline the premarket review pathway and reduce the burden on manufacturers and the FDA.

2.1 Pilot program participants

The FDA received more than 100 applications from different companies. In selecting the participants, the agency considered several factors including company size, excellent quality and organizational management records, clinical focus area and the risk profile of the product.

Nine companies with different characteristics were ultimately selected. The diversity of pilot participants facilitated FDA's understanding of various views on how industry defines organizational excellence and other key performance indicators, which would not disadvantage small companies. The list of 9 pilot participants is shown in Table 1 [7].

Table 1 List of participants in the software pre-cert program

Participant	Location
Apple	Cupertino, California
Fitbit	San Francisco, California
Johnson & Johnson	New Brunswick, New Jersey
Pear Therapeutics	Boston, Massachusetts
Phosphorus	New York, New York
Roche	Basel, Switzerland
Samsung	Seoul, South Korea
Tidepool	Palo Alto, California
Verily	Mountain View, California

2.2 Scope of regulated products

The scope of the program is currently limited to SaMD. SaMD is defined by the International Medical Device Regulators Forum (IMDRF) as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device" [8].

In the future, FDA hopes to expand the scope of controlled products to potentially include all medical device software that meets the definition of Section 201 (h) of FD&CA, including SaMD, software in a medical device (SiMD), and other software that could be regarded as accessories to hardware medical devices [9].

2.3 Working model

Through this pilot program, FDA expected to streamline the premarket submission of some products, which could reduce submission content or interactive reviews, with the goal of reconceptualizing the regulation pathway of digital health products [10]. The program is first focused on software manufacturers or digital health technology manufacturers, rather than products. FDA selected manufacturers with the culture of quality and organizational excellence based on several criteria to ensure the excellence in software design, development, and validation. Eligible manufacturers do not need to be reviewed or can have their premarket review streamlined. Streamlined premarket review process includes reduced submission content and faster review by CDRH. In addition, pre-cert manufacturers can collect post-market real-world data, which in turn can support rapid product development. FDA plans to use real-world data in the future so that manufacturers can use the national evaluation system for health technology (NEST) to evaluate medical devices throughout their lifecycle. Besides, manufacturers can apply advanced data analytics to meet unique data needs and medical device innovation cycles on its own terms. The goal of NEST is to provide better evidence for medical device evaluation and regulatory decisions throughout the device innovation cycle [11].

2.4 Excellence appraisal and precertification

FDA regulates SaMD with a primary focus on software manufacturers or digital health technology manufacturers, rather than specific SaMD products. FDA selects manufacturers with a sustained culture of quality and organizational excellence based on elements of excellence appraisal to ensure the excellence in software design, development, and validation. Eligible manufacturers can sell their low- and medium-risk medical devices without additional review or streamlining premarket review pathway.

2.4.1 Elements of excellence appraisal

FDA would evaluate organizational excellence based on 5 cultures of quality and organizational excellence (CQOE) principles. The 5 excellence principles are:

(1) Product quality: Demonstration of excellence in the development, testing, and maintenance necessary to deliver SaMD products at the highest level of quality.

(2) Patient safety: Demonstration of excellence in providing a safe patient experience and emphasizing patient safety as a critical factor in all decision-making processes.

(3) Clinical responsibility: Demonstration of excellence in responsibly conducting clinical evaluation and ensuring that patient-centric issues, including labeling and human factors, are appropriately addressed.

(4) Cybersecurity responsibility: Demonstration of excellence in protecting cybersecurity and proactively addressing cybersecurity issues through active engagement with stakeholders and peers.

(5) Proactive culture: Demonstration of excellence in a proactive approach to surveillance, assessment of user needs, and continuous learning.

Because software development methods, processes, and practices vary among and within organizations, FDA has proposed 12 specific elements for pre-certification organizations to demonstrate how their specific processes are aligned with the

identified elements and managed objectively to evaluate organizational excellence more effectively. These 12 specific elements are: (1) Leadership and organizational support; (2) Transparency; (3) People; (4) Infrastructure and work environment; (5) Risk management: A patient safety focus; (6) Configuration Management and change control; (7) Measurement, analysis, and continuous improvement of processes and products; (8) Managing outsourced processes, activities, and products; (9) Requirements management; (10) Design and development; (11) Verification and validation; (12) Deployment and maintenance.

2.4.2 Key performance indicators

When conducting an excellence appraisal, FDA will review the performance indicators of the pre-cert organization. Developing and tracking key performance indicators (KPIs) can help organizations monitor, improve and demonstrate performance and provide critical organizational decisions. KPIs can be at the organizational level, group level, and/or project or product level. KPIs, as part of a pre-market excellence appraisal, will drive post-market product assessments based on data related to real-world performance. Besides, evaluating an organization's KPIs as part of a pre-certification excellence appraisal is important for post-market product performance.

FDA intends to collect KPI periodic summary reports (e.g., quarterly) that describe relevant results, highlighting and explaining any outliers or anomalies in the data, and summarizing any actions taken or planned to address those outliers or anomalies. The scope of KPI collection is limited to the scope of the organization's product for the excellence appraisal.

2.4.3 Precertification levels

To ensure that the pre-certified software has the same safety and efficacy standards, FDA proposed a precertification standard of two grades. However, they are not implemented in the program, and are only used for exploration in the future pre-certification program. The specific differences between the two levels of pre-certification are as follows.

(1) Level 1 Pre-Cert: This level of certification is designed to allow organizations to develop and market certain lower risk software without review while requiring a streamlined review for other types of software. This level of certification may benefit an organization with limited or no experience in delivering SaMD, but with established organizational elements and strategies in place that indicate they have or can acquire the capability to deliver and maintain high quality software products that are safe and effective.

(2) Level 2 Pre-Cert: This level of certification is designed to allow organizations to develop and market certain low-and medium-risk software without review while requiring a streamlined review for other types of software. This level of certification may benefit an organization with extensive experience in delivering software products to suggest a level of assurance in the development of safe and effective low-and medium-risk SaMD.

2.5 Review pathway determination

The principal objective for establishing the review pathway determination of the "Software Precertification Program" is to develop a risk-based framework, which is convenient for pre-cert organizations to determine the premarket review pathway for their SaMD products.

2.5.1 SaMD risk categorization

FDA assumes to leverage the risk-category framework for SaMD developed by the IMDRF to inform the risk category. The IMDRF framework establishes types and subtypes of SaMD products based on the state of the healthcare condition and the significance of the information provided by the products.

There are three states of the healthcare conditions that SaMD is expected to use: critical, serious, and non-serious (Table 2).

Table 2 Healthcare conditions of SaMD

Healthcare conditions that SaMD is expected to use	Critical	Serious	Non-Serious
Type of disease or condition	Life-threatening state of health, including incurable states; Requires major therapeutic interventions; Sometimes time critical, depending on the progression of the disease or condition that could affect the user's ability to reflect on the output information	Moderate in progression, often curable; Does not require major therapeutic interventions; Intervention is normally not expected to be time critical in order to avoid death, long-term disability or other serious deterioration of health, whereby providing the user an ability to detect erroneous recommendations	Slow with predictable progression of disease state (may include minor chronic illnesses or states); May not be curable; can be managed effectively; Requires only minor therapeutic interventions; Interventions are normally non-invasive in nature, providing the user the ability to detect erroneous recommendations
Intended target population	Fragile with respect to the disease or condition (e.g., pediatrics, high risk population, etc.)	Not fragile with respect to the disease or condition	Individuals who may not always be patients
Expected use	Specialized trained users	Either specialized trained users or lay users	Either specialized trained users or lay users

There are 3 conditions that SaMD provides the significance of the information to medical decision-making: To treat or to diagnose, to drive clinical management, and to inform clinical management (Table 3).

Table 3 Significance of the information to medical decision-making from SaMD

Condition	Significance of information
To treat or to diagnose	To provide therapy to a human body
	To diagnose/screen/detect a disease or condition
To drive clinical management	To aid in treatment by providing enhanced support to safe and effective use of medicinal products or a medical device
	To aid in making a definitive diagnosis
	To triage or identify early signs of a disease or conditions
To inform clinical management	To inform of options
	To provide clinical information by aggregating relevant information

This risk categorization is divided into 4 classes, with Class I risks being the lowest and Class IV risks being the highest, with higher risks resulting in stricter risk control measures (Table 4) [11].

Table 4 IMDRF risk categorization

Healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

2.5.2 Product level elements of a SaMD

According to the required elements of SaMD products risk categorization, FDA proposes the following list of product-level elements that pre-certified organizations would provide on their SaMD: (1) Significance of the information provided by the SaMD to the healthcare decision; (2) State of the healthcare situation or condition; (3) Core functionality of the SaMD; (4) Device description, which may include a general description of the software device including the following: explanation of how the software works; significant security, technical, and safety risks; information regarding supporting platforms, components, and compatibility; instructions and limitations for use; inputs used; and customer support; (5) SaMD performance, which may include a general description of the software performance characteristics, such as the analytical or clinical performance of the SaMD in the intended healthcare situation or condition, as well as information regarding the SaMD privacy and security policies.

The review determination team would review the information provided to confirm the risk category and that the information is complete. To avoid duplicative submission of the same elements, they would be retained and documented for pre-market review. FDA intends to post the SaMD product-level elements on the FDA website following completion of review pathway determination or following clearance or approval of the SaMD. If the information of the product is incomplete or it is required to change after a streamlined review, manufacturers would revise SaMD product-level elements during an interactive discussion with FDA, prior to public posting.

2.6 Streamlined premarket review pathway

The principal objective of establishing the streamlined premarket review procedure of the Software Pre-Cert Program is to determine the elements necessary for a premarket review and to develop a premarket review procedure that provides reasonable assurance of the safety and effectiveness of a software product from a pre-certified organization. This includes what information would be reviewed, how modifications affect marketing authorization, and how to leverage existing SaMD standards. The FDA also plans to conduct interactive reviews on a case-by-case basis and expects to make marketing decisions on SaMD products of prequalified organizations in a short time than the traditional premarket review pathway [12].

2.6.1 Innovative regulatory model for pre-market review

An innovative regulatory model for pre-market review of a SaMD products of prequalified organizations depend on (1) The IMDRF risk category of the SaMD; (2) The level of precertification of the organization. Table 5 describes how SaMD determines whether a premarket review or streamlined premarket review is required based on the IMDRF risk category and the organization's precertification level (L1, Level 1: L2, Level 2).

Table 5 Proposed level of review for level 1 and level 2 pre certified organizations' SaMD in future pre-cert program

IMDRF risk categorization		Level of review for Level 1 and Level 2 pre-certified organizations' SaMD		
Type	Description	Initial product	Major changes	Minor changes
Type IV	Critical + diagnose/treat	SR	SR	No review
Type III	Critical + drive			
Type III	Serious + diagnose/treat	L1 SR L2 No review	L1 SR L2 No review	
Type II	Serious + drive			
Type II	Non-serious + diagnose/treat			
Type II	Critical + inform			
Type I	Non-serious + drive	No review	No review	
Type I	Serious + inform			
Type I	Non-serious + inform			

2.6.2 Elements necessary for assuring safety and effectiveness of a SaMD product in premarket review

FDA proposes that certain elements traditionally reviewed in a premarket submission for a SaMD product can be evaluated at the organization level during the Excellence Appraisal and at the product level during Review Determination. The elements required in the streamlined review process is listed in Table 6, and the depth of the FDA review varies with the risk of the reviewed devices.

Table 6 The elements required in the process of streamlined review

Module of review	Streamlined review elements
Administrative element	□Cover letter
	□Financial certification and disclosure form
	□Truthful and accuracy statement
Product-specific element	□Clinical algorithm
	□Clinical data analysis and interpretation
	□Cybersecurity product-specific information including threat model
	□Declaration of conformity and summary reports for vertical standards
	□Hazard analysis (product-specific)
	□Instructions for use
	□Labeling review
	□Regulatory pathway specific items (e.g., 510 (k) substantial equivalence comparison)
	□Requirements (product-specific)
	□Revision history
	□SaMD product demo
	□Software architecture
	□Validation (product performance)
Element leveraged from other components	□Excellence appraisal assessment
	□Review determination information (Indications for use, device description, etc.)
	□Real-world performance plan

2.6.3 Interactive streamlined review process for premarket review

Although FDA has different requirements and procedures for 510 (k) submissions, De Novo requests, and PMA applications, there are some common review elements. The streamlined review pathway is focused on what the subject device is and its intended use, so it is the same elements that needs to be submitted.

FDA plans to cancel the administrative review and focus on the following priorities to complete the interactive review: (1) Eliminate duplication: Duplicative information is presented in many parts of the traditional documentation. For example, for a SaMD product, the software/firmware description typically included in the software documentation is duplicative of the product description, because the device is software. In another example, as to the information across precertification processes, many of the elements found in a device description for a device are the same information that is part of review determination. (2) Interactive: Promoting the use of an interactive review process may contribute to a more efficient review. Enhanced early interaction

may benefit and improve the review process because it would expose potential challenges early. Therefore, both parties can proactively plan interactions that move towards the goal of a complete and transparent premarket clearance. (3) Automation: Automation would be used to streamline the review process and to perform administrative functions. FDA is considering to develop templates that help the sponsor to determine if the submission is complete before it is submitted to FDA. This automation should shift the focus of the review process to a technical review of the product rather than an administrative review of the package.

2.7 Real-world performance

During the excellence appraisal, all organizations will demonstrate their capabilities to collect and analyze post-launch real-world performance (RWP) data. RWP data is designed to use these available data analytics to verify ongoing excellence following precertification, identify emerging safety and cybersecurity risks, provide critical feedback to the other components of the program, and support the appropriate use of post-market data in clinical evidence generation.

Given the importance of these functions, FDA anticipates that all pre-certified organizations introducing a product to market through the precertification pathway would be expected to actively monitor RWP data and allow FDA access to analytics on data elements relevant to organizational excellence and product-level safety and effectiveness.

2.7.1 RWP analytics (RWPA) framework

RWPA are defined as systematic computational analyses of data relevant to the safety, effectiveness, and performance of a SaMD product in real-world settings marketed by a pre-certified organization. FDA anticipates that not only data from appropriately instrumented SaMD products may be generated, collected, and analyzed efficiently, but also real-world data from device registries, well-structured data commons, and other electronic health information sources, including patient registries and the NEST currently under development. Manufacturers are required to use different methods of specific data analysis under the RWPA framework, depending on the intended use, function and risk categorization of the SaMD. There are three main types of analysis outlined.

(1)Real-world health analytics (RWHA). RWHA are defined as analyses of real-world clinical outputs and outcomes related to the intended use of the SaMD product. RWHA can inform changes to the intended use of a SaMD product, support expanded functionalities and use in broader target populations, and identify emerging safety issues in post-market use. For lower-risk products, sources of RWHA may come from user complaints, search analytics, and product-level monitoring of human factors measures, such as use errors. For higher-risk products, manufacturers may proactively seek external sources of safety and effectiveness data through various activities, such as participation in registries, partnerships with healthcare systems, or utilization of data sharing or other structured post-market data collection.

(2)User experience analytics (UXA). UXA are defined as analyses of user experience outputs related to the real-world use of a SaMD product. UXA monitoring facilitates timely identification and correction of user's issues and enables improvements to the utilization and effectiveness of the software. Depending on the intended use of the software, UXA can be collected from a variety of sources. Products instrumented to collect UXA may passively monitor measures including use patterns, download rates, and user retention. For metrics related to product satisfaction or user's complaints, organizations can use proactive mechanisms of soliciting or incentivizing user's feedback. To ensure that feedback is representative of the full range of users, excellent organizations would also actively seek UXA from diverse sources, which may include social media platforms, search analytics, or other third-party online networks.

(3)Product performance analytics (PPA). PPA

are defined as analyses of outputs and outcomes that demonstrate the real-world accuracy, reliability, and security of a SaMD product. PPA monitoring enables excellent organizations to address software bugs and security vulnerabilities through timely patches and product updates. As described for UXA, proactive surveillance may be needed to identify product defects and track time to resolution. For SaMD products used on the internet, FDA assumes that pre-certified organizations will demonstrate ongoing commitment in cybersecurity responsibility by monitoring and addressing security vulnerabilities and threats. FDA's recommendations for cybersecurity risk management, including participation in information sharing and analysis organizations, are included in the guidance document "Post-market Management of Cybersecurity in Medical Devices".

2.7.2 RWPA collection plan

FDA requires that pilot participants should develop a RWPA plan in advance of introducing a product to market as a part of 510 (k) submissions or De Novo Requests. According to the principle of least burden, FDA intends to focus its post-launch product monitoring efforts on trends and summary analytics, rather than on raw data. For all products, a RWPA plan should include: (1) Proposed RWP data elements to be collected; (2) Intended frequency of data collection; (3) Intended data structure and format; (4) Commit and stretch goals for each proposed data element [13, 14].

3 Enlightenment and lessons for enhancing digital health regulation in China

3.1 Enhancing regulatory flexibility for digital health software

The software pre-cert program proposes an innovative regulatory pathway, which firstly determines the organizational excellence of the manufacturer at the organizational level, secondly determines the risk categorization of the software at the product level, and finally FDA comprehensively decides whether to conduct a streamlined post-market review. Throughout the process, FDA pays more attention to post-market effectiveness and safety issues, repeatedly emphasizing the use of real-world data during the SaMD lifecycle. It is not difficult to see the "wide-in and strict-out" feature of FDA's regulation of medical devices.

China's regulation of medical devices has the characteristics of "strict-in and wide-out". For example, drug calculation software is approved as a Class II in the United States, but the NMPA considers it to have a threat to health if it is not strictly regulated, so it is approved as a Class III [15]. Strict regulation in the product registration and approval process can effectively ensure the effectiveness and safety of the product, but it may also bring a certain burden to the manufacturers. It is recommended to explore the elements that must be evaluated for registration review based on the rapid iterative nature of digital health software, to reduce the content of submissions and the workload of manufacturers and regulatory agencies, to enhance regulatory flexibility, and to improve the speed of approval.

3.2 Using real-world data for registration submissions and post-market evidence

To transform real-world data into real-world evidence for evaluating the safety and effectiveness of medical device products throughout their lifecycle, regulatory agencies around the world start to issue some frameworks and guidelines. Software pre-cert programs require manufacturers to demonstrate their real-world data collection capabilities at the time of excellence appraisal and to use real-world data to provide clinical evidence for their products.

In April 2019, NMPA released the "China Pharmaceutical Regulatory Science Action Plan", which included "Methodological research on the use of real-world data for clinical evaluation of medical devices" as one of the first research projects [16]. The first part of this research project is the release of the Technical Guidelines for Clinical Evaluation of Real-World Data for Medical Devices (Trial) [17], which

was officially released in November 2020. In March of the same year, the glaucoma drainage tube was successfully approved in the Boao Lecheng pilot zone of international medical tourism [18], which became the first medical device product approved for marketing using real-world data in China. It is recommended that the use of real-world data for clinical evaluation should be used as a starting point, and the scope of real-world data utilization be extended to post-marketing monitoring to achieve real-world data support for the whole lifecycle of products.

3.3 Improving innovation regulation

In recent years, in addition to launching the Digital Health Innovation Action Plan, the FDA has proposed many innovative regulatory approaches for digital health products.. It also proposed to focus on mobile health APPs with high-risk to patients, but not to implement compliance procedures for low-risk mobile health APPs. It did not propose to focus on general health products. Besides, it proposed to establish strategic partnerships with stakeholders [19].

In June 2021, NMPA released a new version of the "Regulations on Supervision and Administration of Medical Devices" [20], which mentioned that "the state improves the medical device innovation system, supports basic research on medical devices, and promotes the application of new medical device technologies". Moreover, according to the China Pharmaceutical Regulatory Science Action Plan, China has gradually approved the establishment of several medical device regulatory science research pilots [21]. It is recommended that the policy-oriented approach should firstly complete the definition of the classification of digital health products, and secondly innovate their registration and regulatory pathway to advance China's regulatory action on medical devices.

4 Prospect

With WHO advocating the priority of digital health in healthcare, the increasing huge demand for digital health, as well as Internet health and telemedicine, the industry has been given a significant boost. More companies are looking forward to bringing their digital health products under development. The U.S. software pre-cert program emphasizes a streamlined premarket review process that relies on post-market evidence generated from real-world data and elements of excellence appraisal to strengthen post-market regulation of SaMDs. However, China's post-marketing surveillance is inadequate, and data is difficult to obtain and utilize, so it is not applicable to our national situation. China can explore the elements that must be assessed for registration review based on the enlightenment brought by this program, reducing the content of submission, which can cut the burden of manufactures and regulatory agencies. At the same time, the state should gradually improve the post-marketing regulatory mechanism, accumulate experience in the management of the whole lifecycle of medical devices, and prepare for the improvement of regulatory innovation capacity.

References

[1] Eggshell Institute. China digital therapeutics white paper (2021) [R]. 2021.

[2] FDA. Changes to existing medical software policies resulting from Section 3 060 of the "21st Century Cures Act" [EB/OL]. (2019-09-27)[2023-01-15]. https://www.fda.gov/regulatory-information/search-fda-guidance-docments/changes-existing-medical-software-policies-resulting-section-3060-21st-century-cures-act.

[3] Kadakia K, Patel B, Shah A. Advancing digital health: FDA innovation during COVID-19 [J]. NPJ Digital Medicine, 2020, 3 (1): 161.

[4] Rodriguez JA, Clark CR, Bates DW. Digital health equity as a necessity in the 21st century cures act era [J]. JAMA, 2020, 323 (23): 2381-2382.

[5] Ma Yanbin, Bai Xudong, Jin Dan, et al. Research and enlightenment of the supervision of FDA on digital health products [J]. China Medical Equipment, 2022, 19 (9): 181-188.

[6] Alon N, Stern AD, Torous J. Assessing food and drug administration's risk-based framework for software precertification with top U.S. health apps: Quality

improvement study (preprint) [J]. JMIR mHealth and uHealth, 2020, 8 (10): 1-12.

[7] FDA. FDA selects participants for new digital health software precertification pilot program [EB/OL]. (2017-09-26)[2023-03-24]. https://www.fda.gov/news-events/press-announcements/fda-selects-participants-new-digital-health-software-precertification-pilot-program.

[8] Moshi MR, Parsons J, Tooher R, et al. Evaluation of mobile health applications: Is regulatory policy up to the challenge? [J]. International Journal of Technology Assessment in Health Care, 2019, 35 (4): 351-360.

[9] Shuren J, Patel B, Gottlieb S. FDA regulation of mobile medical apps [J]. JAMA, 2018, 320 (4): 337-338.

[10] Huang Wenhui, Tian Shaolei. U.S. FDA digital health innovation action plan introduction [J]. China Medical Device Information, 2017, 23 (23): 1-2.

[11] Janetos TM, Xu RS, Walter JR, et al. Reducing FDA regulations for medical devices: Cutting red tape or putting patients' lives at risk? [J]. Expert Review of Medical Devices, 2018, 15: 1-3.

[12] FDA. Content of Premarket Submissions for Device Software Functions [EB/OL]. (2023-12-16)[2023-04-01]. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions.

[13] Yuan Xiaoliang, Dong Li, Meng Lingquan, et al. The enlightenment to the establishment of real-world data applicability evaluation standard in China from "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" of US FDA [J]. Chinese Journal of New Drugs, 2021, 30 (11): 4.

[14] Stern AD, Brönneke J, Debatin JF, et al. Advancing digital health applications: Priorities for innovation in real-world evidence generation [J]. The Lancet Digital Health, 2022, 4 (3): e200-e206.

[15] Yan Shu, Xu Dongzi, Ouyang Zhaolian. Analysis on the regulation and application of united states artificial intelligence medical device [J]. China Medical Devices, 2021, 36 (2): 6.

[16] Huang Yafang, Yan Xiaoyan, Li Xueying, et al. Utilization of real-world evidence in clinical research of medical devices [J]. Chinese Journal of Evidence-Based Medicine, 2017, 17 (12): 5.

[17] Medical Device Technical Evaluation Center of NMPA. Technical Guidelines on the Use of Real-World Data for Clinical Evaluation of Medical Devices (Trial) (No. 77 of 2020) [EB/OL]. (2020-11-24)[2023-04-15]. https://www.cmde.org.cn//flfg/zdyz/zdyzwbk/20201126102802881.html.

[18] Ren Yan, Liang Yuanbo, Liu Mimi, et al. Exploration and practice of real-world data studies on innovative medical products in Boao Lecheng: Analysis based on Chinese first case of approved medical device using domestic real-world data [J]. 2020, 20 (10): 1117-1123.

[19] FDA. Guidance with Digital Health Content [EB/OL]. (2020-10-06)[2022-04-10]. https://www.fda.gov/medical-devices/digital-health-center-excellence/guidances-digital-health-content.

[20] National Laws and Regulations Database. Medical Device Supervision and Management Regulations [EB/OL]. (2021-02-09)[2023-04-15]. https://flk.npc.gov.cn/detail2.html?ZmY4MDgxODE3YjYzYjY3OTAxN2I3YWY3NDQ5MTM0YTM.

[21] Li Anyu, Tong Xiaoyu. Development and implementation roadmap of regulatory science for medical devices [J]. China Food and Drug Administration, 2021, 210 (7): 18-33.