Registration and Regulatory Analysis of Fractional Flow Reserve (FFR) and Related Products in the United States and China

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Abstract

This study collected summary and review reports for Fractional Flow Reserve (FFR) and related products (including iFR, RFR, DFR, CT-FFR, CA-FFR) approved in the United States and China, and briefly analyzed the registration and regulatory strategies for such medical device software in both countries, particularly regarding requirements for clinical data, in conjunction with relevant clinical literature and guidelines. Overall, the US requirements for clinical data for such products are relatively flexible; early FFR products did not provide corresponding clinical data when they did not claim clinical application value; subsequent products submitted consistency comparison data with predicate devices during predicate comparison, and such comparisons were typically not rigorous prospective clinical trials. When clinical trials employing clinical outcomes as endpoints confirmed the clinical application value of such products, corresponding descriptions were also included in the product indications. Additionally, the practice of research data sharing in the US effectively utilizes social resources and is worth emulating.

Full Text

Analysis of Registration and Regulatory Pathways for Fractional Flow Reserve (FFR) and Related Products in the United States and China

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Abstract

This paper collected summary and review reports for fractional flow reserve (FFR) and related products (including iFR, RFR, DFR, CT-FFR, and CA-FFR) approved in the United States and China. By integrating relevant clinical literature and guidelines, we analyzed the registration and regulatory strategies for such medical device software, with particular emphasis on clinical data requirements. Overall, the United States adopts a more flexible approach to clinical data requirements. Early FFR products did not submit clinical data when they made no claims regarding clinical utility. Subsequent products submitted consistency comparison data against predicate devices during equivalence demonstrations, though these comparisons typically were not rigorous prospective clinical trials. Only after clinical outcome-based trials confirmed the clinical value of these products were corresponding claims added to their indications. Additionally, the U.S. practice of efficient data sharing effectively leverages social resources and warrants our consideration.

Keywords: medical device software; fractional flow reserve; clinical data; registration regulation

Introduction

With advances in medical technology, medical device software has emerged in waves. Both the United States and China have recently formulated or updated corresponding product registration guidance to address this trend. In 2021, the U.S. FDA (Food and Drug Administration) released the "Artificial Intelligence/Machine Learning-Based Software as a Medical Device Action Plan" and "Content of Premarket Submissions for Device Software Functions (Draft)." In 2022, China's National Medical Products Administration (NMPA) issued the "Guidance for Medical Device Software Registration Review (2022 Revision)" and "Guidance for Artificial Intelligence Medical Device Registration Review."

FFR (fractional flow reserve) and related products represent coronary physiological assessment technologies beyond traditional imaging examinations in the diagnosis and treatment of coronary artery disease. Over the past decade, these technologies have gained prominence in clinical practice. This paper examines the clinical evolution and registration status of FFR and related products from a medical device software registration perspective, focusing on the clinical data requirements imposed by regulators in both countries.

Since the world's first PTCA (percutaneous transluminal coronary angioplasty) in 1977 opened a new chapter in coronary intervention, continuous improvements in balloons and stents have become the central theme. However, clinical practice has revealed limitations of coronary angiography alone. While IVUS

(intravascular ultrasound) and OCT (optical coherence tomography) serve as beneficial supplements to coronary angiography, they remain fundamentally imaging-based examinations. The correlation between angiographic stenosis and myocardial ischemia, particularly in borderline lesions, has been unsatisfactory. Direct measurement of myocardial blood flow would be ideal but is clinically challenging, making pressure monitoring a practical surrogate.

As early as the late 1970s, Gruntzig performed coronary pressure measurements during the first PTCA procedures [1]. Systematic measurement of distal and proximal coronary lesion pressures (Pd and Pa) began in the 1980s [2], and FFR was formally proposed in the 1990s as the ratio of distal to proximal pressure (Pd/Pa) during pharmacologically induced hyperemia, believed to reflect myocardial flow reserve and correlate better with exercise-induced myocardial ischemia to guide clinical treatment [3]. Subsequent large-scale clinical trials including FAME [4], FAME2 [5], and Compare-Acute [6] established the clinical value of FFR. China's "Guidelines for Percutaneous Coronary Intervention in China" published in 2016 gave FFR a Class IA recommendation [7].

However, FFR measurement requires pharmacological induction of hyperemia, which increases procedure time and can cause patient discomfort. Consequently, resting-state Pd/Pa has remained a subject of continued interest. iFR (instantaneous wave-free ratio) calculates a period during diastole when coronary flow resistance is stable (the "wave-free period"), proposing that Pd/Pa during this interval approximates hyperemic FFR. Large clinical trials have demonstrated non-inferiority to FFR [8, 9], leading to Class IA recommendations equivalent to FFR in European guidelines published in 2019 [10] and U.S. guidelines in 2022 [11], with the consensus that lesions with FFR > 0.8 or iFR > 0.89 do not require intervention.

Subsequently, non-hyperemic indices including RFR (resting full-cycle ratio, the minimum Pd/Pa across the entire cardiac cycle) and DFR (Pd/Pa during diastolic periods below mean aortic pressure with descending waveforms) were introduced. Additionally, angiography-based CA-FFR (which eliminates the need for coronary pressure wire measurement though still requiring conventional aortic pressure measurement) and even non-invasive CT-FFR based on coronary CT have entered clinical practice, sparking a surge in coronary physiological research. Chinese technologies and clinical studies in these fields have achieved internationally advanced or even leading positions in certain areas [12-14].

2.1 United States

A search of the FDA website (March 15, 2023) identified eight FFR and related products (Table 1). These products are classified as Class II medical devices in the United States; therefore, for convenience, terms like "FDA approval" used herein correspond to the official term "clearance." The FDA first approved RadiAnalyzer FFR in 2001 through a predicate device comparison, adding FFR functionality with the description: "Information can be displayed on an inte-

grated screen and/or transmitted to a cardiac monitor. Data includes systolic, diastolic, and mean blood pressure, heart rate, and FFR." The 510(k) summary report made no mention of clinical data. The following year, the device's indication was updated (K022188) to "provide hemodynamic information in the diagnosis and treatment of coronary and peripheral arterial disease; calculate and display various physiological parameters based on one or more electrodes, sensors, or measurement devices in the catheterization laboratory or related cardiovascular laboratories." Again, no clinical data were provided.

Volcano FFR was approved in 2008, also through self-predicate comparison, adding FFR functionality: "The system measures and calculates pressure differences between the aorta and SmartWire/ComboWire pressure sensors located distal to vascular lesions to compute FFR. This pressure measurement can be used in all vessels, including coronary and peripheral arteries." The 510(k) summary report similarly omitted clinical data and did not reference the previous RadiAnalyzer FFR as a predicate device.

Polaris FFR was approved in 2015, using both its own predecessor and RadiAnalyzer FFR as predicates, without clinical trial data. The indication description, beyond statements similar to RadiAnalyzer FFR regarding information display, added: "Can provide hemodynamic information for the diagnosis and treatment of patients undergoing physiological parameter FFR measurement," thereby claiming clinical utility.

The non-hyperemic iFR was approved in 2014 with the indication: "Can be used in all vessels, including coronary and peripheral arteries, for intravascular pressure measurement during angiographic diagnosis and/or interventional therapy." Using itself as predicate, it provided clinical data from the ADVISE II study [15]. This study enrolled 598 patients with 690 vessels, comparing iFR at a cutoff of 0.89 against FFR at 0.8, yielding sensitivity of 73.0%, specificity of 87.8%, and diagnostic accuracy of 82.5%. The 510(k) summary report also presented data for the iFR-FFR hybrid approach within the iFR gray zone (0.86-0.93).

RFR was approved in 2019, using RadiAnalyzer FFR as the primary predicate and iFR as a secondary predicate, adding RFR functionality. The indication stated: "Can provide hemodynamic information for the diagnosis and treatment of coronary or peripheral artery disease; calculate and display various physiological parameters based on one or more electrodes, sensors, or measurement devices in the catheterization laboratory or related cardiovascular laboratories." The 510(k) summary report included a clinical test result from real-world patients, showing diagnostic accuracy of 93.6% for the RFR-FFR hybrid mode versus 92.2% for iFR-FFR. Published literature from the VALIDATE study [16] provided additional information: drawing upon 633 coronary pressure waveforms from the existing VERIFY [17] and CONTRAST [18] studies, the RFR cutoff was determined to be 0.89 based on FFR, with sensitivity of 84%, specificity of 69%, and accuracy of 78%. Using iFR as the standard in 651 waveforms from VERIFY2 [19] and IRIS-FFR [20], RFR showed sensitivity of 97.4%, specificity

of 98.2%, and accuracy of 96.9%. Notably, the summary report added Pd/Pa to the product description: "Relevant display data includes systolic, diastolic, and mean blood pressure, heart rate, FFR, RFR, Pd/Pa, and data from electrocardiograms," though no corresponding clinical data for Pd/Pa were provided.

DFR was also approved in 2019, using Polaris FFR as predicate and iFR as reference device, with indications similar to Polaris FFR. The 510(k) summary report mentioned product performance data, while published literature [21] provided additional details: following a similar approach to RFR, 893 coronary pressure waveform recordings from 833 patients in the VERIFY2 and CONTRAST studies were analyzed. With a cutoff of 0.89 and using iFR as the standard, DFR demonstrated sensitivity of 95.8%, specificity of 99.2%, and diagnostic accuracy of 97.6%.

The first U.S. CT-FFR product, FFRCT, was approved in 2013 via the De Novo pathway. The indication stated: "FFRCT analysis can support functional evaluation of coronary artery disease. Results can assist qualified physicians in evaluating coronary arteries. FFRCT must be used by qualified physicians in conjunction with patient history, symptoms, other examinations, and clinical judgment." The FDA summary report referenced three studies; Discover-FLOW and DeFACTO used previous-generation products, making the HFNXT study [22] the primary clinical evidence. This study enrolled 276 patients outside the United States, evaluating 484 vessels. Compared to FFR, FFRCT showed sensitivity of 83.5% and specificity of 85.8%. The FDA summary report noted that the study's prespecified sensitivity and specificity targets were 65% and 55%, respectively, and that since the study was not conducted in the U.S., these targets had not been pre-agreed with the FDA.

Subsequently, the CT-FFR DEEPVESSEL FFR product from China was approved by FDA in 2022. Using FFRCT as predicate with similar indications, the 510(k) summary report described a clinical validation study conducted in the U.S. and Europe analyzing 311 vessels from 244 patients. Compared to FFR, the study met its prespecified sensitivity and specificity targets of 75% and 70% (see Table 1).

2.2 China

A search of the NMPA website's domestic medical device registration database (March 15, 2023) using the terms "flow reserve" or "quantitative flow" yielded 18 records. Public evaluation reports were obtained for seven products, detailed in Table 2 . FFR and related products are classified as Class III devices in China, and all seven publicly available evaluation reports mentioned clinical trials. Since domestic evaluation reports contain limited information on clinical trials, we provide brief comments on several products.

Taking QFR (a CA-FFR product) as an example, its indication states: "This product can quantitatively calculate the Quantitative Flow Ratio (QFR) based on coronary angiographic images, intended for use by trained medical techni-

cians to evaluate the functional significance of coronary lesions in adult patients. Clinical assessment should integrate patient history, symptoms, other diagnostic results, and physician judgment." Published literature shows QFR had a premarket FAVOR II China study [23] enrolling 332 vessels from 308 patients. Compared to FFR, QFR demonstrated sensitivity of 94.6%, specificity of 91.7%, and diagnostic accuracy of 92.7%. This study was preceded by the FAVOR Pilot study and followed by the FAVOR III China study [12], a postmarket investigator-initiated randomized controlled trial enrolling 3,847 PCI (percutaneous coronary intervention) patients. Using one-year MACE (major adverse cardiovascular events) as the primary endpoint, the study showed QFR-guided PCI was superior to conventional angiography-guided PCI.

Another example is DEEPVESSEL FFR (CT-FFR class), the same product approved by FDA in 2022 discussed above. DEEPVESSEL FFR was approved in China in 2020 with the indication: "Before coronary angiography, to assist trained medical technicians in evaluating functional myocardial ischemia symptoms in patients with stable coronary artery disease (SCAD). Physicians should integrate patient history, symptoms, and relevant diagnostic results for comprehensive assessment. This product is not suitable for acute coronary syndrome (ACS) patients with acute chest pain." The domestic evaluation report did not describe specific clinical trial results, but the FDA information referenced above can be consulted.

Table 2 details the registration information for FFR and related products with published evaluation reports in China, including post-market requirements for each product.

Discussion

This paper has introduced the current status of FFR and related product registration in the U.S. and China, covering eight products in the U.S. market and seven in China, with particular focus on regulatory requirements for clinical evidence. Several differences in registration requirements between the two countries are apparent. First, these products are classified as Class II devices in the U.S. (with one following the De Novo pathway), while uniformly classified as Class III in China. Second, the U.S. maintains flexible clinical evidence requirements: among the eight products, three provided no clinical data, three provided retrospective analytical testing (notably, RFR and DFR utilized existing investigator-initiated studies), and only two provided prospective clinical studies. In contrast, Chinese evaluation reports almost universally mention prospective clinical trials. The U.S. review practice demonstrates flexibility in accepting retrospective data analysis and leveraging previously recorded pressure waveform data from related clinical trials (including investigator-initiated studies), embodying the "least burdensome" principle. The U.S. practice of research data sharing also effectively utilizes social resources and merits our consideration. Third, some U.S. products claim applicability to peripheral or even all vessels without supporting clinical data, whereas China adopts a more

cautious and pragmatic approach, generally limiting the scope to coronary arteries. Meanwhile, we observe that development of FFR and related products in China has been very active in recent years, exceeding the U.S. in quantity. Technologically, China has more products like CA-FFR and CT-FFR that do not rely on pressure wires, while the U.S. market has focused more on non-hyperemic FFR that still requires pressure wires.

The question of whether clinical data are required for FFR and related products, and what kind, has been a particular industry concern. Consider other fields such as cardiac pacing and electrophysiology products. Pacemakers and ICDs contain numerous detection/monitoring functions in each pulse generator, including various arrhythmia event monitors, heart rate-based indices, patient activity monitoring, and respiratory index monitoring—most of which lack supporting clinical trials or data at registration. Three-dimensional electrophysiological mapping systems also contain extensive ECG signal monitoring and computational functions, such as automatic analysis and judgment of various arrhythmias, yet the clinical data provided at registration cannot cover every aspect.

How should we clinically evaluate the detection/monitoring functions of such devices, particularly so-called software post-processing functions? FFR and related products do not perform actual pressure measurements themselves but rather calculate and analyze data from pressure wire measurements (or angiographic/CT flow data without pressure wires). These calculations range from simple ratios like Pd/Pa to complex CA-FFR and CT-FFR requiring artificial intelligence techniques. Whether pressure wire registration requires clinical trials is beyond this paper's scope (though in fact, U.S. regulation does not require it while China does).

Generally, if a product only provides calculated results from existing data analysis, the clinical evidence requirements are lower; if it claims clinical value to guide diagnosis and treatment (i.e., clinical decision support), the requirements are obviously higher. From FDA's review perspective, two early FFR products provided no clinical data. Considering the context, substantial foundational research and strong theoretical support for FFR preceded these products, likely an important FDA consideration, and early FFR indications were limited to providing physiological parameter information. Although FFRCT and iFR provided clinical data, these were only consistency comparisons with FFR, not clinical outcomes, so their indications remained informational. From publicly available information, Chinese premarket studies also involved consistency comparisons without long-term follow-up.

Beginning with Polaris FFR in 2015, indications included language about utility in patient diagnosis and treatment—a strong claim—yet the summary report contained no directly corresponding clinical data. Considering that the large clinical outcome study FAME for RadiAnalyzer FFR (investigator-initiated) was published in 2009, U.S. clinical guidelines recommended FFR as Class IIA in 2011 [31], and the FAME2 study published in 2014 further strengthened FFR's

clinical value, FFR has become the de facto gold standard for this product category. It is reasonable to conclude that FDA recognizes FFR products as having a "class effect," and thus predicate devices using FFR since 2015 have included language about guiding clinical diagnosis and treatment in their indications. Besides FFR, iFR [8, 9], QFR [12], and CT-FFR [14] now have large randomized controlled trials with clinical outcome endpoints, with additional studies ongoing—all postmarket studies. This raises many topics, such as whether diagnostic devices must demonstrate definitive clinical value before approval and how to view differences between regulatory indications and clinical guideline indications, which are beyond this paper's scope.

Notably, different non-hyperemic FFR indices show strong agreement with each other but still have some differences from FFR. Although non-hyperemic FFR appears theoretically flawed, iFR's non-inferiority to FFR in clinical outcome trials has left the clinical superiority question between non-hyperemic FFR and traditional FFR unresolved. Furthermore, no head-to-head randomized controlled trials with clinical outcome endpoints have been conducted between these products, though many studies show they are superior to conventional coronary angiography. Traditional FFR's later clinical trials have also experienced contradictory [32, 33] and even failed results [33-36], likely due to differences in enrolled populations, posing new regulatory challenges for such devices.

Finally, we discuss the U.S. De Novo pathway. China lacks this pathway, creating challenges for innovative medium-risk medical devices. Such products are not in the catalog for exemption from clinical evaluation, and as novel devices, are also not in the recommended clinical evaluation pathway catalog. Although the risk level does not necessarily require clinical trials, predicate comparison is unavailable in the domestic market, seemingly forcing the clinical trial pathway. China's medical device registration regulations have developed rapidly in recent years and gradually matured, particularly forming a distinctive directory-based regulatory system. The disadvantages of directory-based regulation are also clear: products outside the directory still require considerable consultation and communication, creating substantial uncertainty, though China's "green channel" innovation programs have partially addressed these consultation challenges.

This paper has several limitations. First, information was primarily obtained from FDA and NMPA website databases and publicly published literature, inevitably leading to some omissions. The analysis focuses on approved products, excluding technologies under development, and does not address pressure wires as the source of FFR calculations. The paper focuses on initial approved indications without tracking indication updates. Second, although domestic evaluation reports have different postmarket clinical data requirements for different products, limited available information precludes analysis of these varying requirements. Third, similarly limited by public information, we did not analyze clinical data requirements for imported FFR and related products registered in China. For example, we found no information on iFR registration in China, though corresponding domestic clinical studies have been published [37]. Fi-

nally, this paper does not intend to evaluate the relative merits of current U.S. and Chinese registration regulation for FFR and related products, which may require longer-term consideration during which regulatory strategies will undoubtedly continue to evolve, and the final assessment will likely be that each approach has its own advantages and disadvantages. Our concern is the clear and stable thinking behind the regulation, and we are pleased that Chinese regulators have issued corresponding guidance principles and established relevant research platforms including the Artificial Intelligence Medical Device Innovation Cooperation Platform. We believe we will explore a path suitable for China's national conditions. The progress of medical technology continuously presents new regulatory requirements, making this a perpetually evolving topic.

(Note: This article represents the authors' views and does not represent the positions of their employing organizations.)

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Note: Figure translations are in progress. See original paper for figures.