Comparison of Pivotal Studies for High-Risk Medical Devices in Chinese and US Regulatory Practices

Authors: Zeng Zhiyu, Han Lei, Zhang Xiaoxing, Peng Lin, Zeng Li, Zeng Zhiyu

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Abstract

A comparison of pivotal studies for high-risk medical devices between China and the United States (including 40 approved products and some ongoing studies, covering coronary intervention, structural heart disease, left ventricular assist devices, neuromodulation, and electrophysiology, among other fields) reveals that the pivotal studies conducted in China feature relatively simple designs, a greater proportion of quantitative primary endpoint measures, and relatively small sample sizes. While pivotal studies across different product categories are difficult to compare directly, reaching consensus between sponsors and regulatory authorities before initiating pivotal studies for high-risk medical devices should be the direction of our future efforts.

Full Text

Comparison of Pivotal Studies for High-risk Medical Devices between China and the US

ZENG Zhiyu[1], HAN Lei[1], ZHANG Xiaoxing[1], PENG Lin[1], ZENG Li[1]

[1]Boston Scientific Corporation, BSC International Medical Trading (Shanghai) Co., Ltd., Beijing 100020, P.R. China

Author Introduction: ZENG Zhiyu (1973-), male, PhD. Research focus: medical device clinical trials.

Corresponding Author: ZENG Zhiyu. Email: zhiyu.zeng@bsci.com

Abstract

A comparative analysis of pivotal studies for high-risk medical devices between China and the United States, encompassing 40 approved products and several ongoing studies across coronary intervention, structural heart disease, left ventricular assist devices, neuromodulation, and electrophysiology, reveals that pivotal studies conducted in China feature relatively simple designs, a higher proportion of quantitative primary endpoints, and comparatively small sample sizes. While direct comparison of pivotal studies across different product categories is challenging, reaching consensus between sponsors and regulatory authorities prior to initiating pivotal studies for high-risk medical devices should be a future priority.

Keywords: Medical device, High risk, Pivotal study, Regulatory administration

Introduction

With economic development and technological advancement, medical devices are experiencing a period of rapid growth. Class III high-risk medical devices, which may bring substantial clinical benefits to patients while also posing significant clinical risks, have become a focal point for regulatory oversight worldwide. Pivotal studies (or confirmatory trials) for these devices serve as the primary clinical data source and attract considerable attention from all stakeholders. Different regulatory agencies may have varying perspectives on benefit-risk evaluation of medical devices. This paper compares pivotal studies for several high-risk medical devices conducted under the jurisdiction of Chinese and U.S. regulatory agencies, focusing on hot-topic products in the minimally invasive interventional therapy field, including coronary intervention (drug-coated balloons [DCB] and bioabsorbable drug-eluting stents [DES]), structural heart disease (transcatheter aortic valve replacement [TAVR] and left atrial appendage closure [LAAC]), left ventricular assist devices (LVAD), neuromodulation (deep brain stimulation [DBS], spinal cord stimulation [SCS], and sacral nerve stimulation [SNS]), and electrophysiology (pulsed field ablation [PFA]).

2 Materials and Methods

For products approved in both China and the United States, we selected high-risk minimally invasive interventional products that underwent pivotal clinical trials under NMPA oversight from the evaluation reports published on the website of the National Medical Products Administration (NMPA) Center for Medical Device Evaluation (CMDE). A total of 18 products were included, covering drug-coated balloons, bioabsorbable coronary stents, transcatheter aortic valves, left atrial appendage closure devices, left ventricular assist devices, and implantable neurostimulators. Correspondingly, we searched for similar products on the U.S. Food and Drug Administration (FDA) website, selecting only those approved through the original pathway, yielding 22 products. We ex-

tracted study design, sample size, primary endpoints, and follow-up duration for pivotal studies from evaluation reports or Summaries of Safety and Effectiveness Data (SSED).

For information not provided in evaluation reports, we searched various public sources, including published literature (PubMed, Wanfang, CNKI, and other databases), clinical trial registration information (clinicaltrials.gov, Chinese Clinical Trial Registry, etc.), and relevant media reports. For products not yet approved in either country, such as PFA, we also searched for relevant information through these channels. The search cutoff date was November 19, 2022.

Results

Basic information on the pivotal studies for the 18 products under NMPA oversight and 22 under FDA oversight is summarized in . Overall, compared with FDA-regulated pivotal studies, Chinese pivotal studies feature simpler designs, predominantly single-arm studies, a higher proportion of quantitative primary endpoints, and relatively small sample sizes, particularly in the structural heart disease field.

For TAVR, all four pivotal studies under NMPA oversight employed single-arm objective performance criteria designs with sample sizes ranging from 81 to 145 and relatively broad indications. In contrast, 75% (3/4) of FDA-regulated products provided randomized controlled trials (RCTs) with sample sizes of 358–1043 and narrower indications. FDA studies seeking TAVR indications for intermediate- and low-risk patients typically had larger sample sizes, reaching 1,000–20,321 patients [1-4].

For LAAC, NMPA-regulated pivotal studies (identifying four approved products in addition to the two disclosed in evaluation reports) all used single-arm objective performance criteria designs with primary endpoints including left atrial appendage closure rates and sample sizes of 153–214 cases [5-8]. The two LAAC devices approved by FDA both provided RCTs with qualitative clinical event endpoints and total sample sizes of 2,406 and 1,878, respectively. Additionally, information indicates that a domestic left atrial appendage closure device is currently conducting an IDE study under FDA oversight with a controlled design and a sample size exceeding 3,000 [9].

In the LVAD field, differences in sample sizes for pivotal studies between the two regulatory systems are also substantial. For the same product, while a small single-arm study was conducted domestically [10], conducting an IDE study in the United States requires an RCT with sample size significantly increased to 399 cases [11].

Electrophysiology PFA has not yet been approved in either country. Public information shows that domestic studies typically employ single-arm designs with sample sizes of just over 100 cases [12], while IDE studies feature RCT or

single-arm designs with sample sizes of 418–900 [13-16].

The situation for coronary drug-coated balloons is unique, with approval in China preceding that in the United States. Pivotal studies conducted in China were all RCTs with quantitative endpoints and sample sizes of 211–240 [17-20]. The authors' company is conducting an IDE study for a coronary drug-coated balloon in the United States with an RCT design, qualitative endpoint, and a sample size of 600 [21].

Furthermore, significant differences exist in pivotal studies across different therapeutic areas, though direct comparison is difficult due to varying clinical contexts. Nevertheless, notable differences remain apparent between Chinese and U.S. regulatory agencies' perspectives, particularly in structural heart disease (TAVR, LAAC) and electrophysiology (PFA). Surprisingly, while FDA generally imposes higher requirements for pivotal studies of high-risk medical devices, SCS devices can be approved in the United States through predicate device comparison.

Discussion

As regulatory reforms continue to advance [23], China's current regulatory environment has played a positive role in promoting the market entry of innovative products [24]. Whether this innovation-encouraging environment is superior or inferior to the stricter FDA oversight remains difficult to determine. The EU regulatory system is currently transitioning, generally perceived as moving from a more lenient environment to stricter oversight. Previous studies comparing EU and U.S. medical device regulatory systems found that devices first marketed in the EU had more post-market safety alerts and recalls (HR 2.9, 95% CI 1.4–6.2) [25]. Nevertheless, some FDA-approved products included in this study, such as the bioabsorbable DES Absorb and the left ventricular assist device HeartWare, have already been withdrawn from the market.

An important motivation for this study stems from our own experience with a product registration case. Our company planned to market a coronary drug-coated balloon already approved overseas in China. We had completed an RCT in Europe (non-inferiority comparison with a similar product, primary endpoint of 6-month lumen loss, sample size 125 cases). Following the pathway for overseas clinical trial data, we submitted the European RCT, a post-market registry study conducted in the Asia-Pacific region (single-arm, sample size 500 cases), and a small single-arm study conducted in Japan (which had received pre-study acknowledgment from Japanese regulators). During communication with NMPA's CMDE, the center indicated that compared with similar products already approved domestically—where all other products had randomized controlled designs with 9-month lumen loss as the primary endpoint and sample sizes exceeding 200 cases—we should submit more substantial clinical trial data, despite our additional single-arm studies from the Asia-Pacific region and Japan.

This raises an important question: in the absence of corresponding product guidance principles, how should we determine whether clinical trial data are adequate? While reference can be made to previously approved similar products to maintain consistent review standards, should subsequent products still adhere to potentially excessive standards if the first approved product happened to have overly comprehensive clinical data? Furthermore, as products gain broader use and understanding of their efficacy and safety improves, can requirements for clinical data be appropriately reduced, similar to the dynamic adjustments of China's Medical Device Classification Catalog and Catalog of Medical Devices Exempt from Clinical Evaluation? Finally, how should we determine adequacy of data from an RCT with formal hypothesis testing? A better approach might be a pre-clinical trial consensus mechanism similar to FDA's IDE approval system.

Comparison of pivotal studies across different product categories presents another interesting consideration. For instance, left ventricular assist devices carry extremely high risk, yet pivotal study sample sizes in both China and the United States are far smaller than those for coronary stents. Therefore, requirements for pivotal clinical trials depend not only on device risk level but also on comprehensive consideration of clinical benefit, clinical urgency, and patient population size—in essence, a comprehensive benefit-risk assessment. Nevertheless, apparent differences persist between Chinese and U.S. regulatory agencies' perspectives in structural heart disease (TAVR, LAAC) and electrophysiology (PFA). Additionally, it is somewhat surprising that while FDA generally imposes higher requirements for pivotal studies of high-risk medical devices, SCS devices can be marketed in the United States through predicate device comparison.

This study has several limitations. First, the number of included products is relatively small, and the comparison content is limited. Currently, not all product evaluation reports are publicly available on the NMPA website, and the published reports lack detailed clinical trial information, including occasional missing sample size data. However, this study selected high-risk minimally invasive interventional products currently receiving significant attention and supplemented information through various channels, making it reasonably representative. Second, this study did not track post-market performance of these products. For example, FDA-approved products such as bioabsorbable DES have been withdrawn from the market—an important topic that warrants continued attention. Finally, the underlying reasons for differences in pivotal studies for high-risk medical devices between Chinese and U.S. oversight are complex and beyond the scope of this paper.

Conclusion

In summary, notable differences exist between Chinese and U.S. regulatory requirements for pivotal studies of high-risk medical devices. Both NMPA and FDA continue to reform to address the rapid development of high-risk medical devices, and achieving consensus between sponsors and regulatory authorities

before conducting pivotal studies for high-risk medical devices should be a future priority direction.

Conflict of Interest Statement: This study represents the personal views of the authors and does not reflect the position of their employer.

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