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NEWS AND VIEWS

Unveiling quality of clinical trial in China: from concern to confirmation

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The cornerstone of scientifically valid and ethically sound clinical trials is in compliance with established global quality requirements. Although China has made significant progress over the past 20 years in terms of the clinical trial quantity [1], quality and participation in multiregional trials [2], there still remain concerns regarding the trial quality, which could be associated with the self-inspection initiative in 2015 [3].

In fact, the clinical trial quality in China has improved significantly during the past decade, which is reflected in the harmonized development trends of industry quality systems and regulatory quality promotion systems (Figure 1). In 2003, the China Good Clinical Practice (GCP) guidelines have been released, which identified the subject protection and data integrity as two basic principles of clinical trials. Four rigorous management policies started to implement in 2015, which required sponsors to re-evaluate the authenticity, integrity, and compliance of trial data before new drug application [4]. A series

List of abbreviations: EU, European Union; FDA, the US Food and Drug Administration; GCP, Good Clinical Practice; NAI, No Action Indicated; OAI, Official Action Indicated; QbD, Quality by Design; R&D, Research and Development; US, the United States; VAI, Voluntary Action Indicated.

Huiyao Huang, Yiru Hou, Hong Fang contributed equally to this work.

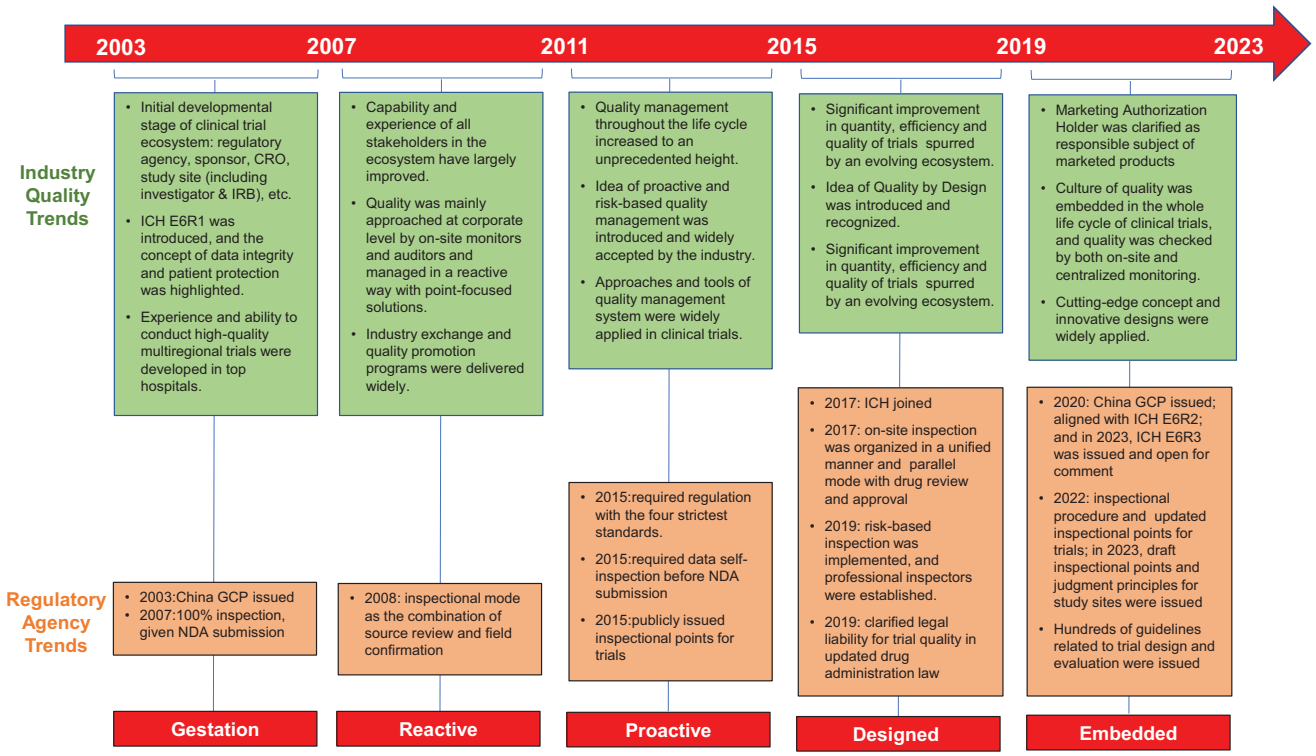

FIGURE 1 Trends of the clinical trial quality system in China over the last two decades. CRO, Contract Research Organization; GCP, Good Clinical Practice; ICH, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; ICH E6R1, ICH Harmonised Tripartite Guideline Guideline For Good Clinical Practice; IRB, Institutional Review Board; NDA, New Drug Application.

of high-profile policies were subsequently announced by the National Medical Products Administration, to improve quality ecosystem [5]. The regulatory supervision of trial quality in China has been significantly strengthened since then. In the meantime, a vital shift occurred since the quality culture in the industry emerged, and the approaches and tools of quality management systems were launched through information exchange and training.

Another milestone of trial quality progress in China was that China officially joined the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and began to integrate into the international drug regulatory system. This alliance initiated a proactive and harmonized process with China pledging to gradually transform its pharmaceutical regulatory authorities, industry and institutions to implement the international coalition's technical standards and guidelines [6]. Universal quality standard GCP guidelines and ideas, such as quality by design (QbD) and risk-based inspection, could be implemented almost simultaneously in China. Gradually, trial quality culture has been embedded in the full life cycle of drug research and development (R&D) in China.

All four regions, including China, the European Union (EU), the United States (US) and Japan, have a common consensus and harmonized standards to ensure the participants' safety, data integrity and GCP compliance, and all have established similar regulatory frameworks for quality compliance (Supplementary Table S1). For example, local and international GCP standards and principles should be established, then inspection processes and checklists with key points for investigational drugs should be employed. In terms of inspection objects, types, requirements and disclosure, we observed consistency in general and slight differences between China and other regions. The difference is driven by that China's inspector put more efforts on scrutinizing trial institutions and laboratories, and relatively less on sponsors compared with the other regions. Notably, China and Japan lag behind the EU and the US regarding the disclosure of inspection findings. This is mainly due to no available database to disclose verification results yet.

Based on the US Food and Drug Administration (FDA) public database, the inspection findings from all the above regions were analyzed [7]. Between January 1st, 2016 and July 20th, 2023, a total of 2,732 eligible inspections were identified, with the majority (93.0%) of inspections occurring in the US. According to the severity of the issues identified, the inspection findings were evaluated and classified as official action indicated (OAI), voluntary action indicated (VAI) and no action indicated (NAI).

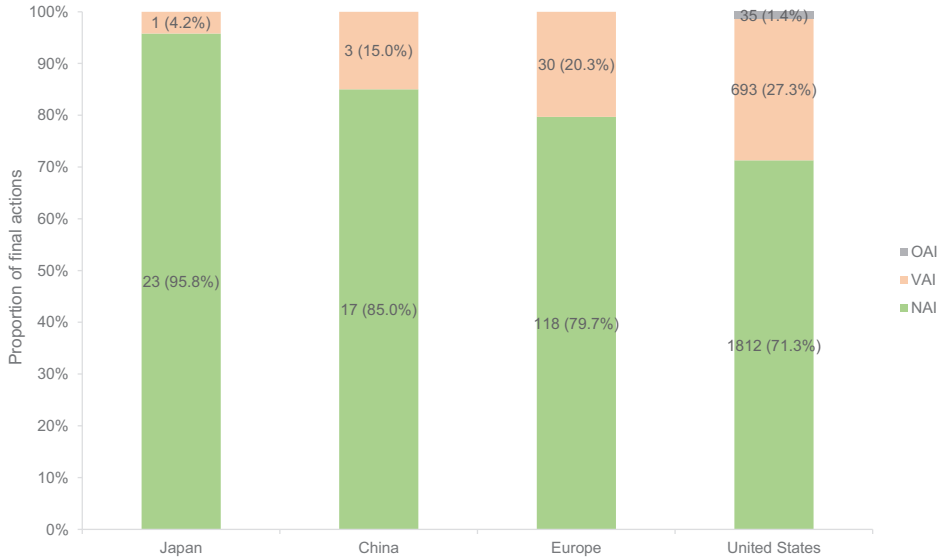

FIGURE 2 Distribution of final actions after FDA inspections in different regions. FDA, U.S Food and Drug Administration; NAI, No Action Indicated; OAI, Official Action Indicated; VAI, Voluntary Action Indicated.

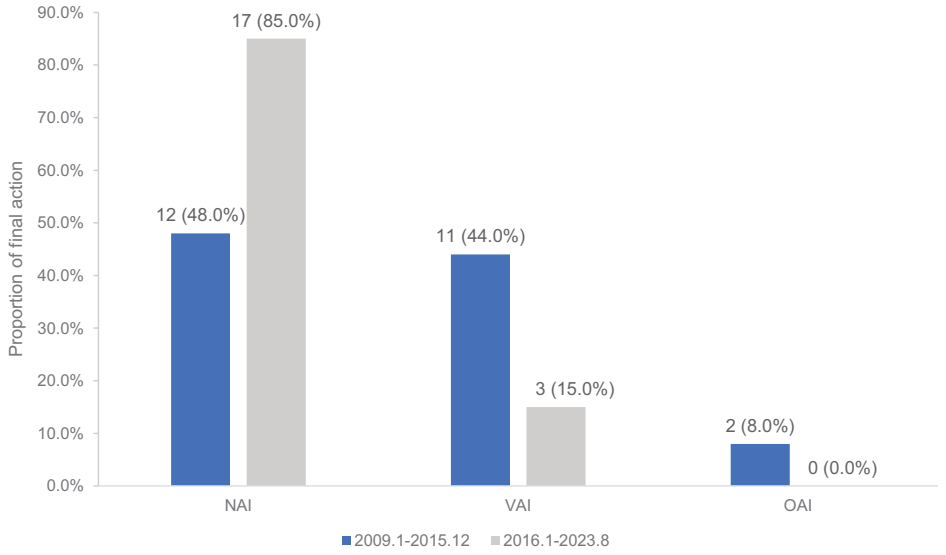

FIGURE 3 Comparison of FDA inspection results for clinical trials conducted in China from 2009 to 2015 and 2016 to 2023. FDA, U.S Food and Drug Administration; NAI, No Action Indicated, OAI, Official Action Indicated; VAI, Voluntary Action Indicated.

Over past 7 years, the proportion of NAIs in the US was 71.3%, which was relatively lower than those in Japan (95.8%, $P = 0.008$) and Europe (79.7%, $P = 0.027$) (Figure 2). In addition, 35 (1.4%) inspections were classified as OAIs in the US, and inspection details of 31 inspections can be pinpointed. The main reasons for those OAIs were incomplete study records (100.0%), poor protocol compliance (87.1%), and non-compliant or inadequate informed consent (80.6%) (Supplementary Table S2). No significant differences in NAI proportion were noted between China and Japan ($P = 0.316$), the EU ($P = 0.768$), and the US ($P = 0.178$) (Figure 2). The possible reason for the lowest proportion of NAIs observed in the US might be the potential selection bias of included inspections. The inspections included in other three regions were multiregional trials only, while those included in the US covered all registered trials. Therefore, the conclusion should be interpreted with caution considering potential bias, as the data generated were solely from the US FDA to ensure unity.

Between January 1st, 2009 and July 20th, 2023, 45 US FDA inspections on trials conducted in China were carried out. The proportion of NAIs has increased from 48.0% (2009-2015) to 85.0% (2016-2023) ($P = 0.018$) (Figure 3), demonstrating a significant improvement in trial quality in China.

The established trial quality ecosystem would benefit China in the long term and accelerate China's full integration into the global pharmaceutical R&D competition.

Meanwhile, we should also be aware that China is still facing some quality challenges.

First of all, China has yet to establish a transparent system to disclose inspection results [8]. Disclosure of verification results can help the industry focus on the main problems, proactively conduct risk management and closely collaborate with regulators to improve the overall trial quality. The annual reports of aggregated inspection findings have been publicly available, and the transparent inspection databases with trial-level information are highly expected.

Additionally, there are some emerging institutions in China that lack sufficient experience and sound quality management systems. Regulations and measures have been taken by both Chinese health authority and emerging institutions to improve their quality systems [9].

Finally, the quality challenges driven by decentralized trials and the application of new technologies are worth noticing. Similar to the rest of the world, China needs to implement the rule of QbD to fully transform the quality of clinical studies from reactive to proactive management. Modernized regulations should be developed and adopted. Regulatory inspection should focus more on critical quality aspects of trial conducting and reporting, instead of on verifying the accuracy of each datum.

AUTHOR CONTRIBUTIONS

Huiyao Huang, Yiru Hou, and Hong Fang contributed to framework planning and draft writing, as well as information collection, quality control, analysis and interpretation. Ning Li, Wenbao Zhang, and Gongtao Lan led the overall framework planning and data interpretation. Ling Xu, Yue Yu, Huifang Zhang, Jing Zhang, and Yu Tang participated in information collection, quality control, and data interpretation. All the authors reviewed and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors disclose no competing interests.

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Not applicable.

ETHICS STATEMENT

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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