Pharmaceutical digital transformation in China:

Digital Quality Assurance Takes the Driver's Seat

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The development of automation, the Internet of Things (IoT), artificial intelligence (AI), big data, and other digital technologies has made it imperative for pharmaceutical companies to undergo digital transformation to improve their research and development capabilities, increase the quality of their products, lower operating costs, and gain a competitive edge. One of the most crucial steps in the life-cycle risk management chain for drugs is digital quality assurance (DQA). Based on a literature review, questionnaire survey, and expert consensus, a panel of experts was convened in Shanghai to generate a set of conceptual, pharmaceutical manufacturing-specific DQA specifications. The goal of the consensus is to advance common practices that use digital tools to quickly collect, record, evaluate, and review particular forms of data to enhance the automation of quality assurance and make drug quality activities more efficient.

1. Introduction

Digital transformation in the pharmaceutical industry

The pharmaceutical industry, which is highly regulated, has long been cautious about digital transformation. In recent years, with the development of automation, IoT, AI, big data, and other digital technologies, digital transformation has become an important way for pharmaceutical companies to enhance research and development capabilities, improve product quality, reduce operating costs and build competitive advantages [1-4].

With mandatory requirements of drug life-cycle risk management constantly being emphasized in China, the reliability and efficiency of quality assurance activities in pharmaceutical manufacturing have received increasing attention from marketing authorization holders (MAHs) and regulatory authorities [5-7]. To ensure that the products are being consistently produced and controlled according to quality specifications, Good Manufacturing Practice (GMP) is the bottommost requirement that a drug manufacturer must meet in their production processes. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated by testing the final product [8]. Moreover, to comply with regulatory requirements, the data integrity of a GMP plant should be at a high level to provide foundational assurance to demonstrate that medical products are safe and effective for their intended use [9].

Indeed, a majority of drug injury events in China were caused by intentional will or technical reasons, suggesting that there are still gaps between the holder's due diligence ability and high regulatory expectations[10]. Since the revised Drug Administration Law was enacted in 2019, the key drug quality responsibilities of MAH have been further clarified but not adequately implemented; one possible reason for this situation could be a lack of technical capability. For further thoughts on this, automated quality assurance techniques could be a promising approach to risk prevention and control because they may provide more timely and effective GMP compliance gap analysis scores (Fig. 1).

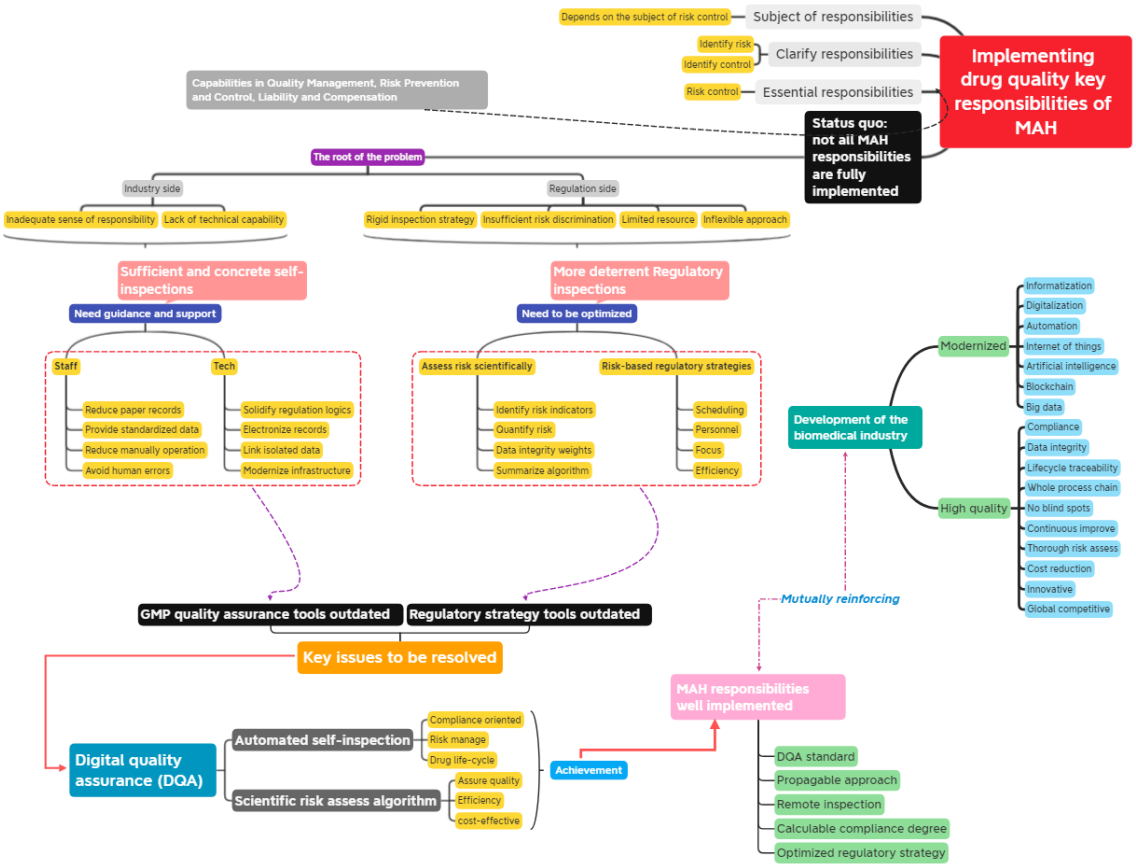

Fig. 1 Marketing authorization holder (MAH) responsibility implementation and regulatory strategy optimization call for digital quality assurance (DQA)

What is digital quality assurance?

Regulatory authorities of China encourage the adoption of modern manufacturing techniques to ensure drug safety in its life-cycle risk management chain. Regulatory science research in this area has also been promoted, of which DQA is one focused research topic [11-15]. DQA is a set of programs, modules, functions, algorithms or components that operate digitally to regulate and oversee pharmaceutical life-cycle processes to achieve the purpose of aiding analysis, review, decision making and risk prevention in quality activities to enhance self-checking and self-inspection capabilities and play the role of compliance grip and bridge.

Compared with traditional manual quality assurance (QA), digital QA adopts digital means and methods, data collection is more efficient, accurate and comprehensive, the QA error rate is lower, and risks are detected in a timelier manner. A detailed comparison of digital QA and ordinary QA is shown in Table 1.

Table 1 The difference between digital quality assurance (QA) and ordinary QA

Compared with existing digital quality management systems, such as trackwise systems commonly used in the pharmaceutical industry, the scope of digital QA is broader and more holistic

	Information bearing	How it is recorded	Data volume	Timestamp	Modifying the mark	Review	Physical space	Search	Backing up	Review time costs
Ordinary QA	Paper	Manual	Fragments	Handwritten	Sign	In person	The archive	Carrying and reading	Photocopying	On a monthly basis
Digital QA	Electronics	Automatic	Massive	System generated	Audit trail	Remote tag	Machine room or cloud	Electronic terminals	Copying	In seconds

and intelligent. DQA reconstitutes certain compliance issues into computable problems, and may not only provide useful approaches to assessing the safety, efficacy, quality, and performance of products, but also facilitate remote regulation assessment during the pandemic[16-18].

In December 2022, the group standard "Technical requirements for digital quality assurance in pharmaceutical manufacturing" was awarded the "Shanghai Standard"[19].

Why does pharmaceutical manufacturing DQA need to be standardized?

To better understand the current status of the domestic pharmaceutical manufacturing digitalization process, we initiated a questionnaire survey and collected the results with a sample size of 184 respondents from 28 of all 34 provinces in China. The respondents are drug R&D and drug manufacturing companies in China, both from developed eastern provinces such as Jiangsu, Zhejiang, Shanghai, and Guangdong and from cities in less developed western provinces such as Qinghai and Gansu. The types of products or services they provide include chemical drugs, biological products, Chinese medicine, final sterilized products and sterile products. The questionnaire survey included the establishment of their drug manufacturing digital system, type of IT infrastructure, continuous manufacturing technology adoption, establishment of digitalization-related standard operating procedures (SOPs), application of electronic signatures, modules adopting electronic records, data acquisition approach, pain points or difficulties in digitalization, current problems of IT supply, self-evaluation of their company’s digitalization level, etc.

The results (Fig. 2) showed that most enterprises have started digital transformation and initially established digital platforms, but they have encountered a series of challenges in this process. The common problems include unclear requirements and objectives, lack of suitable or available software options, lack of professional maintenance, cost constraints, suppliers unfamiliar with regulations, weak universality, large verification workload, poor compatibility, etc.

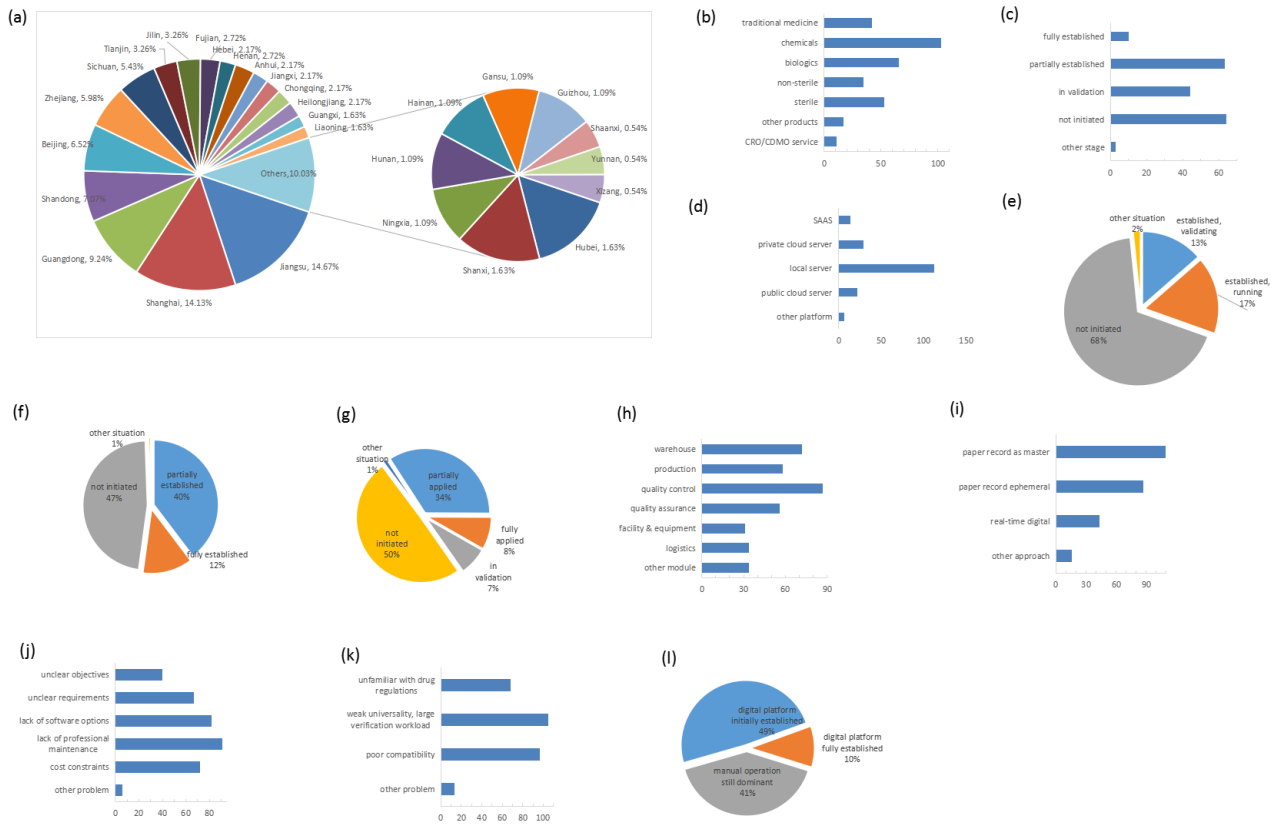

Fig. 2 Analysis of pharmaceutical manufacture digitalization status in China. **a** Company location; **b** type of product/service; **c** establishment stages of drug manufacture digital systems, e.g., QMS/LIMS/MES/SCADA/SAP/ERP; **d** type of IT infrastructure; **e** continuous manufacturing technology adoption; **f** establishment of digitalization-related SOPs; **g** application of electronic signature; **h** modules adopting electronic record; **i** data acquisition approach; **j** pain points or difficulties in digitalization; **k** current problems of IT supply; **l** self-evaluation of the company's digitalization level. QMS: quality management system; LIMS: laboratory information management system; MES: Manufacturing Execution System; SCADA:Supervisory Control And Data Acquisition;SAP:System Applications and Products; ERP: enterprise resource planning; SOPs: standard operating procedures

It is very promising that with the aid of DQA, compliance anxiety and resource shortage concerns in the long journey of digital transformation could become solvable, and trust could be better built between industry and regulatory authorities. However, in consideration of the weak universality and poor compatibility issues, there is still a lack of corresponding standards in this field on, e.g., how to monitor and control mistakes, manipulation and negligence in critical data affecting drug quality, how to focus and refine manufacturing data collection, calculation and output, and how to coordinately and efficiently apply and assess DQA technologies. Therefore, it is important to establish a consensus on the DQA-related technology used in pharmaceutical manufacturing, both in concept construction and implementation practice.

Building consensus between industry and regulation

A panel of experts was established in Shanghai to develop a set of conceptual, pharmaceutical manufacturing-specific specifications for DQA based on a literature review, questionnaire survey, and expert consensus. The consensus is intended to promote standard approaches utilizing digital tools to obtain, record, assess and review specific formats of data on time to improve the automation of quality assurance, making drug quality activities more reliable, compliant, available, synergistic, and accurate. The meetings of the expert panel were sponsored by Shanghai Center for Drug Evaluation and Inspection. The consensus specification was built as technical requirements for the DQA.

The development of the DQA technical requirements framework was guided by several key questions focusing on (1) the scope and extent of digital quality assurance, (2) the input, computation, and output requirements of DQA automation tools, and (3) the relevant management principles.

Scope and extent

The goal of DQA standardization is to provide constructive and feasible specifications for drug quality assurance automation projects, which could be agreed upon by both the industry and the regulator. At the panel meetings, experts' thoughts were gathered to set up the scope and extent of the technical requirements. It was agreed that the basic requirements for DQA construction should include accessibility, traceability, controllability, analysability, and generality. That means, safe access to drug manufacturing data should be obtainable with proper interfaces; basic data generated in the drug manufacturing process can be interconnected and correlated in retrieval; any installation should not adversely affect product quality; process signatures should be ready for identifying gaps between the collection and expectation before and during production; and critical technical design documentations relevant to construction shall be audited according to good practice guidelines.

It is recommended that a DQA preferentially be equipped with the following functions: monitoring the stability and consistency of the drug production process; monitoring the precision and accuracy of drug manufacturing data; periodically evaluating the operation of the drug production management system, with special attention to finding, handling and preventing deviations; testing the level of quality assurance capability by using quality assessment tools during periodic review; and periodically and independently implementing requalification/revalidation to the qualified/valid systems.

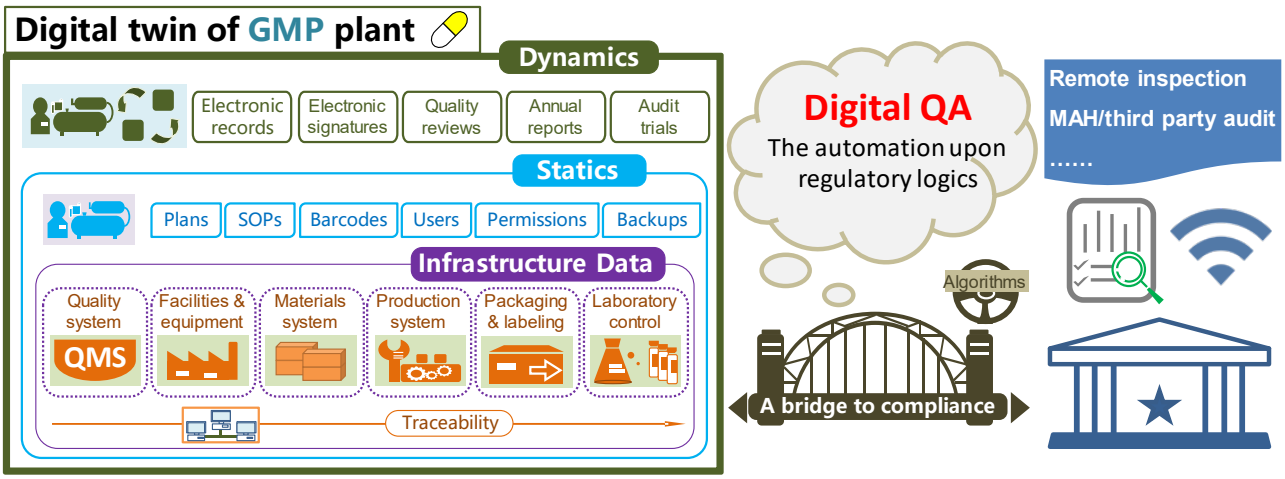

Fig. 3 Scope and extent of digital quality assurance (DQA)

The consensus confirmed that a DQA could be defined as a set of programs, modules, functions, algorithms, or components that operate digitally to regulate and monitor the life cycle process of a drug product. The digital QA tool is coded with regulatory logic, which not only acts as an assistant to human QAs but also plays an important role in helping to bridge the compliance gap between the pharmaceutical manufacturing factory and the audit subject by automatically analysing due diligence status through the digital twin of the GMP plant (Fig. 3). Digital elements in a GMP plant may include infrastructure data, static management data, and dynamic records. The results of the DQA analysis can be used to support the inspection of such a GMP system, enhancing the accuracy and breadth of risk control. Moreover, the advances of the DQA may also extend to business-to-business inspections such as commissioned production audits, which are also an obligation imposed by the law on MAHs.

The main composition of input and output (I-O)

DQA technical requirements were drafted by specialist working groups tasked with developing consensus on construction bases, application functions, data acquisition, compliance management, and early warning. This technical note presents a schematic summary of the key thoughts (Fig. 4).

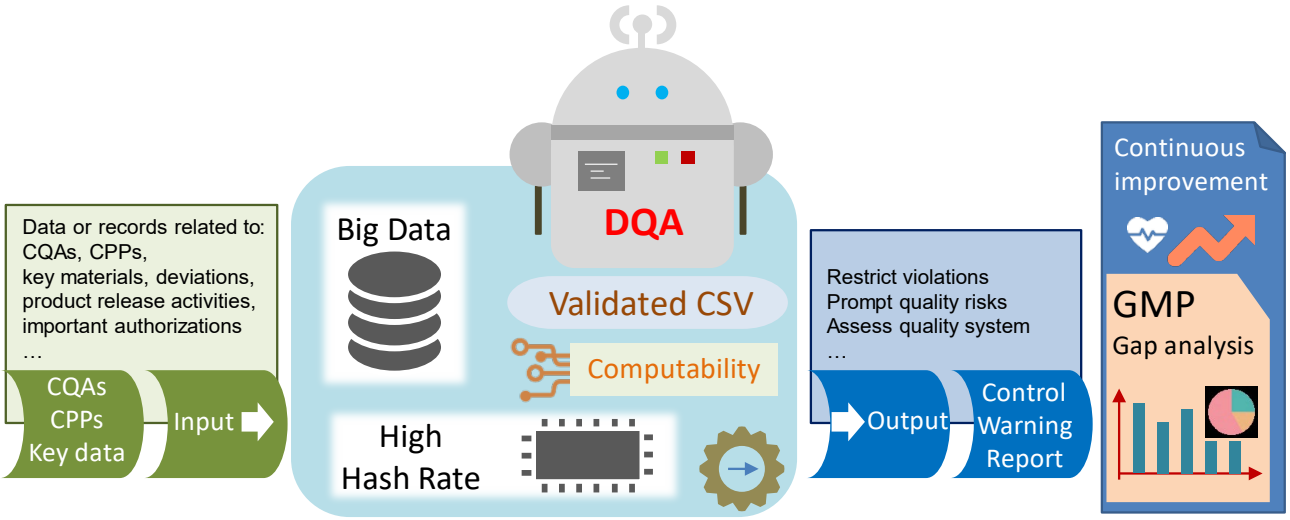

Fig. 4 Input, computation, and output considerations.

The inputs are usually provided by drug manufacturing data acquisition, of which granularity and efficiency should be considered. In a digitalized drug manufacturing plant, huge amounts of data are generated every millisecond. For quality assurance, simply copying all data out of each computerized system immediately is considered too resource-consuming and inefficient. The consensus provided the answer to the question of which data should be collected and when the acquisition should occur. For data collection, those important elements related to critical quality attributes (CQAs), critical process parameters (CPPs), key materials, deviations, release activities, and key authorizations should be given priority. In certain circumstances, e.g., individual paper records or devices with no transmission function existing in the system, not all data are available online in time. The timeliness of data acquisition should be consistent with the relevant risk level, and data should be transmitted in a timely manner to the relevant information system or converted into electronic form to ensure authenticity, integrity, and traceability. It is recommended that data timeliness be managed at three levels: real-time, periodic, and delayed.

Storage space and the hash rate of the computing unit should be rationally designed and flexibly configured for holding data sets and running DQA algorithms, with adequate resource reservation for further research, expansion, and continuous improvement. In algorithm research, it is necessary to carry out long-term cooperation between industry and regulators with assistance from professional associations because GMP compliance issues need to be accurately translated into computable issues, which is a prerequisite for DQAs to work appropriately.

The computed outcome of DQA is mainly reflected in compliance management and early warning. For high-risk cases, such as failure to record and/or investigate abnormal incidents that may affect product quality, attempt to perform unauthorized operations, use of another person's account without authorization, or operating in violation of critical steps required by SOPs, direct restriction to the operation violation should be considered. In the case of moderate-risk situations, risk notification sent to the responsible person on time would be recommended. The low-risk data, after a period of accumulation, could be analysed to assess the healthiness of the quality system at regular intervals.

Management principles

In addition to technical requirements for I-O, brief guidance for implementation was also discussed. It is recommended that, on initiation of a DQA project, the scope of the current stage be defined based on the risk assessment approach to determine what specifications to meet according to the drug product quality standard. Then, procedures should be established for how to implement the project, with written documents taking effect under the GMP quality system framework. All activities involved in the DQA life cycle require close collaboration among the workforce from all related departments of the pharmaceutical company, with responsibilities clarified and training conducted accordingly. When the development is completed and tested, formal deployment may be carried out, which should follow communication and training of DQA procedures by relevant functional personnel, by plans, and evaluated for effectiveness. It is suggested that the life cycle management of components/systems involved in DQA shall be carried out following the requirements of the GMP specification for computerized systems. Design reviews and validation of DQA or its components should be conducted, including but not limited to initial deployment and changes, based on risk assessment. Quality assurance is a continuous process, and the performance of the DQA itself should be monitored after implementation. The quality assurance staff shall ensure that the DQA continues to operate effectively for its intended use and collect user feedback during its operation for optimization and improvement, with periodic review to ensure that it is always maintained in a validated state and under control. Moreover, all changes of the DQA in the life cycle shall meet the requirements of quality system change management and be implemented under a preapproved plan, including upgrading, replacement, and retirement.

An overall consensus on the need for risk management of digital quality assurance itself with considerations of data formats and interfaces was also included. It is recommended that risk management run through the DQA life cycle and fit in with the drug product life cycle risk management, especially the key steps including determining the scope and requirements, analysing the effectiveness, and assessing the potential impact on existing processes and change management.

Discussion

In this technical note, a new concept of DQA as an automated GMP compliance assessment tool

for bridging the pharmaceutical manufacturing industry with regulation is introduced. A panel of experts developed a set of conceptual, pharmaceutical manufacturing-specific specifications for DQA, which provided technical requirements on the scope and extent of the I-O as well as the relevant management principles. These consensus recommendations could help to improve the quality management level in GMP systems, with better risk prevention where mistakes, manipulations, and negligence could be automatically monitored and controlled, especially on critical data that might directly impact drug quality. To the best of our knowledge, this is the first time that the pharmaceutical manufacturing DQA concept has been clarified and standardized. Considering that the medical product industry is a highly regulated field in China and that the MAH's due diligence ability desperately needs to be elevated, the DQA taking the driver's seat on the road to GMP digitalization has important practical significance and can speed up the journey to high-quality modernization of the domestic pharmaceutical industry.

In the future, many advanced technologies will be adopted in pharmaceutical manufacturing, which requires more modernized QA tools. For example, to validate the process analytical technology systems used in continuous manufacturing, continuous quality assurance should be provided; for autologous cell-therapy products, a digitalized material traceability system is needed. We believe that the DQA technique will play a more important role in these emerging technology areas. Nevertheless, the study of DQA is still in the initial stage. We hope this technical note helps to share and discuss the feasibility of these specifications with international counterparts.

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Author contributions

YYG and MC involved in conceptualization, investigation, visualization, writing (original draft, review and editing) ;HC, BH,JCZ involved in conceptualization and discussion;ZYY, YWW, BFZ, KPR, YYP, YZ, TJT, ZZL helped in investigation and visualization;HMY and GLC involved in conceptualization,supervision and writing—review and editing.All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

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