Applications and regulatory of nanotechnology-based innovative in vitro diagnostics

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Abstract
Nanotechnology-based in vitro diagnostics (nanoIVDs) are widely studied for disease diagnostics with promising sensitivity, specificity, and convenience. However, it is still a major challenge for both regulatory authorities and scientific researchers to accelerate the clinical translation of such an innovative technology. Herein, this perspective discussed the benefits and challenges of nanoIVDs as well as the administration considerations on the distinguish features of nanoIVDs by regulatory authorities, so as to further achieve the evaluation, translation, and application of nanoIVD products.

KEYWORDS
COVID-19 (SARS-CoV-2) detection, in vitro diagnostics (IVD), nanomaterials, nanotechnology-based in vitro diagnostics (nanoIVDs), regulatory science
1 | INTRODUCTION

Regulatory science has been established as a new scientific discipline, which is the scientific and technical foundation for supporting policy, notably regulated objectives. Regulatory science plays a crucial role in the administrative affairs of medical devices. Specifically, regulatory science provides the fundamental methodologies for improving the capacity of administrative authorities for safety and efficacy evaluations, ability to supervise medical devices both during application development and marketing, modernizing current regulatory pathways, as well as developing new regulatory measures when currently there is a lack of sufficient solutions. The innovation of in vitro diagnostics (IVDs) and their transformation into products, services, or new applications can be improved greatly with the development of regulatory science.

As a result of the considerable achievements of nanotechnology, numerous innovative nanoIVDs have been developed by introducing different nanomaterials (NMs). NanoIVDs have become promising analysis platforms with better specificity and higher sensitivity compared to conventional IVDs. In a sense, nanotechnology will bring IVDs into a new era. With the establishment of nanoIVDs, NMs play a variety of crucial roles, such as a signal generator, signal converter, signal enhancer, reaction vessel in IVDs, and powerful tools to improve the extraction and separation processes in sample preparation. The unique properties of NMs contribute to improving the analytical performance of nanoIVDs and serve as new detection platforms as well. Thus, the emergence of nanoIVDs can decrease the threshold of IVDs for the detection of specific biomarkers at extremely low concentrations in complicated biofluids. However, only a few successes for nanoIVDs in the commercial market have been reported. A frustrating fact is that nanoIVDs have seldom represented superiorities in real-world clinical diagnosis and therapy data over conventional IVDs. It remains a major challenge for global regulatory authorities to accelerate the clinical transformation of such innovative nanoIVDs technology under the premise of convincing safety, efficiency, and quality control.

Herein, we focused on the regulatory science of nanoIVDs from this perspective and discussed how to reform the scientific regulatory requirements both in review and approval procedures. Moreover, further exploration was provided on how to improve nanoIVD technology to satisfy regulatory requirements more satisfactorily, by combining with the characteristics of nanoIVD technology (Figure 1).

2 | BENEFITS OF NANOTECHNOLOGY FOR IVDs DEVELOPMENT AND COVID-19 (SARS-COV-2) DETECTION WITH nanoIVDs

2.1 | The crucial roles of NMs in nanoIVDs

IVD technology is a series of methods that turn in vivo information into easy-to-handle signals, such as strips, ELISA, electrochemical biosensing, and so on. Recently, in a parallel with chemistry and nanotechnology, NMs have been explored for IVD development, and several crucial aspects are involved in the establishment of nanoIVDs, including signal generation, amplification, conversion, and collection (Figure 2). The emerging nanoIVDs could be a versatile and effective paradigm for biochemical analyses.

NMs are promising candidates as signal generators for IVDs and provide more options for conventional IVDs, benefiting from their unique size-dependent physical and chemical properties, such as optical, thermodynamic, and magnetic performances. In comparison with fluorescence probes, quantum dots (QDs), up-conversion nanoparticles (UCNPs), and long-persistent NMs exhibited the superior features of high fluorescence brightness, good stability, and low background noise. Therefore, the fluorescent NMs have been explored as fluorescent/colorimetric generators in point-of-care tests (POCT) strips, nano-linked immunosorbent assays, and DNA microarrays, which realized improved accuracy and more sensitive detection. Some of the nanoIVDs based on colorimetric NMs can realize equipment-free on-site detection of biomarkers. Besides the traditional gold NPs (AuNPs) and magnetic NPs (MNPs), photonic crystals

FIGURE 1 The common efforts of regulatory science and scientific research devoting to NanolIVDs application
show significant changes in a Bragg diffraction spectrum or color and have been widely used as the visual signal of nanoIVDs, which have an impressive potential to be a vital aspect of visual detection in the future. Moreover, the related fluorescent nanoIVDs, such as QDs-based immunochromatographic test strips, have been commercialized for clinical application.

NMs have been widely used as enhancers to tremendously amplify the signal of IVDs for trace biomarker detection. The large specific surface area of NMs enables multi-labeling of signal molecules, such as enzymes and fluorescent materials, to enhance the signal intensity produced by a single target molecule, which has been employed to multiple detection methods such as nano-ELISA. Furthermore, the signal can be enhanced profoundly by taking advantage of the impedance, surface plasmon resonance (SPR), refractive index signal of metal NPs, and the signal enhancement of photonic crystals.

NMs can also achieve the signal conversion by combining with unique and representative traits, including nanozymes catalysis and fluorescence resonance energy transfer (FRET). Nanozymes refer to enzyme mimics with catalytic activity, such as peroxidase, oxidase, and catalase, which can overcome the intrinsic drawbacks of natural enzymes. Some metal NMs and metal-organic frameworks (MOFs) can catalyze substrates with an obvious color change or chemiluminescence signals. Nanozymes have attracted wide attention in pathogenic bacteria, biomacromolecules, and heavy metal ions detection with low cost and high stability. NMs with unique optical properties have injected new energy into the FRET system. As energy donors/quenchers, NMs can significantly reduce background noise and achieve high fidelity, for rapid homogeneous detection without extraction.

NMs can serve as the ideal reaction vessel for IVDs, because of their efficient catalytic performance, unique photothermal effect, and ultra-high detection sensitivity. The typical representatives are nanopore reactors and nanoheaters that significantly improve enzyme activity and catalytic efficiency, and contribute to more sensitive detection. The hollow NMs (silica, metal, metal oxides, and MOFs) have been considered as the ideal nanoreactor due to the special encapsulated nanocavity containing catalytic...
In addition to the nanopore reactor, the unique photothermal effect of plasma NMs leads to efficient conversion of light into heat, enabling them to act as superior nano-scale heating vessels. Furthermore, some metallic NMs (nanorod, nanosphere, nanofilm, and nanobipyramid) have been designed for plasmon-driven ultrafast photonic polymerase chain reaction (PCR) technology based on the near infrared photothermal effect of heating a PCR solution. This PCR replacement reactor can overcome the issues of commercialized thermocyclers, such as expensive Peltier-block heating, heterogeneous temperature fields, and prolonged reaction time, and it has a broad application prospect for nucleic acid analysis and detection.

NMs are committed to rapid and efficient sample extraction and separation of IVDs, with the advantages of simple synthesis, low cost, good biocompatibility, high magnetic moment, and superparamagnetic properties. Magnetic solid-phase extraction (MSPE) technology is one of the most mature applications based on the electrostatic adsorption, affinity, hydrogen bonding, or ion exchange to achieve separation and extraction of proteins, nucleic acids, and cells. The nucleic acid extraction kits and circulating tumor cells (CTCs) testing kits based on magnetic beads have been commercialized and widely applied. Another important extraction application is the zinc oxide nanomultigonal shuttle (ZnO NMS) that enables efficient cell lysis at room temperature in two minutes, and high purity DNA targets isolation (100 times more than commercial spin-column kits) in 15 minutes. Meanwhile, combining the ZnO NMS with multiple devices can improve the extraction efficiency and variety, and realize the portable extraction.

2.2 The COVID-19 detection and approval of nanoIVDs by regulatory

COVID-19 rapidly spread across the world and caused a global pandemic, and it is extremely urgent to establish quick detection methods with on-demand accuracy for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Ribonucleic Acid (RNA) and antiviral antibodies. It is a major challenge for the conventional high-throughput sequencing (HTS) to realize rapid screening of COVID-19 within a large population because of the time-consuming process and expensive cost of HTS. Most of the commercial methods for early diagnosis of SARS-CoV-2 RNA are based on the gold standard real-time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test with SYBR Green/TaqMan oligonucleotide probes and primers for N/S genes of SARS-CoV-2 RNA. Fortunately, NMs provided great benefits compared to the conventional detection strategies. To simplify the sample processing steps and shorten the extraction time, MNPs are employed with automated extraction for a nasopharyngeal swab RNA sample-based on MSPE. Then, more isothermal amplification assays (Loop-Mediated Isothermal Amplification [LAMP], Recombinase Polymerase Amplification [RPA]) and Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)-based assays show promising potential. Moreover, a peptide-based magnetic chemiluminescence enzyme immunoassay has also been proposed for COVID-19 detection. As for the nucleic acid amplification products, AuNPs are introduced as the detection signal based on color change for naked-eye readout. Furthermore, POCT are more suitable compared to ELISA for rapid screening of a wide range of communities without laboratory infrastructure. AuNPs, fluorescent NMs, and NMPs have been widely used in the lateral flow for SARS-CoV-2 antibodies (IgM, IgG) detection within 10-15 minutes. Further, the related commercial 2019-nCOV IgM/IgG test products, including the colloidal gold method, fluorescent microsphere immunochromatography, and magnetic microparticle chemiluminescence methods have been approved to facilitate rapid screening and testing of COVID-19. At present, the POCT lateral flow immunoassays are usually used by combing with RT-PCR for large-scale rapid screening of COVID-19 patients. We posit that powerful nanoIVDs technology can help to diagnose viruses, curb the infectious spread, and reduce mortality.

Despite the great potential for biomedical diagnosis, nanoIVDs also face some challenges meeting the requirements of regulatory approval. One of the major bottlenecks is the interface problem: due to the large specific surface area and high surface energy, the NMs are prone to agglomeration. Further, the NMs have a poor affinity toward the lower surface energy matrix and are not miscible, resulting in voids at the interface and phase separation.

3 REGULATORY SCIENCE EFFORTS TOWARD APPROVAL OF nanoIVD PRODUCTS

3.1 Status of China IVD market and regulation of innovative IVD products by National Medical Medical Products Administration

IVD is a rapidly developing industry in the world. China’s IVD market has become the second largest market in the
world after the United States. The IVD market in China presents an “olive type” market structure that exhibits stagnant growth of low-end market, rapid expansion of mid-end market, and gradual development of high-end market. In 2019, the National Medical Products Administration (NMPA) approved 3245 IVD reagents, accounting for 38.3% of the total number of medical devices registered in China. IVD reagents account for a large proportion of both domestic and imported medical devices. In recent years, the NMPA has further promoted the reform of medical device evaluation and approval system, accelerating the innovation and development of medical devices. In order to realize more professional and efficient approval of the products in the pipeline of innovative IVDs, the Center for Medical Device Evaluation (CMDE) carries out scientific review through early intervention, special reviewers in charge, multiple chances for communication, expert consultation and other measures. Under the premise of “no compromise of standards and no reduction of procedures,” the CMDE will give priority to the innovative IVDs. The average review and approval time of innovation priority is 83 days shorter than that of other products under normal review. The period from research and development (R&D) to marketing of innovative products is also shortened. Since the release of regulation “special approval procedures for innovative medical devices,” 236 products have entered the special review channel of innovative medical devices, and 73 innovative products have been approved until December 31, 2019. Of note, there were 14 diagnostic devices and 14 IVD reagents approved, which accounted for 38.4% of all approved products. In recent years, the CMDE has made considerable progress to modify the evaluation with clinical orientation. Currently, a reasonable evaluation process of medical devices, including IVD products, has been formed. The registration workflow of the CMDE is depicted in its website. In technical review of IVDs, the CMDE focuses on critical scientific evidence that can prove that the clinical benefits from evaluated IVDs outweigh their risks significantly. The development of regulatory science enormously improves the capability of the CMDE to balance benefits and risks for innovative IVDs, including nanoIVDs, on which there is still a lack of established evaluation tools, such as standards and guidance.

3.2 Status of COVID-19 test kit review and approval

Since the outbreak of novel coronavirus pneumonia (COVID-19), the timely approval of a test kit has been of great importance for the quick diagnosis and effective prevention on COVID-19. Since January 20, 2020, the CMDE has started the emergency review and approval procedure for medical devices according to the “Emergency approval procedure for medical devices” issued by the NMPA in 2009. The CMDE accelerates the review procedure on COVID-19 IVDs products, following the principle of “unified command, early intervention, review at any time, scientific approval” and the requirements of product safety, effectiveness, and quality control. Although these COVID-19 IVDs products were approved via the emergency approval procedure, their review procedures and standards were not compromised or reduced. On January 26, 2020, the first four products passed the emergency approval by the NMPA. As of June 12, 2020, 42 products have obtained medical device registration certificate that can fully meet the clinical needs of COVID-19 screening and diagnosis in China (data from NMPA website).

Because the COVID-19 pandemic has spread rapidly in the United States, according to the 564th article of the federal Food, Drug and Cosmetic Act (FD&C act), the FDA issued the application guidelines for the EUA of SARS-CoV-2 RNA nucleic acid detection reagents on February 29, 2020, and updated the “Emergency Use Authorization” policy on March 28, 2020. As of May 12th, 2020, the FDA has authorized a total of 93 COVID-19 detection reagents in the form of the EUA policy, including 12 antibody detection reagents and one antigen detection reagent.

3.3 Discipline points of CMDE regulatory on IVD reagents

According to the “Basic principles for the safety and performance of medical devices” issued by the NMPA for the evaluation of IVD reagents, the major concern lies on the physicochemical incompatibility between the materials used in IVDs and the tested samples, analytes, or markers, such as biological tissues, cells, body fluids and microorganisms, and the leading possibility of damaged analytical performance. IVDs should achieve the claimed analytical and clinical performance properties suitable for their intended uses. In an IVD technical review, the analytical performances and clinical performances are the most crucial parameters for the CMDE judgment, which are depicted in Figure 3. When the performances of IVDs depend on the use of calibrators, the assignment of calibrators or quality control materials should be traced through reference measurement procedures or higher level reference materials.
The considerable advances of nanotechnology have substantial impacts on many pharmaceutical industries. The FDA has established a nanotechnology task force to supervise the application of nanotechnology, or a broad spectrum of products associated with NMs, including food, cosmetics, drugs, medical devices, and veterinary products. In 2014, the FDA issued the guidance: “Considering whether an FDA-regulated product involves the application of nanotechnology.” This guidance describes an overarching framework for FDA’s approach to the regulation of nanotechnology products and identifies two points to consider that are broadly applicable to all FDA-regulated products. The FDA has already approved several IVDs that contain nanotechnology, such as products containing AuNPs, DNA barcoding device, and IVDs that use MNPs. In January 2015, the European scientific committee on emerging and newly identified health risks, SCENIHR, released “Guidance on the determination of potential health effects of NMs used in medical devices.” This is the first guideline for NMs used in medical devices issued by regulatory authorities in global. The NMPA has also been paying attention to the application of nanotechnology in the field of medical devices. Currently, the NMPA and the National Center for Nanoscience and Technology (NCNST) of China are carrying out a joint research program on the safety and effectiveness evaluation of NMs used in medical devices.

### 4 | Perspective on the Advances of Regulatory Science and Approval of nanoIVDs

#### 4.1 | Considerations of regulatory science on the approval of nanoIVD products

Until now, only a few IVD reagents using NMs could be found on the NMPA website. Among them, only one rapid detection kit for human chorionic gonadotropin (HCG) confirms presence of “carbon nanotube-colloidal gold complex.” Several IVDs using quantum dots, colloidal gold, and nano-scale magnetic beads may also be regarded as NMs-containing IVDs. Overall, there are few successful cases of product development and registration compared to the abundant basic research results of nanotechnology. Currently, NMs and nanotechnology are rarely included in regulations and normative documents issued by the NMPA. It is only mentioned in “The basic principles of safety and performance of medical devices” that “when design and production of medical devices, the particles released into the body of patients or users should be appropriately reduced in order to imitate risk related to the sizes and properties of particles except the products that contact with intact skin. Special attention should be paid to NMs.” In terms of regulation drafting and issuing, regulatory authorities in most countries, particularly in China, lag behind the rapid development of nanoscience, technology, and product advancements. Nevertheless, the NMPA will draft and issue relevant regulations to strengthen oversight of nano-pharmaceutical products and keep pace with nanotechnology development, as well as development and application of related products. Regulatory authorities, such as the FDA and NMPA, view the IVD as a whole system, encompassing specimen collection detection, and
results. The IVD must demonstrate reproducibility, perform as expected, and prove safe and effective for its intended use. While some IVDs involve the application of nanotechnology, they should be reviewed during the application process just like IVDs that do not use NMs.76

In the current evaluation of IVD reagents, the main concerns are the accuracy and sensitivity of the product in laboratory tests, as well as in clinical use. From the reviewers’ perspective, it is not important whether the product uses NMs and nanotechnology or not. This principle will notice to researchers in related fields: they should consider whether NMs and nanotechnology offer additional advantages over existing technologies and products in the above aspects. At the same time, due to the nature of NMs, the possible physical and chemical incompatibility of the products and possibility of damage to the analytical performance caused by this incompatibility should be studied carefully. Regarding batch stability, repeatability, and uniformity in mass production, the corresponding research and verification work should be conducted according to relevant regulations and guidance of CMDE and NMPA. Stability of an IVD reagent reflects its ability to maintain consistent performance characteristics over time, which includes shelf-life stability and in-use stability.77 For shelf life stability, at least three lots of products should be evaluated. The key performance indicator, the acceptance criteria of each metric, and the statistical confidence and power desired in the resulting analysis should be considered for stability testing. For nanoIVDs, the stability of NMs, as well as other materials, can affect the stability of reagents. The stable large-scale production of NMs with acceptable quality criteria will contribute to its utility in nanoIVDs. One critical issue with manufacturing NMs for regulatory authorities is how to ensure a reproducible nanoIVD product on a large scale. This aspect should be evaluated during the reproducibility study and submitted in application dossiers. Analytical performance of different material lots (at least three lots) should be tested in the reproducibility study. In addition, calibrators/quality control materials for IVD products must meet rigorous standards. However, most newly developed NMs lack available calibrators/quality control materials, limiting their application in the IVD field. Special precautions should be taken for nanoIVDs labeling to ensure proper disposal of NM when it is considered hazardous, which depends on the NM used in IVDs.

4.2 Advances toward regulatory approval of nanoIVD products

Based on general IVDs approval criteria, technical adjustments and efforts should be made for nanoIVDs. While the nanoindustry appears healthy, approval may be hindered due to the lack of certainty and safety research. FDA-approved NMs seem to be more promising candidates for health and safety nanoIVDs. The structure activity relation knowledge can be used to design and produce safer NMs by modifying or changing physical and chemical properties. Researchers are also expected to achieve controllable preparation of mass products with high batch stability, uniformity, and biocompatibility through improved manufacturing processes and surface modification, along with further exploration of available calibrators/quality control materials for newly developed NMs. In addition to the above improvements, rather than blindly pursue sensitivity, researchers should focus on improving accuracy to meet quality control requirements, particularly from the perspective of regulatory agencies. Each chain of nanoIVDs will affect the final test results, potentially causing “false-negatives” or “false-positives.”

To address this issue and ensure accurate and repeatable performance, researchers can improve sample extraction efficiency and purity, design patented technology for sample preservation, optimize reaction systems, adopt standardized clinical laboratories, and introduce advanced automatic detection and analysis workstations. Moreover, filling gaps in traditional IVDs is the most important significance of nanoIVDs. It also remains highly challenging to determine trace biomarkers, such as transfer potential CTCs and short sequences/high autoploid microRNA, for traditional IVDs detection. New nanoIVD techniques lack the ability for making it possible to detect trace biomarkers accurately, simply, and sensitively. Due to the inherent limitation of intracellular imaging by traditional IVDs, the gap of in situ imaging for quantitative analysis could be filled by nanoIVDs. Rapid detection of biomarkers is integral to applications in clinical diagnostics and biotechnology due to increased demand for fast on-site detection. Despite the substantial progress of nanoIVDs, development of simple, inexpensive, highly sensitive, and portable POCT/bedside testing diagnostic devices for early detection of infectious diseases remains an urgent need in our country. While some traditional IVDs effectively amplify nucleic acids for detection (such as PCR), they require instrumentation that is not portable, precluding their deployment in the field. Demand for instrument-free nucleic acid nanoIVDs has driven development of multiple methods for isothermal amplification.

5 CONCLUSION AND OUTLOOK

In summary, the nanoIVD displayed distinct sensitivity, specificity, and convenience compared with the traditional IVD. Their clinical transformation will promote the
improvement of disease detection. However, the premise of convincing safety, efficiency, and quality control requested by global regulatory authorities still remains a major challenge for nanoIVD toward further translation advances. The CMDE, NMPA has been paying attention to the application of nanoIVDs and promoting the reform of medical device evaluation and approval system to accelerate the innovation and development of IVDs. Since the outbreak of COVID-19, the CMDE started the emergency review and approval procedure in time, and approved first batch of COVID-19 test kits within 1 week after their submission. CMDE regards IVDs as a whole system, encompassing specimen collection, detection, and results. In technical review of IVDs, the CMDE not only evaluate the materials, the reaction system, the production procedure, but also the analysis performance and clinical performance to guarantee their safety, quality, and efficiency of clinical application.

The criteria for the market approval of nanoIVD product are the same as those for conventional IVDs. Researchers should recognize the importance of the following aspects. First, the possible physical and chemical incompatibility of the nanoIVDs and possibility of damage to the analytical performance caused by this incompatibility should be studied carefully. Second, regarding batch stability, repeatability, and uniformity in mass production, the corresponding research and verification work should be conducted according to relevant regulations and guidance of CMDE and NMPA. The effective interpretation of regulations can promote the nanoIVD from laboratory research for evaluation, translation, and application in clinic.

The regulation practice of various countries in recent decade has proved that the regulatory authorities should timely draft and release specific evaluation guidances and technical regulations for NMs used in medical products, for instance, nanoIVDs, based on the research results of regulatory science. These guidances and regulations will help the development of medical industries and improve the accessibility of medical products using nanotechnologies. For example, after the FDA issued two guidance documents, namely “Considering whether an FDA-regulated product involves the application of nanotechnology” and “guidelines on the safety of cosmetics NMs,” more than 100 nanodrugs and nano-medical devices have entered clinical practice in the United States. Therefore, it is necessary for NMPA to carry out regulatory science research in order to develop new standards and methods for quality control safety assessment of nano-medical devices and nanoIVDs. Furthermore, NMPA will also draft and issue relevant guidances on nano-medical devices and nanoIVDs. These measures can enhance the scientific basis of China’s international competitiveness in nanotechnology and provide regulatory and management policy guarantee for the healthy and sustainable development of nanotechnology in medical products industry.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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