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Review

Regulation and quality evaluation system for HIV diagnostics in China

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ABSTRACT

A sophisticated regulatory framework has been constructed for *Human immunodeficiency virus* (HIV) diagnostics in China, which have developed over the past 30 years. China National Institutes for Food and Drug Control acts as the legal institution in this regulatory framework, launching important activities to ensure the quality of HIV diagnostics. These include the analysis of the main problems faced in developing domestic HIV diagnostics, by investigating the quality of HIV diagnostics and their development; exploring the key factors affecting the quality of HIV diagnostics, to determine the criteria for screening national reference samples; the development of new technologies and methods for preparing reference samples; and the establishment of nine types of national reference panels and nine national standards to evaluate the quality of HIV diagnostics. Based on these researches, a quality evaluation system was established, including nine types of national reference panels, nine national standards for HIV diagnostics, and five sample banks (HIV-positive sample bank, HIV-negative sample bank, common international genotype sample bank, seroconversion series sample bank, HIV virus bank) to evaluate the quality of HIV diagnostics in China. The regulatory framework and the quality evaluation system are pivotal in ensuring the quality of the HIV diagnostics licensed in China.

1. Introduction

The HIV-1 epidemic has become more visible worldwide since the first case of HIV-1 infection was reported in 1985 [1]. In the past 30 years, many efforts have been made to develop an effective vaccine to prevent HIV-1 infection, but unfortunately, no immunologically protective effect was demonstrated in clinical trials of the experimental HIV vaccines. The number of reported HIV/AIDS cases is increasing every year, and HIV has spread throughout China [2]. Currently, increasing numbers of HIV/AIDS patients benefit from HIV prevention and treatment program, which are significantly supported by the Chinese central government. HIV diagnostics, including anti-HIV antibody assays, HIV-1 viral load assays, HIV-1 nucleic acid tests (NATs), and assays for the analysis of HIV-1 drug resistance, play a pivotal role in ensuring safety of blood by screening HIV among blood donors and the selection of the appropriate antiretroviral treatments.

In parallel with the international development of HIV diagnostics, the first HIV diagnostic test developed in China in 1985 was an immunofluorescence assay to detect anti-HIV antibodies [3]. With advances in scientific technology, increasing numbers and types of HIV diagnostics were developed, including anti-HIV antibody assays based on enzyme-linked immunosorbent assay (ELISAs; 1st-generation assays, 2nd-generation assays, 3rd-generation assays, and 4th-generation assays; see Table 1), anti-HIV antibody rapid tests, anti-HIV antibody assays based on western blotting, HIV-1 viral load assays, and HIV-1 genotypic resistance assays. In the course of the

Abbreviations: HIV, Human immunodeficiency virus; AIDS, Acquired Immuno-Deficiency Syndrome; NAT, nucleic acid tests; ELISA, enzyme-linked immunosorbent assay; NIFDC, National Institutes for Food and Drug Control; CFDA, China Food and Drug Administration; GMP, good manufacturing practice; gp41, glycoprotein 41 of HIV; gp160, glycoprotein 160 of HIV; p24, core antigen of HIV; IVD, In Vitro Diagnostic; CTSs, Common Technical Specifications; FDA, Food and Drug Administration; CBER, Center for Biologics Evaluation and Research; PMA, premarket approval.

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Table 1
Development of anti-HIV ELISAs.

	Methodology	Coated material	Labeled material	Target	Characteristic	Window period
1st-generation assay	Indirect ELISA	Antigen (HIV virus lysate)	HRP-labeled IgG against human IgG	Human IgG	High false positive rate	~10 weeks
2nd-generation assay	Indirect ELISA	Antigen (recombinant HIV antigen or synthetic peptide)	HRP-labeled IgG against human IgG	Human IgG	Improved specificity	~10 weeks
3rd-generation assay	Double antigen sandwich method	Antigen (recombinant HIV antigen or synthetic peptide)	HRP-labeled antigen (recombinant HIV antigen or synthetic peptide)	Human IgM, IgG, IgA, etc.	Improved specificity and sensitivity, reduced window period	3–4 weeks
4th-generation assay	Double antigen sandwich method; and Double antibody sandwich method	Antigen (recombinant HIV antigen or synthetic peptide) Antibody (monoclonal antibody against p24)	HRP-labeled antigen (recombinant HIV antigen or synthetic peptide); Biotin-labeled polyclonal antibody against p24; HRP-labeled streptavidin	Human IgM, IgG, IgA, etc.; HIV-1 p24	Improved specificity and sensitivity, further reduction in the window period	2–3 weeks

Abbreviations: HRP: Horseradish peroxidase; ELISA: enzyme-linked immunosorbent assay; IgG: Immunoglobulin G; IgM: Immunoglobulin M.

development of HIV diagnostics, a sophisticated regulatory framework was constructed in China. In this framework, the National Institutes for Food and Drug Control of the People's Republic of China (NIFDC, China), which is a subordinate agency of the China Food and Drug Administration (CFDA), had launched several important activities to ensure the quality of HIV diagnostics. First, the quality control system used to evaluate HIV diagnostics, based on national technical standards, was officially established and these national technical standards were applied to licensing, lot release, and the supervision of postmarket surveillance. Second, a lot-release system for HIV diagnostics to screen blood donors was developed by the NIFDC. Third, as a legal obligation of the NIFDC, planned supervision tests in postmarket surveillance, sponsored by the China Food and Drug Administration (CFDA), were routinely conducted by the NIFDC. In total, the NIFDC plays a key role in ensuring the quality of HIV diagnostics with this regulatory framework. However, some modifications may be required to improve the quality of HIV diagnostics and the effectiveness and levels of their regulation. In this manuscript, we review the regulation of and the quality evaluation system for HIV diagnostics in China.

2. Registration and management of HIV diagnostics in China

Based on the laws and regulations related to HIV diagnostics, including the *Regulations on the Administration of Drug Registration, China*, the *Implementation of Regulations on the Administration of Drug Registration, China*, and the *Regulations for the Registration and Management of In Vitro Diagnostic Reagents*, a complete system was established for the registration and regulation of HIV diagnostics. Under this system, different subordinate agencies of the CFDA undertook a series of regulatory activities, including inspection (research and development on-site verification, clinical trial on-site verification, manufacture on-site verification, quality system inspection or good manufacturing practice (GMP) inspection), technical dossier review, and quality control and evaluation (developing quality control and evaluation systems, registration testing, lot-release testing, and postmarket surveillance). Based on the results of these activities, the CFDA makes the final decision on issuing a registration license to specific HIV diagnostics. Before July 2007, all HIV diagnostics were regulated as biologics. Currently, HIV diagnostics are regulated as biologics or medical devices (Table 2). For both types of diagnostics, registration testing is conducted to ensure that the diagnostics meets the quality requirements for licensing, and national market surveillance ensures the quality of the HIV diagnostics in the postmarket context.

2.1. HIV diagnostics regulated as biologics

In China, the assays for donor screening, including 3rd-generation and 4th-generation anti-HIV antibody assays based on ELISAs and NAT, are regulated as biologics. For anti-HIV antibody assays based on ELISAs, lot release has been regulated by the NIFDC since 1995 to ensure the quality of HIV diagnostics in the market place, according to the *Notice of the Implementation of Lot Release on In Vitro Immunodiagnostic Reagents Used for Donor Screening* of the Ministry of Health, China. In the first stage of lot release, the anti-HIV antibody assay stored at 4 °C is tested using the corresponding national reference panels, and accelerated stability tests have been included in the lot-release assessment since July 2006. A national surveillance of marketed drugs is also undertaken each year by the CFDA, and each type of assay used for donor screening, including anti-HIV antibody assays (ELISAs), is included in this annual market surveillance.

2.2. HIV diagnostics regulated as medical devices

Currently, all HIV diagnostics, except those regulated as biologics, are regulated as medical devices (class III, high-risk), including anti-HIV rapid tests, HIV antibody confirmatory assays (anti-HIV antibody assays based on western blotting), HIV-1 viral load assays, and HIV genotyping assays for drug-resistance mutations. Like biologics, these HIV diagnostics are also brought under national market surveillance according to the integral plan for market surveillance.

2.3. National market surveillance of HIV diagnostics

The national market surveillance of drugs (including HIV diagnostics regulated as biologics or medical devices) by the CFDA is carried out each year. Every year, a variety of drugs brought onto the national market is subjected to surveillance. During this surveillance, sampling must be representative, so several key factors must be considered: (a) the manufacturers must be representative; (b) the products (HIV diagnostics) must be sampled from representative regions of China; (c) the quality stability of specific HIV diagnostics is tested (e.g.: several lots of product manufactured by specific manufacturers must be sampled); and (d) the impact of the distribution channels (manufacturers, distributors, users) on the quality of the products is examined. The evaluation of the quality of the sampled HIV diagnostics must be scientific and objective. It is important to evaluate the quality of the sampled HIV diagnostics

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