Profile of In-vitro Diagnostic Reagents Registration Control

National Institute of Food and Drug Control
2012-09-25
Outline

Ⅰ. Regulatory History
Ⅱ. Regulatory status
Ⅲ. Regulatory trend
I. Regulatory History

◆ In the early 1980s, in-vitro diagnostic reagent industry has just started in China. Major products were blood cell analysis, biochemical, urine reagents. Enterprises are mainly concentrated in a few large cities such as Beijing, Shanghai. Absence of a dedicated management department, resulting in varying product quality and disorder markets.

◆ In the 1990s, part of the diagnostic reagents were managed by Administration of Drug Registration Law issued by MOH. Part of them were controlled by Medical Device Product Registration Management Approach issued by former State Administration of Medicine.

◆ SFDA was established in 1998. In-vitro diagnostic reagents duly appropriated to management of SFDA.
I. Regulatory History

- In July 2001, SFDA released the “Opinions of Regulating Management of In-vitro Diagnostic Reagents (State Drug Administration's Office [2001] No. 357),” the opinion provides: Medical Devices Division is responsible for the registration of the random special diagnostic reagents; Drug Registration Division is responsible for the registration of other in-vitro diagnostic reagents except the random special diagnostic reagents.

- In Sep. 2002, SFDA issued a "Notice on In-vitro Diagnostic Reagents Category Management (State Drug Administration's Office [2002] No. 324)”. The notice provides: Category management on in-vitro diagnostic reagents, in-vitro biological diagnostic reagents are management as drugs. In-vitro chemical/biochemical diagnostic reagents and other categories of diagnostic reagents are controlled as medical devices.
I. Regulatory History

In Apr. 2007, SFDA released the “In-vitro diagnostic reagents Registration Regulation (Trial)”:  

◆ Determined the definition of management of in-vitro diagnostic reagents as medical devices.  
◆ Cleared in-vitro diagnostic reagents used for the blood screening and labeled with radionuclides belonging to the category of drug administration  
◆ proposed classifying in-vitro diagnostic reagents into type I, II and type III, category management model according to the degree of risk.
Outline

Ⅰ. Regulatory History
Ⅱ. Regulatory Status
Ⅲ. Regulatory Trend
Management Ascription of Diagnostic Reagents

**In-vitro diagnostic reagents Registration Regulation**

( SFDA [2007] No. 229 ) ( enacted on April 19, 2007)

**Article III:**
- National statutory in-vitro diagnostic reagents used for blood screening and labeled with radionuclides belong to drug administration.
- Other in-vitro diagnostic reagents belong to medical devices management.

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**In-vitro diagnostic reagents management**

- Pharmaceutical and Biological Products Management
- Medical devices management
Article 39: Before the products are sold or imported, including vaccine products, blood products, in-vitro diagnostic reagents used for blood screening, and other biological products listed by drug regulatory department of the State Council, they should be tested or approved in accordance with provisions of by drug regulatory department of the State Council. Ones test failed or have not been approved, should not be sold or imported.
Varieties of blood screening reagents by MOH in 1990s:

- A, B, O blood grouping reagents;
- Hepatitis B surface antigen ELISA diagnostic reagents (HBsAg ELA);
- Hepatitis C virus antibody enzyme-linked immunosorbent diagnostic reagents (anti-HCV ELA);
- HIV antibody enzyme-linked immunosorbent diagnostic reagents (anti-HIV ELA);
- Diagnostic reagents for syphilis (RPR and USR)
Varieties of Blood Screening Reagents

Diagnostic reagents included in "Chinese Pharmacopoeia 2010":

- Syphilis rapid plasma prime diagnostic reagents
- Syphilis toluidine red unheated serum diagnostic reagents
- Treponema pallidum antibody diagnostic kits (ELISA)
- Hepatitis B virus surface antigen diagnostic kits (ELISA)
- Hepatitis C virus antibody diagnostic kits (ELISA)
- Human immunodeficiency virus antibody diagnostic kits (ELISA)
- Anti-A, anti-B blood grouping reagents (human serum)
- Anti-A, anti-B blood grouping reagents (monoclonal antibody)
The batch release management mode for blood screening reagents

- The batch release refers to the mandatory inspection and audit system for each batch of products being marketed or imported, including vaccine products, blood products, in-vitro biological diagnostic reagents used for blood screening and other biological products listed by SFDA.

- Batch release testing or audit can be implemented as document review alone, and also can be done as the combination of data review and sample inspection. The sample inspection divided into all projects inspection and part of the projects inspection.

The blood screen reagents are batch inspected by NIFDC.
Nucleic Acid Detection Kits for Blood Screening

- Compared with ELISA reagents, nucleic acid reagents are faster, higher sensitivity and shorter detection window.

- "Notice on 2010 Blood Banks Nucleic Acid Detection Pilot "and" Embodiment "released by MOH; SFDA released “Notice on Accelerating Technical Review of Blood Screening with Nucleic Acid Diagnostic Reagents “:
  - Nucleic acid diagnostic reagent (HBV, HCV, HIV) should be approved as drugs.
  - Speed up the application of such kind of reagents.
  - Up to now, 4 species of 3 domestic companies and 2 species of 2 foreign enterprises had been approved.
Radioactive reagents — Drug Administration

- Radionuclide-labeled in-vitro diagnostic reagents are classified as general chemicals management.
- Above reagents should be inspected in agencies with the ability of inspection.
- State has special requirements on test environment (e.g. exhaust ventilation equipment, mobile or fixed protective barriers, etc.)
“In-vitro Diagnostic Reagents Registration Regulation” clearly states: The in-vitro diagnostic reagents managed as medical devices, can be used alone or with instruments, apparatus, equipment or system combination. Including reagents/kits/calibration products/QC materials used for human samples in vitro detection during the process of disease prevention, diagnosis, treatment, monitoring, prognosis observing, health state evaluation, and hereditary diseases forecasting.

“Notice on the implementation of the ‘In-vitro diagnostic reagents registration regulation “states:

- NIFDC is responsible for organizing the preparation, calibration and provision of national standards and reference products of in-vitro diagnostic reagents.
- Registered testing of in-vitro diagnostic reagent products are undertaken by the corresponding ability of medical device testing institutions.
Main Parts of the Registration Control

- Product Development
- Clinical Trials
- System Assessment
- Registration Test
- Review & Approval
1. File and sample preparation: technical documents, consecutive 3 batches of the product.

2.2. Product testing by SFDA Testing Center (3-6 months)

2.3. Hospital clinical research (6-18 months)

4. Declare materials submit to SFDA Reception Center (5 working days)

5.1 SFDA CMDE: Technical review (60 working days)

5.2 Additional requirements for file/detect/clinical (60 working days)

6. SFDA administrative approval (30 working days)

Approval documents released (10 working days)
Basic Requirements of Registration Link

1. Total clinical samples are not less than 1000 cases.
2. At least two provincial units involved.
3. Does not require the approval of the relevant departments.

- **Development**: Includes material selection, process confirm, standard formulation, stability studies, reference value confirm, and product performance assessment.
- **Units**: Should be compatible with research project staff, space, equipment, etc.

**1. Product development**

**2. Clinical Trials**

**3. System Assessment**

**4. Registration test**

**5. Review & Approval**

- **Registration test**: Agencies test samples and issue report according to product standards submitted by the applicant.
- **Testing agency**: SFDA approved, with the corresponding testing qualification.

- **On-site sampling**: Extracting 3 batches, each batch is 3 times of test dosage.
- **Apply for SA**: Enterprise application; Drug Admin Depart completes SA in 50 working days and issues the report.

- **Total clinical samples are not less than 1000 cases.**
- **At least two provincial units involved.**
- **Does not require the approval of the relevant departments.**

**Review & Approval**: Registration materials are reviewed and approved by Drug Admin Depart; Medical Device Registration Certificate is issued.

**Registered declare**: After development, assessment, trials, and registration test, apply for Drug Admin Depart. to submit registration materials.
Issues in Registration Link
(1) Sample size of the clinical research

- **General requirements:**
  - The third class products: Total number of samples for clinical research is at least 1000 cases.
  - The second class products: Total number of samples for clinical research is at least 200 cases.
  - First class products: Do not need to conduct clinical research in general settings.
    ---- The proportion of positive and negative samples is 1:3 (the minimum requirement of the positive samples).

- **Special requirements:**
  - The country legally used for blood screening project, and the diagnostic reagents with expected use for blood screening: the total number of samples for clinical research is at least 10,000 cases.
  - The diagnostic reagents for pathogen detection with in-vitro nucleic acid amplification (PCR) method: the total number of samples for clinical research is at least 500 cases.
Special requirements:

- The diagnostic reagents related with narcotic drugs, psychotropic substances, medical toxic drugs detection: the total number of samples for clinical research is at least 500 cases.

- Radionuclide-labeled in-vitro diagnostic reagents: the total number of samples for clinical research is at least 500 cases.

- New diagnostic reagent products (products are not approved for domestic registration. the products are same, but the sensitivity indicators are not in the approved registered product range by state, and products have new clinical diagnostic significance), their size of clinical research samples are required as same as the third class products (at least 1,000 cases).

- For rare disease, special diseases and special circumstances, the sample size can be reduced, but explanation should be provided and to meet the needs of the evaluation (not less than 10%).
(2) Quality management system assessment

- **First time registration**
  - Applying for first registration, assessment should be done in accordance with the “In-vitro diagnostic reagents production implementation rules” and Appendix C “The on-site verification requirements of in-vitro diagnostic reagents development”;
  - Applying for the first registration of effectively cover of quality management system, assessment only need be done with Appendix C " The on-site verification requirements of in-vitro diagnostic reagents development”;

- **Re-registration**
  - Apply for re-registration, assessment should be done in accordance with the "Implementation Rules " (excluding Appendix C" The on-site verification requirements of in-vitro diagnostic reagents development ");
  - Re-registration can not apply for the system effective coverage.
（3）Registration test

- First time registration of in-vitro diagnostic reagents:
  - First class products generally do not need registration test;
  - The Second and third class products need registration test;
  - For the third class products, registration test should be carried out for 3 consequent batches of products samples;

- Medical device testing institutions should carry out the registration test within granted test range, and should issue test report within the prescribed time limit.
Basic Flow of the Test

Samples sending units

Fill in the Application Form by samples sending units

Register, number, input by office

Register, number, input by office

Receiving

samples issued to test units

Test, review, and fill out the report by test units as required

Finance Office

Finance Office

Fill out the charges notice papers

Charge

Report to sending unit

Print Report, proofreading, sealed

Review

reviewed and issued by Director

Reviewed by Principal Business Department

Reviewed by head of test units

Report

Print Report, proofreading, sealed

Print Report, proofreading, sealed
（4）Reference Material

- There are 3 sources of reference materials of diagnostic reagents now in China. They are National Bureau of Quality Supervision, National Centre for Clinical Laboratories of MOH and NIFDC. Preparation units and application of these reference materials are different, so roles they play are different, too.

- NIFDC is national reference materials development and preparation unit of diagnostic reagents. Centre of Medical Devices Technical Review, SFDA always hold the principle of priority pass for national of reference materials prepared by NIFDC, when conducting registration review.
Choice of raw materials of in-vitro diagnostic reagents reference materials for infectious diseases:

**Source:** Samples from infected patients and healthy population (serum, plasma, etc.), also be derived from genetic engineering construction or laboratory culture.

**Components:** Usually composed of positive, negative, minimum detectable amount, precision reference material, etc.

**Positive reference materials:** Selected from a large amount of samples, wide coverage, geographical representation, the gene representation or antibody spectrum representative, and try to cover strongly positive, moderately positive and weakly positive samples.

**Negative reference materials:** From healthy population and easy to produce cross-reactive samples.
Minimum detectable amount reference material: Usually consists of one or several of the validated serial dilutions of positive samples.

Precision reference material: Usually consists of one piece of the validated moderate positive sample.

Other requests:

- Raw and reference materials need to be verified and confirmed with domestic and abroad approved methods.
- A sufficient stability.
- For infectious materials, pay attention to laboratory safety.
- Raw materials and its detection system for identification, and the test results should have traceability.

Negative reference material: 12 pieces, including virus similar to H1N1 virus structure, such as the seasonal H1N1, H3N2, H5N1 virus; seasonal influenza B virus strains; also including the virus with similar clinical symptoms, such as respiratory syncytial virus, parainfluenza virus, and adenovirus.

Minimum detectable amount reference material: 5 pieces, consist of 1 (H1N1) influenza virus positive reference material, with fold diluted to $10^{-5}$-$10^{-9}$, 5 dilution.

Precision reference material: One piece.
(5) Issues of Quality Control Materials

- Currently, there are some confusion in understanding the definition, application and role of quality control material. Sometimes it is treated as the quality internal control material of an enterprise product, has the characteristics of reference material; sometimes it is calibrator for closed instrument; in most cases, it is a kind of experiment EQA standards.

- Registration review only accept those control materials, which supporting the use of the specific detection system and reagents, and require control samples with determined target value, determined detection system and the exact clinical use, such as reagents used in automatic closed detection system for calibrating the instrument and testing accuracy of system. Registration review does not accept other application, such as for external QC or own QC, QC materials for those purposes—not directly used for clinical diagnosis, so these products do not need to apply for registration.
(7) Stability test

- **Effective period final stability test**: Real-time detection of the expiration date, the best method to evaluate product stability. But providing the effective final products and guarantee on authenticity of the product, will bring some difficulties in the implementation of effective period final stability test.

- **Thermal stability test: an accelerated destruction test**: It can overcome the lack of effective period final stability samples before the product being delivered or quality system assessed. Blood screening reagents (immunological reagents) thermal stability test for years proved its stringent better than effective period final stability test.

- **Heating days of thermal stability test**: Heating days, calculated by heating product with 37 °C for one day is equivalent to store them at 2-8 °C for 1.6 month: heating (days) = product remaining validity period (months) ÷ 1.6 (month / day), Results taking the integer part, fractional part directly rounding.
(8) Minimum Requirements of the Batches for Approval

<table>
<thead>
<tr>
<th>Reagents</th>
<th>Minimum Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme-linked immunosorbent reagents</td>
<td>1 million copies /</td>
</tr>
<tr>
<td>Chemiluminescence reagent</td>
<td>1 million copies /</td>
</tr>
<tr>
<td>Colloidal gold diagnostic reagents</td>
<td>3,000 people / bath</td>
</tr>
<tr>
<td>PCR method of diagnostic reagents</td>
<td>3,000 people / bath</td>
</tr>
<tr>
<td>Biochip reagents</td>
<td>2,000 people / bath</td>
</tr>
</tbody>
</table>
Outline

I. Regulatory History
II. Regulatory Status
III. Regulatory Trend
Management Trend

1. Blood screening Reagents belonging
2. Quality improvement
3. Pre-evaluation of registration standards
4. supervision and sampling test
5. Daily monitoring
6. Reference material development
In Sep.6, 2010, the State Council Legislative Affairs Office released the Medical Devices Regulations (Amendment Bill) to the society for comments, Article 61 of the draft provides that: When selling or importing in-vitro diagnostic reagents used for blood screening and other medical devices confirmed by SFDA , A copy of proof of testing or approval certificate for each batch issued legally by food and drug supervision and management departments must be provided and affix corporate seal. Test failed or unapproved should not be sold or imported.

Notes: "Medical Devices Regulations "has not yet been approved, But the trend of placing blood screening reagents under the management of medical devices is increasing."
Quality Improvement

Three collections of “Chinese Pharmacopoeia 2010” contain 8 standards of in-vitro diagnostic products. The main points of amended contents are:

➤ For ELISA reagents, the addition of the reaction time is set in the preparation procedure, in order to ensure sufficient reaction of the antigen antibody. The content is described as” In the detection process, the reaction time after adding the sample should not be less than 60 minutes. After adding the enzyme conjugate, it should not be less than 30 minutes. The color reaction time should be no less than 30 minutes.”

➤ To ensure the biological safety, added the process of warming for 1 hour at 60 °C in the preparation process of the negative control.
Quality Improvement

- Added the sources and preparation requirements of positive (negative) control in the items of the special raw materials and manufacture.

- Hepatitis B virus surface antigen diagnostic kit (ELISA): According to the update national standard, the request of positive reference material coincidence rate is amended as “No false negative appeared when detecting 3 pieces of HBsAg positive reference material concentration value greater than $5 \times 10^4$ IU/ml”. The request of the minimum detectable amount is amended as “The minimum detectable amount of HBsAg adr, adw and ay subtypes should be consistent with the requirements”

Improvement and refinement of 8 standards of in-vitro diagnostic products in three collection of “Chinese Pharmacopoeia 2010”, makes the standards more perfect, standardized and rigorous, which plays guiding and leading role for the same type of diagnostic reagents managing as medical devices.
In order to improve medical device products registration, in Nov. 2010, SFDA issued a "Notice on distributing provisions of medical device testing institutions to carry out the standard pre-evaluation of medical devices products".

Points of standard pre-evaluation:

- Detecting agencies should carry out pre-evaluation for standards of the registered product.
- Detecting agencies should first feedback the evaluating comments to enterprises, and record the confirmed evaluating comments by enterprises.
- Pre-evaluation comments and the pre-evaluated standard should be stamped with the same seal and Jifeng of the detection report, issued together with the detection report.
The main content of the standard pre-evaluation:

- Referential integrity of the current mandatory national standard Industry standard, suitability of reference standard, the applicability of items in the standard.
- Referential integrity of the current recommended national standard Industry standard, suitability of reference standard, the applicability of items in the standard.
- If references involved related content of the Chinese Pharmacopoeia, its referential integrity, suitability and applicability.
- Whether the test methods of the product standard can be traced back or not, whether compatible with the test requirements or not.
Standards of registration product

Pre-evaluation of the registered product standards

Meet

Basically meet the requirements

Communicate with the enterprise

Not meet

Unmodified product standards

agreedisagree

Modify the product standards

Comprehensive Evaluation advice

Basically meet the requirements

Comprehensive Evaluation advice

Product standards need further be revised in the following areas

Enter the product detecting program
Supervision and Sampling Test

Limited times of supervision and sampling test for diagnostic reagents were conducted since carrying out medical devices supervision and sampling test in 2001. The largest one is the research and sampling test of in-vitro diagnostic reagents in 2009.

- Feature of sampling test for in-vitro diagnostic reagents in 2009:
  - Combination of research and sampling test.
  - Combination of data evaluation and sampling.
  - Legal standard test combined with the proposed program evaluation.
Supervision and Sampling Test

- **Results:**
  999 batches of valid samples, covered all categories of the planned sampling. Results: 173 batches of samples are unqualified according to legal standard detection by detecting agencies. Unqualified items of 152 batches are non-performance indicators like packaging, logos and brochures. 21 batches are unqualified because of performance indicators, failure rate of the main performance is 2.1%.

- **Problems:**
  - Confusion in products classification
  - Approval scale for reagents varies in local area.
  - Phenomenon of using undocumented reagents existed in medical institutions.
  - Serious problem of non-performance indicators.
  - The lack of national standards, industry standards, national standards, reference material.
Daily Monitoring-TB Serological Reagent Survey

- July 20, 2011, WHO reports:
  - In the diagnosis of active TB, serological reagents currently used in the market often lead to misdiagnosis and inappropriate treatment.
  - Considerable evidences show that comparing with microbiological or molecular detection methods, serological testing produce a large amount of false-positive or false-negative error results.
  - Recommended accurate microbiological or molecular detection method and prohibited the application of inaccurate and unauthorized serological detection method.

SFDA and the relevant departments pay more attention to the policy recommendations for active tuberculosis detection means issued by WHO.
In October 2011, NIFDC reported WHO recommendations to SFDA, and submitted a proposal of strengthening the supervision of TB blood test reagents.

April 16, 2012, SFDA issued the "Notice on Further Strengthening TB blood test reagent regulatory matters" (FDA Office of mechanical [2012] No. 48), required the Food and Drug Administration of the provinces, autonomous regions, municipalities to carry out inspections on registration and review of TB blood test reagents in the administrative area, in accordance with the notice requirements.
Problems found in the inspection

- Existed undocumented sale and illegal approval: Nearly one hundred types of TB serological diagnostic reagents in the market, approved ones are only 33. In those approved products, 29 of them are approved by SFDA 4 of them are approved in provincial level (illegal approval).

- Artificially high sensitivity and specificity: 26% of the products clinical studies have shown that the sensitivity and specificity are more than 90% (actual average of 80%). Doubt existed in the authenticity of those data, related with the following problems: Data processing is not rigorous in the clinical research, sample selecting is not random and the lack of objective evaluation.
Suggestions:

- The current situation in China is that 70% of TB patients are culture negative, so serological diagnostic reagents, as a method of supporting diagnosis on TB culture negative, has its certain advantages. Recommended not to ban it.

- For the problems of clinical studies found in the inspection, it is recommended to develop guidelines for clinical evaluation of TB serological diagnostic reagents, to standardize clinical study.

- The illegal sale of the products should be banned.
<table>
<thead>
<tr>
<th>Approval Agency</th>
<th>Reference Material</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SFDA</strong></td>
<td>Pathogenic microbial antigen, antibody, standard and reference products of nucleic acid detection reagents.</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Standard and reference products of narcotic and psychotropic drugs detection reagents.</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Tumor markers, standard and reference products of hormone detection.</td>
<td>45</td>
</tr>
<tr>
<td><strong>National Standards Commission</strong></td>
<td>Biochemical (or other) reagents reference material</td>
<td>About 10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>159</td>
</tr>
</tbody>
</table>
Currently, more than 40 kinds of standard material are developing. A plurality of research projects involved the development of diagnostic reagents reference materials, such as:

- **Twelfth Five major national projects**: "Quality evaluation techniques and reference materials development of the major infectious disease diagnostic reagents (2012ZX10004702)", involving more than 30 types of reference materials development.


The reference material of in-vitro diagnostic reagents has been a high degree of concern in the industry, we will further accelerate the speed of development, explore a new type of management mode to meet the need of the industry and the rapid development.
药品安全性评价
• 含马兜铃酸中药安全性评价

关注的安全性问题: 肾毒性
难点: 要系统收集和分析临床数据和非临床研究数据，敏锐把握信息走向

问题的解决:
- 主要不良反应为急、慢性肾损害；长期使用有可能诱发癌症；马兜铃酸肾病与剂量和用药时间长短呈相关性，且剂量有累加效应；马兜铃酸致癌性与剂量和时间长短有相关性
- 结果: 上报国家局，已采取行政措施

Thank You