National Institutes for Food and Drug Control

Safety evaluation in administrative permission — Necessity and reality of GLP

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Statement

- Presenter is responsible for the contents
- The opinion in the presentation doesn't represent the opinion of my organization

Content

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2. Quality assurance of safety evaluation
   — GLP
3. The status of GLP in China

1. Safety evaluation of chemical products

1.Safety evaluation of chemical products

Risk evaluation principal

Biological evaluation should undergo risk assessment based on risk analysis. That is, clarify intended use & purpose and biosafety characteristics, identify known or predictable hazard (harm on health due to genetic toxicity, allergenicity and chronic toxicity), then predict risk (residual risk, probability and extent of harm on health). Even if the result is positive by this risk analysis method, it only means the hazard is detected or identified but it doesn't mean the product can't be used. The product safety should continue to undergo risk evaluation, this is, compare evaluated risk and given risk principal, then determine risk acceptability.

1.Safety evaluation of chemical products

Administrative permission

- Chemical products such as pesticides, veterinary medicines, common chemicals(new chemicals), drugs, medical instruments, cosmetics and health foods, need administrative permission — effect on human health and environment
- In China, different government departments are in charge of these products.
- The administrative permission processes are almost same: application-acceptance-technical review- administrative permission
- The target of technical review: safety test(mainly refer to toxicity test)——（Safety Evaluation）
- Technical review results support administrative permission.

1.Safety evaluation of chemical products

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Permission type

- The products include: pesticides, veterinary medicines, common chemicals(new chemicals), drugs, medical instruments, cosmetics, health foods, food additives, feed additives and so on
- Also include biological products（biotech drugs and transgenic organisms & products）
- Some of these products are overlapped.
- Classification and competent governments are different in different countries.

1.Safety evaluation of chemical products

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Competent department

- Pesticides, veterinary medicines, feed additives and transgenic organisms & products—Ministry of Agriculture
- New chemicals—Ministry of Environmental Protection
- Drugs, medical devices, health foods, cosmetics—CFDA
- Food additives—Ministry of Health set standard

1.Safety evaluation of chemical products

Example：administrative permission of CFDA

1. Project name: approval of clinical trials on drugs

2. Permission content：

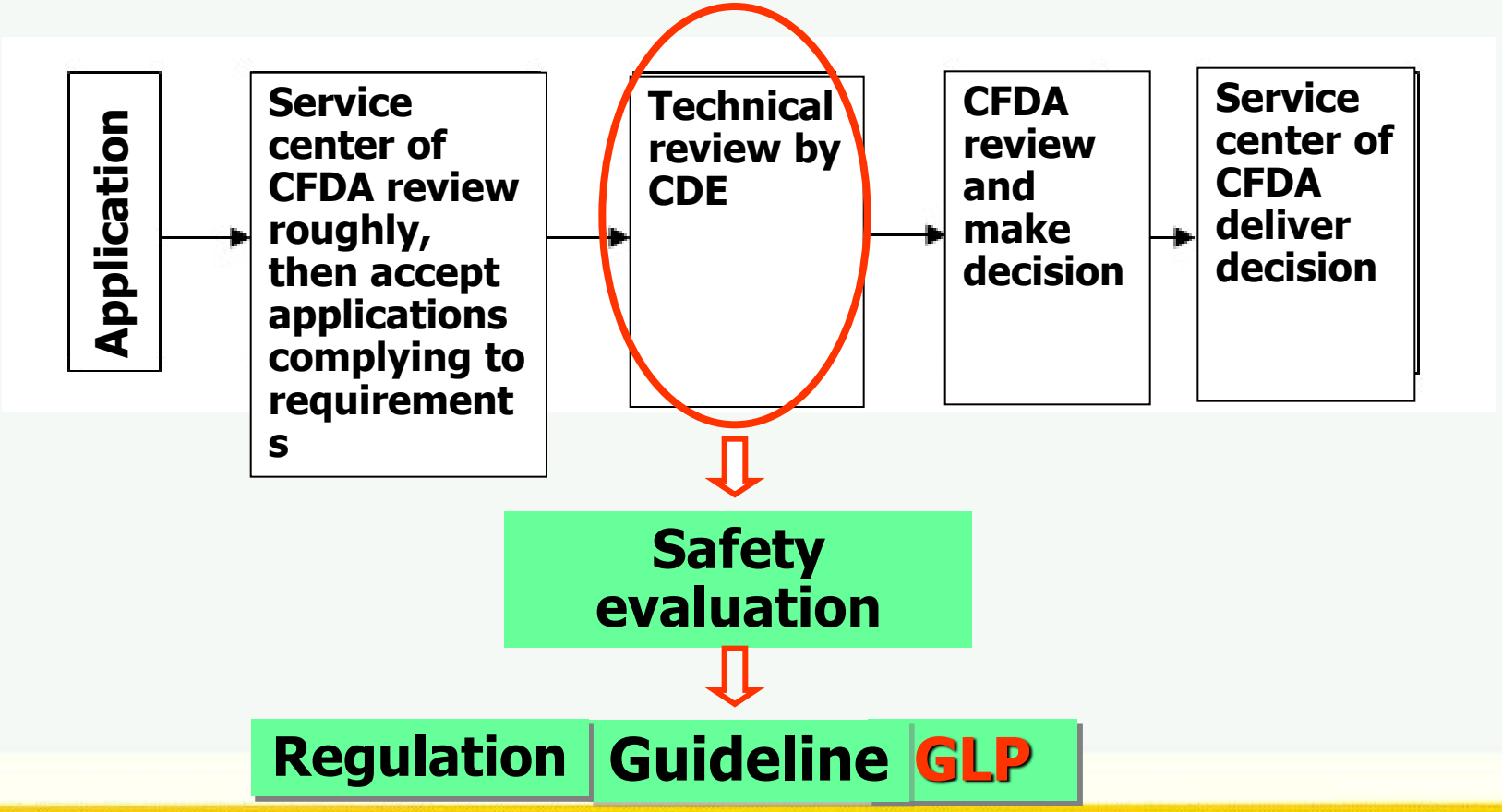
Approvals of clinical trials on chemical drugs (domestic), include contents of registration classification in annex 2 of *Drug Registration Regulation*

3. Legislative authority for setting and implementing permission：

Law of PRC on the Administration of Drugs, Implementation Rules of Law of PRC on the Administration of Drugs, Drug Registration Measures

1.Safety evaluation of chemical products

Example：administrative permission of CFDA



2. Quality Assurance for Safety Evaluation-GLP

2. Quality Assurance for Safety Evaluation-GLP

Regulation- CFDA example

1.Drug Administration Law of the People's Republic of China (Order of the President of the People's Republic of China No.45)(2001-02-28)

2.Provision for Drug Registration (Order of the Food & Drug Administration No.28) (2007-07-10)

3.Regulation on the Supervision and Administration of Medical Devices (Order of the State Council of the People's Republic of China No.276) (2000-1-4)、 Medical Devices Registration Administration Method (Order of the Food & Drug Administration No.16)(2004-08-09)

4.The Food Hygiene Law of the People's Republic of China , Administrative Measures on Registration of Health Foods (trial implementation) （Order of the Food & Drug Administration No.19 ）(2005-04-30)

5.Regulations concerning the hygiene supervision over cosmetics, Detailed Rules for the Implementation of the Regulation on the Hygiene Supervision over Cosmetics, Health and health-related products-the administrative licensing procedures, Rules for the application of administrative licenses for cosmetics, Outlines for Acceptance and Examination of Administrative License of Cosmetics

6.Issues Relevant to Sanitation Administrative Licensing of Cosmetics (Issues Relevant to Sanitation Administrative Licensing of Cosmetics (Order of The State Food and Drug Administration Office No.503 2008)

2. Quality Assurance for Safety Evaluation-GLP

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Technical Guideline （Standard）

1. **Drug：**

   Adopt technical guideline of OECD、ICH and CFDA, for example:

   OECD：Guideline for Testing of Chemicals #471、#472、#473、#474 etc.；ICH：S2A、S2B、S2(R1) etc.

2. **Medical devices：**

   Adopt GB/T 16886—ISO 10993 Biological Evaluation of Medical Devices serial standards.

3. **Health foods and cosmetics：**

   Hygienic Standard for Cosmetics, technical standard for Health foods inspection and assessment, Procedures and methods of safety evaluation for toxicological assessment on food safety (GB15193-2003)

2. Quality Assurance for Safety Evaluation-GLP

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GLP related regulation - Drug example

Drug Administration Law of the People's Republic of China

Article 30: The institutions for non-clinical safety evaluation and study and clinical study institutions shall respectively implement the Good Laboratory Practice for Non-Clinical Laboratory Studies (GLP) and Good Clinical Practice (GCP).

Drug Registration Regulation

Article 22: Pre-clinical study of a drug shall be conducted in accordance with relevant regulations, where the drug safety evaluation must be conducted in accordance with Good Laboratory Practice for Pre-Clinical Laboratory Studies (GLP).

2. Quality Assurance for Safety Evaluation-GLP

Good Laboratory Practice for Pre-Clinical Laboratory Studies (administration order No.2 2003-08-06）

Law

First GLP regulation in China

Drug GLP

Current status?

Farm chemical GLP

Chemical GLP

OOO GLP

Medical instrument GLP

2. Quality Assurance for Safety Evaluation-GLP

What is GLP

- GLP: Good Laboratory Practice
- Quality assurance for biological test (toxicological test)
- Essential requirement for biology safety evaluation studies
- International practices
- Drug GLP is governed by the law of China

GLP-Good Laboratory Practice-also been called Laboratory Quality Management Practice. GLP first appeared in the drug registration process as normative documents, and then have developed as an essential requirement for biology safety evaluation of medical instrument, chemical, farm chemical, food additive and cosmetic etc., and become as regulatory documents in developed countries to regulate according areas listed above.

2. Quality Assurance for Safety Evaluation-GLP

The purpose of GLP

- To guarantee the quality of non-clinical safety evaluation study and the facticity, integrity and creditability of the registration application documents.

• GLP Study:

1.All key elements related to the study design and implementation should be under strictly control.

2.Apply the QA (Quality Assurance) theory on the quality assurance of study data.

3.Need to establish according systems and guarantee to follow on: organization and responsibility mechanism, education and training, took full advantage of equipment/facilities and maintenance on necessary, establish SOP, study design and study operation, sample and raw data storage, report technical writing etc.

As a summary, the essential of GLP is to strictly control every section of safety evaluation study, and eliminate all kinds of subjective and objective elements that could potentially affect the study result; reduce the study errors; guarantee the quality of study data and the credibility of study result.

2. Quality Assurance for Safety Evaluation-GLP

Several common issues need to pay attention:

- **GLP studies must base on scientific feasible principle, such as clear study aim, correct study principle and appropriate study method. GLP principle should submit to scientificity.**
- **GLP study should clearly record the experimental animals' genus, sexuality, age, weight and the rearing condition from the purchase date to the study beginning date (including in vitro studies).**
- **GLP study should clearly indicate the dosage setting basis. When setting the dose value through pre-test, must provide the according documents(the in vitro pre-test also need to follow GLP standard)**
- **When unexpected abnormal condition occurs during GLP study, the key that guarantee the credibility of the study is not the GLP principle but the scientific method and action.**

2. Quality Assurance for Safety Evaluation-GLP

GLP in foreign counties

- **GLP in US（FDA vs.EPA），Federal law**

  Pigments, food additives, feed additives, human drugs, veterinary medicines, biological products, medical devices for human, electronic products and so on.

- **7 GLP in Japan，3 of them are laws**

  Agricultural chemicals, common chemicals, manufacturing products, drugs, medical devices, veterinary medicines, food additives

- **OECD GLP—Guideline—No law force**

  OECD guideline and guidance document cover all types of products

- **Most of OECD member countries have a series of GLP for all the products**

2. Quality Assurance for Safety Evaluation-GLP

GLP in China

- Drug GLP—Law
- Farm chemical GLP
- Chemical GLP
- CNAS GLP

The essential of GLP are concordant with each other between China and other countries

3. GLP status in China

3. GLP status in China

Drug GLP

- National science and technology commission organized and drafted medicine GLP in March,1991
- National science and technology commission started a key program in the ninth five plans in 1993 supporting National center for drug safety evaluation & detection and other three units.
- National science and technology commission issued Pharmaceutical Non-clinical Research and Quality Management Rules (Trial) in December, 1993
- SDA issued Pharmaceutical Non-clinical Research and Quality Management Standard (Trial) in October, 1999
- SDA inspected National center for drug safety evaluation & detection and other three units as pilot in May, 2002
- SDA announced the four units passed through the examination on Drug GLP
- CFDA issued Pharmaceutical Non-clinical Research and Quality Management Standard in August, 2003

3. GLP status in China

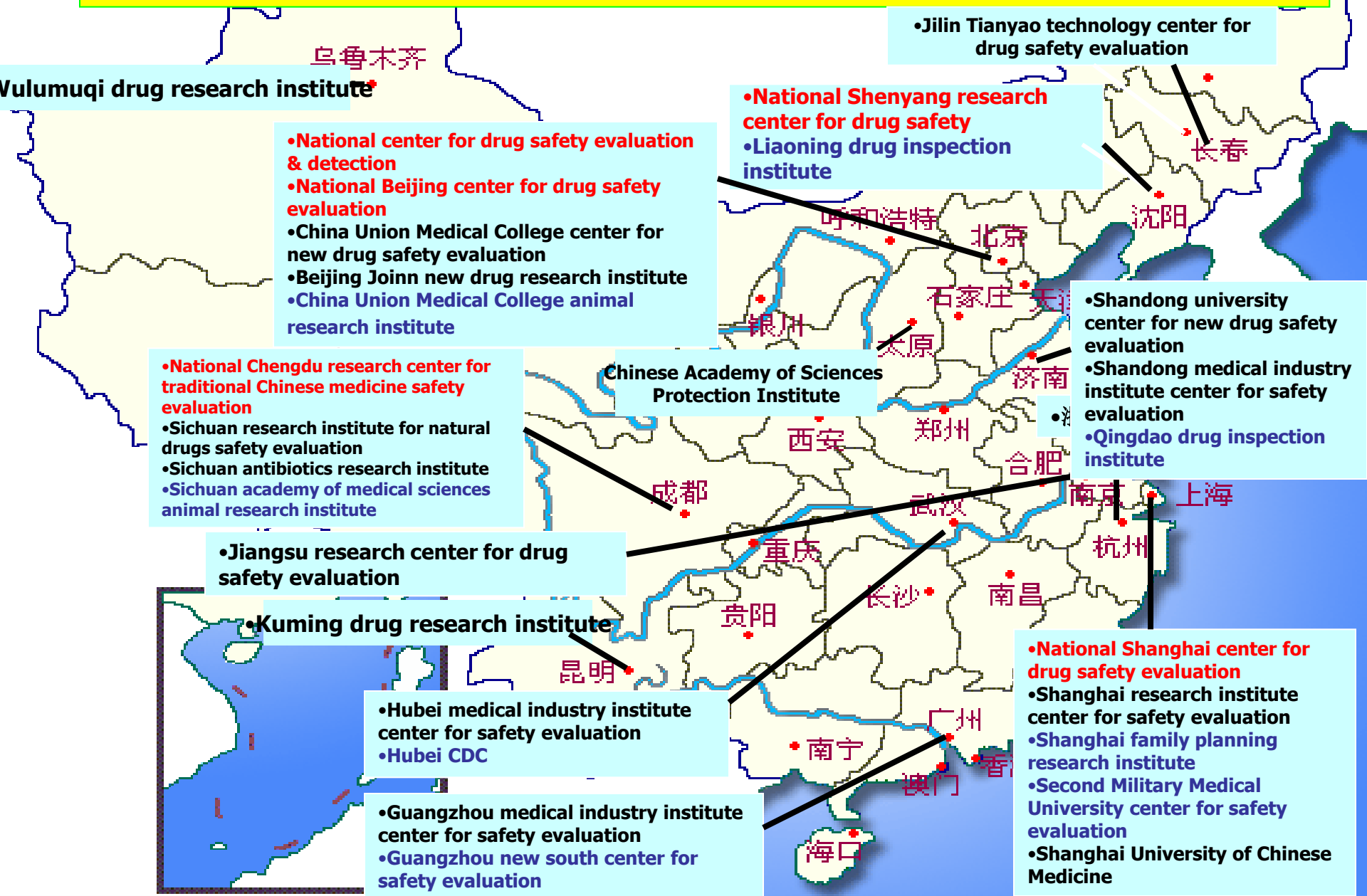
Drug GLP Inspection

- **Inspection Methods on Pharmaceutical Non-clinical Research and Quality Management (Pilot) was printed in August, 2003.And officially started GLP inspection on GLP labs. 2003.It is substantial step on GLP construction in China.**
- **Notice on pushing Pharmaceutical Non-clinical Research and Quality Management Rules was issued in**

Certificated Status on Drug GLP

- **50 agencies obtained certification by December,2012**

Distribution map on China research institutes on drug GLP (Totally 50 institutes by December,2012)



3. GLP status in China

Drug GLP certified test project

- Toxicity test with single and multiple dose (rodent)
- Toxicity test with single and multiple dose (non-rodent)
- Reproductive toxicity test (phase I、 phase II、 phase III)
- Genetic toxicity test (Ames, micronucleus, chromosome aberration, mouse lymphoma test)
- Carcinogenicity test
- Local toxicity test
- Immunogenicity test
- Safety pharmacological test
- Physical dependence test
- Toxikenetics test

3. GLP status in China

GLP for pesticide

- On Nov. 8th, 2006, MOA issued Notice 739-*Appraise Measures for Pesticide*
- Comply with OECD GLP

A complete set of technical specification —Industrial standard

- GLP for safety evaluation of pesticide toxicology
- GLP for pesticide environmental safety evaluation
- GLP for pesticide physico-chemical analysis
- GLP for pesticide residue test

3. GLP status in China

GLP for chemicals

- Jan., 2010, *Measures for environmental management of New Chemicals*, Order 7 of MEP
- Jan., 2012, *Measures for Qualified lab of Chemicals test*, MEP informed to adopt GLP system with international standard
- Dec., 2012, published the first batch of 8 GLP labs after *Measures issued* (Notice 77,MEP)
- Adopt industrial or national standard?

3. GLP status in China

CNCA GLP

- Aug., 2001, State council established Certification and Accreditation Administration of PRC (CNCA)
- June, 2008, *Notice on the Disclosure of the Relevant Documents of GLP and Evaluation Procedure*
- Aug., 2008, National Standards Commission issued 15 national standard related to GLP
- Dec., 2008, CNCA approved the first GLP lab
- Evaluation basis – Adopt OECD GLP

3. GLP status in China

Advantage and highlight

- Competitive GLP industry has been established in China
- Some GLP experimental instruments have reached the level which US and EU can accept. It is proved that the data quality can be accepted by US and EU
- The opportunity to work and study with western cooperative partners is increased. Some labs operate according to US GLP standard, improve the level continually
- Researchers understand GLP very well, have high professional skills

3. GLP status in China

Current gaps

- GLP certificate: CRO or national designated lab? US, EU or Japan style?
- Align with international standard: between labs or Bilateral mutual certificate?
- Quality of the registration application dossiers: on-site inspection?
- Diversity and gaps in each area: Learning from each other?
- GLP upgraded to law：must be!

3. GLP status in China

Current gaps

- The overall level of GLP conformance need to be improved
- Low level lab automation, for example LIMS
- Insufficient human resource
  - Veterinarian
  - Veterinary Pathology
  - QA
  - Ophthalmology
  - Bioanalysis

3. GLP status in China

Current gaps

- Some research lack experience and historical data
  - Short term carcinogenicity study of biotech mice
  - 2 years bioassay
  - Reproductive toxicity study of nonhuman primate
  - Remote sensing measurement of cardiovascular safety pharmacology
- Insufficient assisted support
  - Feed and Bedding Materials (source and quality)
  - Animal source
  - Transportation of the bio-samples

3. GLP status in China

GM product safety assessment as reference

- **Essence：safety evaluation study need quality assurance**
- **Reality：study data and study report need to conform to the rules**
- **Measure：adding on-site inspection and study audit segment**
- **Way out：Issue regulations to gradually align with the international standard**

Thank you!