Challenges that China GLP Compliance Laboratories Face during Internationalization

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Presentation Outline

1. Current status of China GLP compliance labs
2. Opportunities and outlook
3. Challenges during Internationalization
Labs passed SFDA GLP inspection

- A total of 35 institutes
  - National Beijing Center for Drug Safety Evaluation and Research (NBCDSER)
  - National Shanghai Center for Drug Safety Evaluation and Research (NCDSER)
  - National Shenyang Center for Safety Evaluation of New Drug (NCDSE)
  - National Chengdu Center for Safety Evaluation of Drugs (NCCSED)
Labs passed SFDA GLP inspection – Conti.

- Jiangsu Center for Safety Evaluation of Drug
- Guangzhou Institute of Pharmaceutical Industry
- Zhejiang Center for Safety Evaluation of New Drugs
- National Center for Safety Evaluation of Drugs (NCSED)*,
  State Food and Drug Administration (SFDA)
- Joinn Laboratories*
- Others

* FDA inspected these 2 labs in 2009

Basically, FDA accepts China GLP regulations and standards for GLP inspection
1. Current status of China GLP compliance labs

2. Opportunities and outlook

3. Challenges during Internationalization
Opportunities and outlook

1. Governments support GLP compliance laboratories (provide funding to establish 31 labs in the country, e.g., 6 in Beijing, 6 in Shanghai, 4 in Shangdon, 3 in Sichuan, 2 in Guangzhou, Jiangsu, Shenyang, etc)

2. Nurturing a number of competent pharmaceutical toxicologists

3. Relatively ample animal resources
   - Several non-human primates supply areas
   - Marshall Beijing Beagle dog breeding center

4. Improving animal management (e.g., a total of 6 SFDA GLP compliance labs is AAALAC accredited)
Opportunities and outlook – Conti.

5. SFDA provides GLP training to researchers, inspectors, and applicants, as well as set up a GLP inspection team.

6. Standards held by SFDA for inspection are getting closer to those of international regulatory agencies.

7. Multinational pharmaceutical corporations adding or moving R&D centers to China.

8. Booming of new drug development companies & R&D centers of domestic drug companies (prior generic focus).

9. International large CROs established labs in China (e.g., Charles River Laboratories, Covance, MPI, etc).
1. Current status of China GLP compliance labs
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Challenges

- Facility qualifications
- Personnel qualification system
- Computerized data collection system
- Animal quality
- Historic/background information on animals
- Equipment management system
- Analytical and bioanalytical capacity
- New technology/methodology adoption
1. Facilities
2. Laboratory Personnel
3. Animal Management
4. Laboratory Management
5. Technology Level
Facilities

- Domestic architects/designers do not understand GLP and animal management
- Locations should be distant from residential areas and sources of contamination
- Understanding and detailed record of neighborhood environment
- Distinct division of functional areas to minimize potential contaminations
- Qualified for national standards (e.g., monitor and validate the environmental values)
Facilities – Conti.

- Emergency plans (backup electricity, water, air, conditioning, alarm systems, etc)
- Occupational safety protection (ventilation, test/control article management/facilities)
- Hazard categorization/collection and treatments; regular sewage self-monitoring
- Archives management (water, fire, theft, humidity, and pest proof; alarm system)
- Generally smaller sizes
Laboratory Personnel

- Educational system of Experimental Animal Sciences resulting insufficient qualify veterinarians
- No certification systems for scientific staff involving GLP studies (QA and pathologists)
  - The Chinese Society of Toxicology initiated certificate examination in 2009 for toxicologists (CTCST or Certified Toxicologist of Chinese Society of Toxicology)
- Limited training on diverse drug development topics
  - Systemic training is warranted (for SDs, PIs, etc)
- Limited training on techniques
Animal Management

- Limited experimental animal species and models
- Animal welfare programs vary significantly among GLP compliance laboratories (though not a prerequisite for GLP, AAALAC accreditation helps animal management enhancement)
- Quality of animal diet and bedding
- Spontaneous animal sickness
- Animal background information
- Limited equipments, cages and appliances involved in animal experiments
1. Facilities
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Laboratory Management

- Equipments should fulfill requirements of regulatory submissions
  - What is available domestically (QAU involvement)
  - Detailed management procedures to ensure equipments operate normally (calibrations, validation plan and executions, etc)
    - Attention to “trivial” appliances, such as refrigerators (temperature monitor and alarm)
  - Out of specification management (recording and action)
  - Backups (affordability is oftentimes the issue)
Lab Management – Conti.

- Management of test and control articles
  - Security
  - Special conditions
    - Light protection, temperature, humidity, etc
  - Cross contaminations
  - Homogeneity, stability, and dose formulation analysis
    - DFA for biologics and herbal extracts
Lab Management – Conti.

- Management of reagents, other experimental materials and data
  - Sources of in vitro assay materials
  - Attention to quality of reagents, standards, and control articles as well as corresponding data
  - Reliability of background information
    - How was the information gathered, processed?
  - Computerized data collections
    - Again, affordability is the main issue
1 Facilities
2 Laboratory Personnel
3 Animal Management
4 Laboratory Management
5 Technology Level
Technology Level

1. Carcinogenicity test for new drugs
   - Carcinogenicity plays an important role in safety evaluation of many drugs
   - SFDA recently reinforced carcinogenicity test for approval of new drugs
   - Most, if not all, domestic labs lack of experience
   - Limited, if any, animal background/historic information
   - Alternative animal models, e.g., transgenic mouse
     - Experience, background info, and supply issues
Technology Level – Conti.

2. Safety pharmacology studies

• Generally speaking, ICH guidance requires all techniques involved to be “harmonized”

• Telemetry has been routinely used in western preclinical toxicology labs; yet limited labs in China have adopted the techniques

• The parameters measured in GI and CNS/FOB tests are limited

• Respiratory tests are carried out differently

• hERG and other in vitro channel tests
Technology Level – Conti.

3. Toxicokinetics (TK) for new drugs
   • TK could be critical in interpreting mammalian toxicity studies
   • Western regulatory authorities require TK analysis for repeated dose and reproductive toxicity, as well as carcinogenicity studies
   • Very limited experiences in most, if not all, domestic GLP compliance labs
     - Method development, validation, etc.
     - Cost-related issues, e.g., equipments, validation software
Technology Level – Conti.

4. Developmental and reproductive toxicity (DART) studies

• Very limited experiences in conducting peri- and post-natal toxicity (i.e., ICH segment 3 study)

• Limited supply and quality issues regarding pregnant rabbits (for ICH Segment II usage)

• Limited, if any, experiences in large animal DART studies
5. New biological entity (NBE) safety evaluation and alternative models

- Cross reaction, immunogenicity, hypersensitivity, immune tolerance are of concern and should be included in drug safety evaluation

- Limited experiences in biomarkers (e.g., flow cytometry and biomarker certificates employing the equipment)

- No experience in developing novel biomarkers
Technology Level – Conti.

6. In vitro models
   • Reduces drug usage, increases screening capacity, and reduces cost
     - High throughout Ames screening test
     - In vitro micronucleus
     - In vitro screening model for liver and kidney toxicity
     - CYP450 tests (metabolism, induction, and inhibition)
Technology Level – Conti.

7. Toxicologic pathology
   • Limited histopathology knowledge/skills
   • Lacking digital pathology system
   • Need to harmonize toxicologic pathology terminology
   • Limited toxicologic pathologists available due to educational system in the areas, not to mention experienced ones
Conclusions

• 17 years since China launches GLP regulation
• China government supports GLP development
• Significant progress has been made in the past decade, esp. past 4 years
• Local talents contributed in this process and development
• Still limited capacity/experiences in China GLP compliance labs
• Other challenges China GLP laboratories are facing in their final stage of internationalization

• These labs will play a significant role in international drug development in the foreseeable future!