Opportunities and Challenges of Conducting GLP Bioanalysis in China

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Outline

- Introduction
- Opportunities
- Challenges
  - Operational
  - Compliance and Regulation
  - Technical
- Summary

Introduction

- Emerging Market -China

- Fast growing, China would be 2nd biggest pharmaceutical market in the world by 2020
  - Increasing government and private investment in pharma and biotech R&D – from manufacture to innovation
  - Increasing MNC investment in China last 5 years

- Government infrastructure support
  - Chinese government grant tax incentives to encourage foreign investment in China, e.g. Tax refund for business tax.

Introduction

- Emerging Market -China
- Patient pool and needs of medical products
  - Naïve patient population for clinical research is the advantage
  - Conducting clinical trials in China may save study cost and reduce enrollment time
- Large talent pool
  - Over 6.5 million college graduates/year
  - Highly motivated, eager to learn new technologies
  - Returnees with strong technical skills and drug development experience – half million returnees in the past 5 years in life science

Opportunities

High quality GLP Bioanalytical Labs in China

- From Global to China
- To register new drugs in China, Global Pharma conduct PK study and phase 3 clinical studies in this country; Require International quality standards for bioanalytical work performed locally.
- China is part of the global trials. Global submissions require consistent quality of bioanalysis executed in China.

- From China to Global
- More Chinese pharmaceutical and biotech companies are planning to enter global market. i.e. dual filing strategy in China and US, nonclinical safety studies must meet China and US FDA GLP regulations.

Operational Challenges

- **Issues:**
- Require import permit for biological samples and critical reagents i.e. antibodies.
- Lead time for special materials is about 4 weeks in China. Difficult to support urgent studies.
- **Solution:**
- Understand government policy on import/export and custom requirements
- Utilize same logistic team to support Central Lab and BioA lab, share previous experience to resolve complex logistics issues.
- Team up with Regulatory Affair team, who guides the preparation of application documentation.
- Provide feedback to government offices and influence the change to simplify the import process.
- For urgent studies, leverage global resource, ship special reagents from our oversea labs.

Operational Challenge

- **Issue:**
- Talent war. China is a growing market, employees have ample job opportunities from Pharmas and CROs.
- **Solution:**
- Made significant effort to attract and retain talents
- Create culture of caring
- Provide career development opportunities
  - Drug development course
  - Develop future Bioanalytical PI through continuous training on client communication and project management
  - Develop new technical capabilities, i.e. peptide and ADC analysis by LC/MS/MS
- Our staff turnover rate is less than 10% which is much lower than China market average.

Compliance Challenges

- **Issue/Challenge:**
- Covance US/EU labs had extensive inspection history, China lab is relatively new, need to establish our own inspection history.
- **Solution:**
- Strong support from Global QA team
  - Our QA Director is internal transfer from Covance UK
  - Establish and maintain high quality system
  - Share the audit experience from oversea labs, learned the new trend from regulatory inspection globally.
  - Extensive regulatory compliance training and enforcement to ensure quality
- Passed multiple international regulatory inspections:
  - Continue to be monitored against the OECD GLP Principles by the Belgian GLP monitoring authority
  - One of the first facilities in China inspected by the UK MHRA
  - Passed China FDA GLP inspection and obtained accreditation/certification.

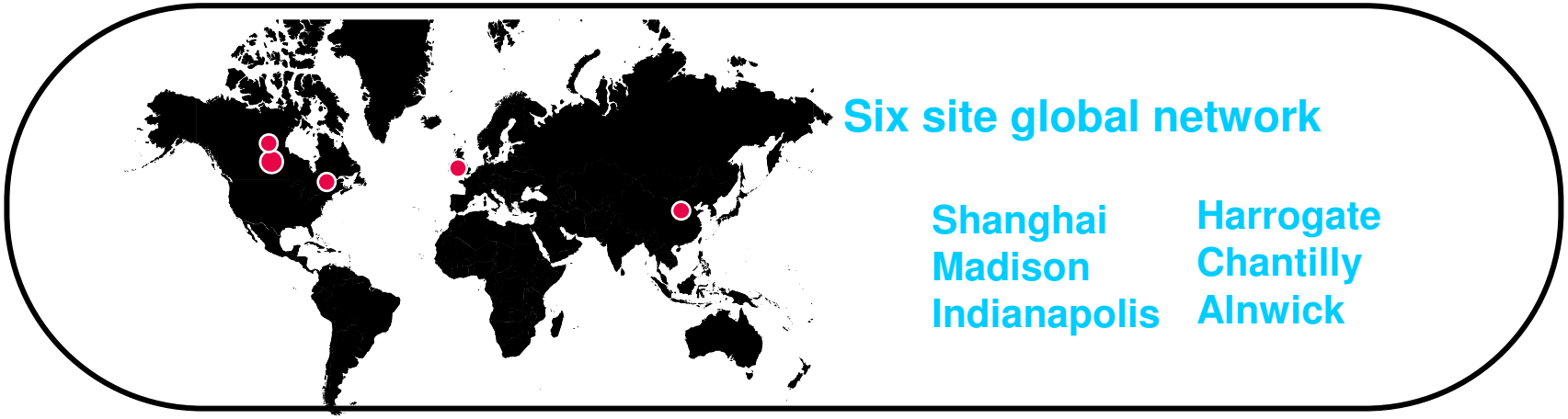
Compliance Challenges

- **Issues:**
- Facilities in China must have a CFDA GLP certificate before a claim of CFDA GLP compliance can be made for nonclinical safety studies.
- CFDA has some special requirements on SOP, documentation, Instrument calibration, QA inspection, protocol/report approval etc**.**
- **Solution:**
- Understand CFDA GLP requirements, 280 Item checklist
- Implement SOPs for CFDA special requirements. Translated all SOPs to Chinese.
- Since electronic data is not very common in government owned GLP labs, we hosted Computer System Validation Workshop to share the knowledge with CFDA officials and government labs.
- Well prepared application documents including the study documentation.
- First international CRO obtaining the CFDA GLP certificate
- Inspected by CFDA for dual-filing studies on regular bases

Compliance Challenges

- **Issue/Challenge:**
- Global clinical trials require consistent quality in all countries. Many countries including China are adopting US or EU standards but how these are implemented may vary country to country and lab to lab.

- **Solution:**
- Covance implement global SOPs on method validation, sample analysis to ensure the quality consistent cross all labs. The SOPs meet the regulations from multiple agencies (FDA, EMA, OECD).
- Conduct cross validation if samples from a single study are analyzed at more than one lab.
- Have defined procedures and acceptance criteria for cross validation in our global SOP



Case study 1 for Compliance: Cross validation to validate the results from different labs

- **Issue:** Covance Shanghai conducted a Phase 3 study in APAC region.
- Sponsor noticed APAC plasma exposure was higher than that of US and EU.

- **Solution:**
- Sponsor decided to conduct a cross validation study between sponsor's lab and Covance Shanghai.
- Cross validation samples include QC samples and pooled study samples.
- Both sponsor lab and Covance Shanghai analyzed the cross validation samples in a blinded manner, Covance Shanghai results meet the acceptance criteria which is 2/3 of samples were within 20%.
- Cross validation study validated the APAC study results and provided relief to the study team.

Technical Challenges

- Covance globally has extensive experience with GLP bioanalysis. China lab is new, needs to develop technical expertise and built our own study experience.

- **Solution:**
- Experienced US colleagues were in China lab for 6 month, provide China staff technical training
- Continuous cross training between US/UK and China site
- Recruited technical experts as Bioanalytical Project Leaders
- Leverage strong scientific and technical experience from our global team
- Frequently communicated with our colleagues in oversea labs when transferred methods to China lab, shared the knowledge with the method.

Case Study 2 for Technical Challenge: Peptide Analysis by LC/MS/MS

- **Issue of the study:**
- A Chinese Pharma is developing a peptide drug (~5000 Dalton) for treatment of diabetes, clinical study was on hold due to lack of PK method with high sensitivity
- **Solution:**
  - Covance UK has validated insulin LC/MS/MS assay; Covance Shanghai has experience with LC/MS/MS analysis of small peptides
  - Covance Shanghai successfully developed a sensitive LC/MS/MS assay (LLOQ 50 pg/mL) with the strong support from UK colleagues
  - We successfully supported SAD study, will support MAD study later this year

Summary

- China is an emerging market with many opportunities
- Companies with global footprint will be in a better position to support client's R&D activities globally
- Success factors for a GLP Bioanalytical Lab in China
  - Understand current International and CFDA regulatory requirements
  - Leverage strong technical and compliance experience from our global team
  - Need greater support from logistic for material and sample shipment
  - Built and retain the talent team
  - Have good communication with government office

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Thank You!!
Questions?