The situation on GMP- and regulatory compliance for APIs manufactured in China

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Introduction of CHNMED

- A private professional consulting company with good reputation in Chinese pharmaceutical industry
- Established good relationship with government, pharmaceutical companies and associations
- Provide consultation for the purpose of
  
  Regulatory advices for SFDA
  
  Practical solutions for enterprises
Self introduction

- **Yueping Sun** – Master degree of medicine, registered pharmacist
  - 12 years research experiences in pharmacology and toxicology
    - Department of Pharmacology, Beijing Institute for Drug Control
    - Department of Pharmacology, Capital University of Medical Sciences
    - Department of Toxicology, Karolinska Institutet, Stockholm
  - 18 years experiences in pharmaceutical companies
    - Xi’an Janssen Pharmaceutical Co., Ltd., registration manager
    - HELM AG Beijing Office, registration manager
    - Beijing CHNMED Pharmaceutical Consulting Co., Ltd., vice general manager
The legal aspects

The control of SFDA on the APIs manufactured for the domestic market of China

- API manufacturers must have Drug Production License
- API manufacturers must have their API products registered in SFDA and get approval number for each product
- API manufacturers must get GMP certificate for every API before selling in domestic market
The legal aspects

- New regulation issued by SFDA for the control of exported medicines (APIs) – valid on Sep 6, 2007
  - The manufacturer should assure that its exported product complied with the standard of the country (region) of importer or with the contract requirements.
  - SFDA will establish and announce the good and bad records of exportation enterprises periodically.
  - Any exportation company who avoid or neglect product examination or do falsification will be amerced at the value of three times of goods and confiscate the illegal products and profit at same time.
The status of API manufacturers in China

- **5,000 pharmaceutical companies, including**
  - Over 1,000 API manufacturers with GMP certificate issued by SFDA, about 50% of APIs for exportation
  - Over 800 enterprises for traditional medicines

- **Other companies related with APIs**
  - Over 2,000 chemical companies for the manufacture of intermediates, APIs, plant and animal extracts, and biological products, they have no GMP certificate and are not controlled by SFDA
The situation of GMP compliance for API manufacturers in China

- The main differences between Chinese GMP and ICH Q7A
  - The guidance special for APIs is too simple and little consideration on specialties of chemical, fermentation, and biological processes
  - Scope of GMP control and concept of starting materials: is not clearly defined
  - Responsibilities and personnel of Quality Department: less responsibilities and personnel requirements
  - Clean room for refine process: at lest 300,000 class
  - Change control: no responsibility to inform its users because of different registration system
  - No guidance for reworking, reprocessing and recovery processes
The situation of GMP compliance for API manufacturers in China

- **Quality assurance level of API manufacturers based on ICH Q7A**
  - Depends on knowledge of ICH Q7A and intention to follow it;
  - Some manufacturers have weakness or deficiencies in implementation of GMP since the lack of routine inspection;
  - Some manufacturers, less than 100 companies, have passed FDA and EU inspections;
  - There are several training classes or forums every year focusing on ICH Q7A, so the level is elevated in recent years.
The situation of GMP compliance for API manufacturers in China

- Frequent occurred problems as per ICH Q7A
  - Quality assurance system
  - Personnel of QA/QC department
  - Validations
  - Control of starting materials and intermediates
  - Change control
  - Recording and documentation
  - Treatment of waste water
The situation of GMP compliance for API manufacturers in China

- **APIs manufactured without GMP certificate**
  - Many chemical and biological companies also manufacture and export APIs by means of “chemical products” at low price since they do not have GMP system
  - Some pharmaceutical companies do not apply GMP certificates for the APIs only for export, but manufacture the products under GMP
The situation of GMP compliance for API manufacturers in China

- The problem of APIs with blank label:
  - Appearance: some trading companies want the APIs with blank label
  - Reason: to stick the label of the trading company to hide information of real manufacturer, or the label of another manufacturer to maximize the profit
  - The risks of this behavior:
    - Avoid monitoring and inspection
    - Confuse the resource of pharmaceutical materials
    - Interfere API market and price system
    - Uncertain quality of APIs
Problems in Chinese regulation

- The inspection system in China
  - The difference between certification and inspection
  - Connection between market monitoring and GMP inspection
  - Connection between drug registration and GMP inspection
  - All of above problems are being improved since 2006
Problems in Chinese regulation

- The registration system of APIs
  - The problem of independent registration of APIs
  - Insufficient materials (comparing with CTD format)
  - Evaluation standards are not as strict as ICH guidelines
  - The concept of “registration approval”, improved in new version of regulation issued in this year
CHNMED’s proposals to the government in last two years

- **Reports and proposals related with GMP to SFDA**
  - The comparison report and proposals on international GMPs and inspection systems (2005.12)
    - Proposal on the structure of new version of Chinese GMP
    - Proposal of equivalent adoption of ICH Q7A as second part of Chinese GMP for manufacture of APIs
    - Proposal of improving GMP inspection system
    - Proposal of establishment of QP system
  - 5 Self-audit guidelines (2007.1)
  - Revise of new GMP guideline (2007.3)
CHNMED’s proposals to the government in last two years

- Reports and proposals related with drug registration to SFDA
  - The proposal of changing registration procedure of APIs (2006.10)
  - The proposal of re-evaluation procedure for approved medicines (2006.12)
  - The proposal of use of CTD format in drug registration documentation (2006.12)
  - Investigation report and proposals on drug naming policy (2007.5)
The regulatory progress of China API industry

- New regulations and key compliance issues of SFDA
  - The revise of GMP
  - The revise of drug registration regulation
  - Strengthen GMP inspection since last year
  - The inspections based on registration approvals
  - The issue of self-audit guidelines
  - Trial QP system in Guangdong Province
  - Plan to elevate the standards of medicines (and APIs)
The regulatory progress of China API industry

- **National policies that affect API industry**
  - “Green GDP” policy in 11th five-year plan since 2005
    - Energy consumption of unit GDP should reduce by 20%
    - The contaminative companies must be controlled
  - “The Emission Standard of Contaminative Materials for Pharmaceutical Industry” will be issued in 2007
    - Pre-emission standard: rise from 1,000 COD to 500 COD
    - Emission standard: rise from 300 COD to 150 COD, three transitional years at 200 COD
    - The limit as per total emission amount and special type of APIs will also be stipulated
    - Local standards may higher than national standards
The regulatory progress of China API industry

- **New policy and standards have affected API industry**
  - More investment on GMP compliance and international registration
  - Some major API manufacturers have put more money on waste water treatment, for instance:
    - Shijiazhuang Pharm: 350 million yuan
    - NCPC: 200 million yuan
    - Hisun Pharm: 130 million yuan
    - Guangji Pharm: 43 million, and 20 million every year
  - Many small companies were closed since high production cost
  - The prices of many APIs are growing up in 2007
How to minimize the risk in the global supplying chain of APIs?

- **Main considerations:**
  - Specification: qualification of product, to ensure the purity and stability of APIs
  - Manufacturing site: qualification of manufacturer, to ensure the steady quality of APIs during manufacture
  - Trading and transportation: qualification of trading company, to ensure no cheat or fraud in the whole trading procedure
  - End users: audit and quality control to ensure the APIs used in formulation process are qualified
How to minimize the risk in the global supplying chain of APIs?

- What actions should be taken by China?
  - Adopt ICH Q7A as GMP for APIs
  - Change the registration procedure for APIs, however, there is too big influence on the existing products
  - Strengthen the inspection on API manufacturers, however, no mutual recognition and information exchange with western countries
  - Control the APIs produced by chemical companies, however, it is not the responsibility of SFDA
How to minimize the risk in the global supplying chain of APIs?

- **What global actions should be taken?**
  - Do not purchase APIs from non-pharmaceutical companies
  - Strengthen the administration on end users of APIs on the audit of suppliers and quality control of APIs used for formulation
  - Establish a mutual guideline to qualify trading companies, to prevent from purchasing APIs from wrong sources and any cheating behaviors
  - Enhance the information exchange, to prevent any violation, fraud and misuse in the global supply chain of APIs
SUMMARY

- To qualify the APIs from China, it is crucial that EU and Chinese governments should have harmonization of regulations, mutual recognition of GMP certificates and information exchange.

- The NGOs like pharmaceutical associations in EU and China could work as coordinators to promote above targets and cooperate in the third-party audit on API manufacturers.

- CHNMED would like to cooperate with APIC and EFCG to organize a conference in China and invite government officers, associations and manufacture representatives from different regions to discuss the safety of the global supplying chain of APIs.
Sincere thanks go to APIC/CEFIC and Concept Heidelberg for the kindly invitation and arrangement, and also to Mr. Guy Villax and Mr. Chris Oldenhof for the earnest guidance in preparation of the representation.
ANNOUNCEMENT

The viewpoints in this representation are personal opinions only for discussion on APIC Conference, please do not quote them without the permission of reporter.
Appendix: Import Drug License for the importation of APIs into China

- **Requirement for IDL application:**
  - Applicant should be either the branch company in China or an authorized Chinese company;
  - The manufacturer should have both marketing authorization and GMP certificate;
  - CEP or EDMF are acceptable (but in Chinese version);
  - For new APIs, the phase II clinical trial has to be approved in western countries. The pre-clinical data should be submitted, and clinical trial will be required (use the dosage form of APIs);
  - APIs with CP monograph do not need clinical trial.
Appendix: Import Drug License for the importation of APIs into China

Time table of IDL registration procedure:

- ** APIs with CP monograph (minimum):**
  - Submission and format evaluation: 5 working days
  - Technical evaluation: 160 working days
  - Executive procedure for IDL approval: 40 working days

- **New APIs (minimum):**
  - Submission and format evaluation: 5 working days
  - Pre-clinical data evaluation: 90 working days
  - Clinical data and production evaluation: 150 working days
  - Executive procedure for IDL approval: 40 working days