The Implementation Status and Schedule of China Drug GMP Supervision

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Content

I. The Implementation Status of China Drug GMP Supervision

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- Regulations for Implementation of The Drug Administration Law of The People's Republic of China, Article 9：

  The pharmaceutical manufacturers must follow the GMP formulated by Drug Supervision and Administration Department of State Council in accordance with this regulation. Drug Supervision and Administration Department carry out certification to pharmaceutical manufacturer on the requirement by GMP, and issue notary certification to those eligible for requirements.

  The implementation methods and procedures are regulated by Drug Supervision and Administration Department of State Council.

I. The Implementation Status of China Drug GMP Supervision

Regulations for Implementation of The Drug Administration Law of The People's Republic of China, Article 5 :

Drug supervision and administration department of provincial government and the superiors should carry out the certification of pharmaceutical manufacturers, in accordance with GMP and implementation method and procedures formulated by Drug Supervision and Administration Department of State Council, and issue Certificate of Certification to those who are eligible. Among which, the certification of injective and radioactive drug producers and biological pharmaceutical products manufacturers are performed by Drug Supervision and Administration Department of State Council.

The format of GMP certificate is formulated by Drug Supervision and Administration Department of State Council.

I. The Implementation Status of China Drug GMP Supervision

- Regulations for the Implementation of the Drug Administration Law of The People's Republic of China, Article 6 :

  Newly established pharmaceutical manufacturers, new drug formulations, or newly built workshop of pharmaceutical manufacturers, should apply for GMP certification within 30 days after having achieved drug manufacture certification files or production approval. The drug supervision and administration department should carry out certification in accordance with GMP within 6 months after having received the application form, and issue certificate to those who are eligible.

I. The Implementation Status of China Drug GMP Supervision

- Regulations for the Implementation of the Drug Administration Law of The People's Republic of China, Article 7:

  The Drug Supervision and Administration Department of State Council should establish a GMP certification inspector database. The inspector must be eligible for requirements by Drug Supervision and Administration Department of State Council. The certification inspection group is composed of inspectors randomly selected from the database for inspection and certification.

I. The Implementation Status of China Drug GMP Supervision

- According to Drug Administration Law of People's Republic of China and its regulations, issue the GMP.
- Based on basic condition in China, and drug varieties, safety and risks, the regulation is forcedly implemented in stages and in procedures.
- Formulate and issue GMP Certification Methods of drug production, and Operational Procedures for Drug GMP Certification.
- Organized and carry out drug GMP certification according to Inspection Evaluation Standard for Drug GMP Certification.

I. The Implementation Status of China Drug GMP Supervision

- The major reference for drug GMP in China is WHO GMP regulations including contents about TCM production.
- Decoction production of TCM related GMP regulations is also formulated.

I. The Implementation Status of China Drug GMP Supervision

- Since approved number management of raw materials has been utilized in registration of drug management in China, the raw materials should carry out GMP certification individually according to GMP regulations.

- Two-stages certification, special drug GMP certificate, 5-year-validity, and certification renewal on expiry date.

I. The Implementation Status of China Drug GMP Supervision

- SFDA and each provincial drug administrative department establish drug certification administrative center which is responsible for GMP certification work.
- Build up drug GMP inspector team, which is composed of technical and administrative supervision staff at all levels who successfully passed drug GMP training and employed by state bureau.

  Inspector should receive further training and improvement annually.

I. The Implementation Status of China Drug GMP Supervision

- By the end of 1998, all blood products have passed certification;
- By the end of 2000, powder-injection and high-capacity injection passed certification;
- By the end of 2002, low-capacity injection passed GMP certification;
- On June 30, 2004, production of all preparations and raw material must be eligible for GMP requirements and received GMP certificates;
- Since Jan. 1st, 2008, all manufacturers of Decoction Pieces of TCM must carry out production under conditions meet GMP requirements.

I. The Implementation Status of China Drug GMP Supervision

- According to Article 68 of Drug Administration Law of People's Republic of China, drug supervision and administration department should perform tracking inspection to eligible certificated drug producers after certification, by referring to GMP.
- Article 79: Give warning to the drug manufacturers which does not follow GMP and order them to correct within a definite time; those does not correct in time should stop production and rectify and be fined RMB 5000 ~20000 Yuan; those have serious problems, the drug production license should be withdrawn.

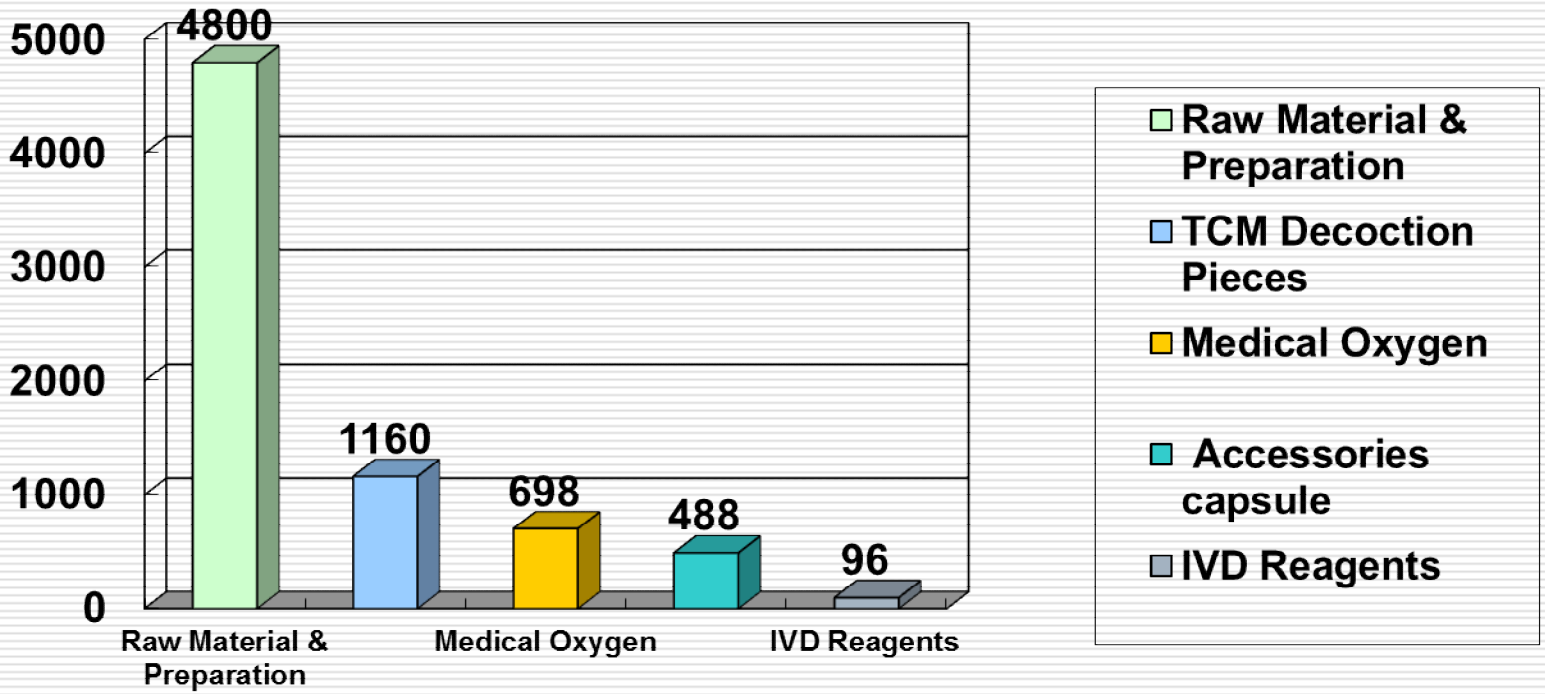
I. The Implementation Status of China Drug GMP Supervision

- According to Article 63 of Drug Administration Law of People's Republic of China, the drug manufacturers should be punished according to the Article 79 of Law of Drug Administration when the following occasions happen:
- Newly established drug manufacturers, newly-built workshops and new formulation which need proceed the production but failed to receive the GMP certification within the stipulated time by the Drug Administration Department of the State Council.

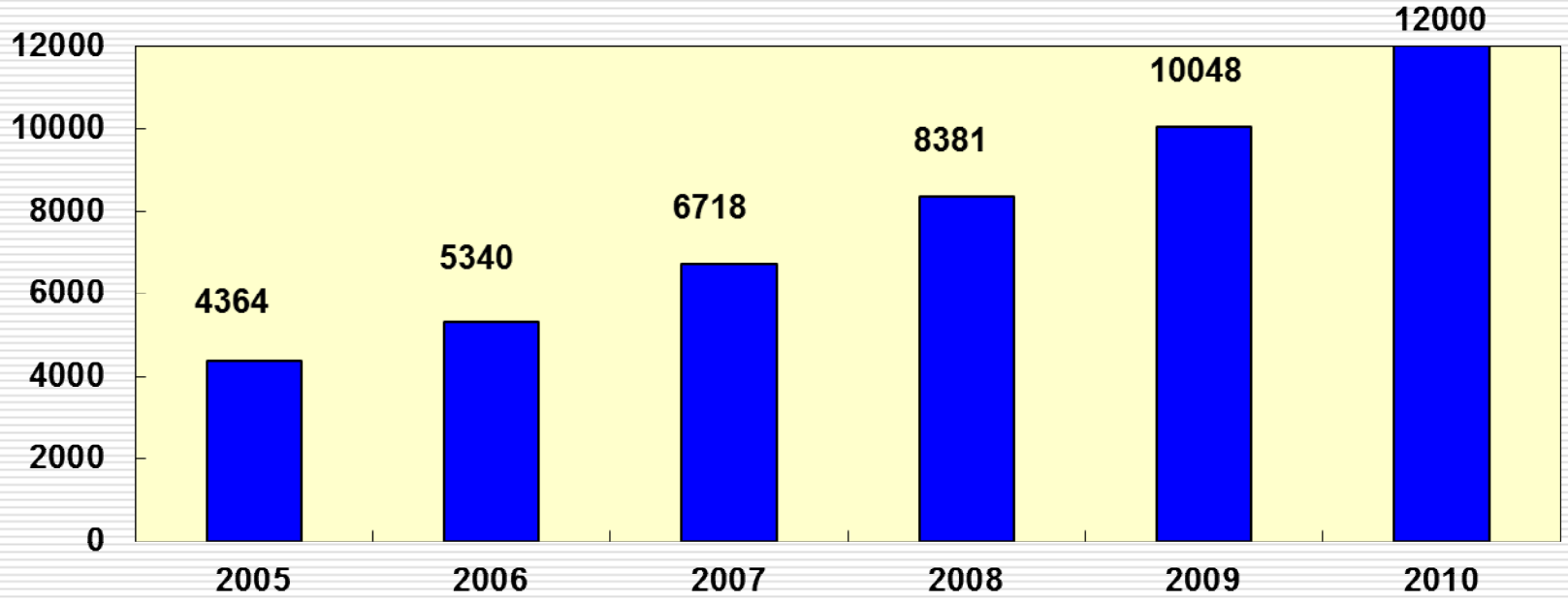
I. The Implementation Status of China Drug GMP Supervision

- Carry out tracking inspection to enterprises passed certification;
- Innovative monitor mode（flight check and accredit inspector）
- Facilitate building of quality system for manufacturers and commit quality responsibility of manufacturer（ quality authorized personnel）
- Legally punish enterprises got out of line: warning, deadline to correct, stop production for consolidation, withdraw GMP certificate, product recall, license revoke.

Drug Manufacturer Classification Statistical Chart



2005-2010 Pharmaceutical Industry Total Output Value（Unit: RMB 100 Million Yuan ）



（Quoted from SFDA Southern Pharmaceutical Economic Institute）

II. Amendment of New Drug GMP

II. Amendment of New Drug GMP

- Organize contrast research between domestic and foreign drug GMP
- Organize experts and launch GMP amendment officially
- Convene dozens of experts consultation meeting to discuss detail amendment content and summarize into exposure draft
- Based on expert amendment draft, revise the exposure draft many times
- Extensive research and argumentation

II. Amendment of New Drug GMP

Ministry of Health, P.R.C
Decree No.79

Good Manufacture Practice, GMP (2010 revised) has been adopted by ministerial meeting on Oct.19, 2010, and will come into effect as of March 1st, 2011.
CHEN ZHU, Minister of MOH
Jan.17, 2011

II. Amendment of New Drug GMP

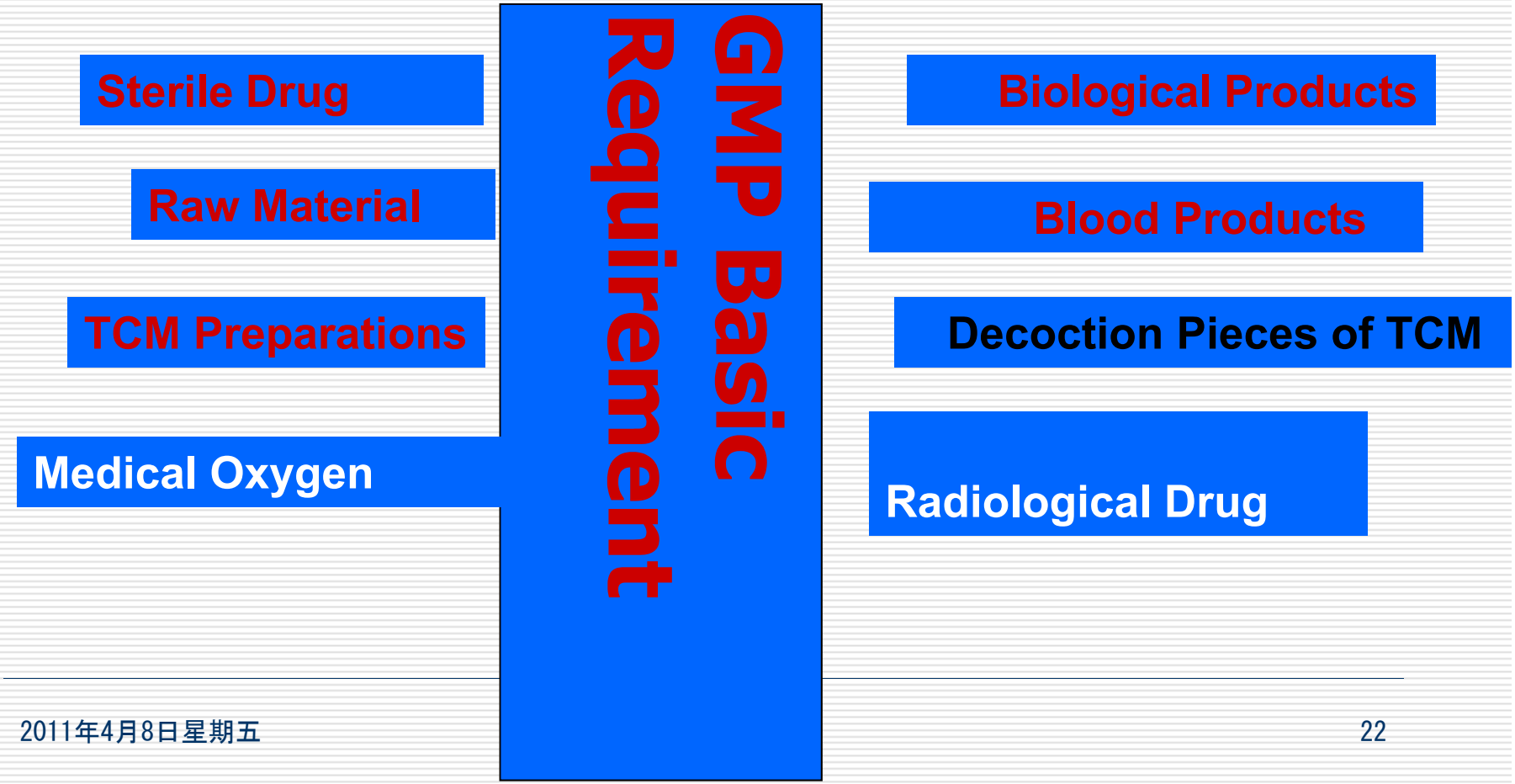
State Food and Drug Administration Announcement

No.16, 2011

Announcement on Issuing Administrative Affairs Related to 5 Annexes (Sterile Drugs, etc) of Good Manufacture Practice, GMP (2010 revised)

SFDA
Feb.24, 2011

II. Amendment of New Drug GMP



II. Amendment of New Drug GMP

- Thoroughly considering actual condition in China, integrate the conclusion and moderate foresight, referring to GMP standard by WHO and European Union, fully display the thoughts of quality risk management and dynamic monitor of whole process of drug production.
- The newly revised GMP borrows from the latest requirement of WHO and international advanced drug GMP thought , strengthen manufacturer in building up through quality management system and establish quality licensee system.

II. Amendment of New Drug GMP

- Add a series of system including supplier audit, changes control, deviation management, constant stability examination, product quality retrospective analysis, etc.
- Borrow from the content of Q7, Q8, Q9 and Q10 of ICH, and refine related system's content.

II. Amendment of New Drug GMP

- **Enhancing qualifications of key personnel**

The key personnel should be full-time staff of enterprise, at least including chief of enterprise, chief of production management, chief of quality management, and quality licensee. One person mustn't assume the responsibility of quality control and production control at the same time. The chief of quality control and quality licensee could be borne on one person.

The chief of enterprise is the major responsible person of drug quality, comprehensively in charging of daily enterprise management. To ensure enterprise realizing quality target and strictly follow this regulation in production activities, the chief of enterprise should be responsible for providing necessary resources, reasonably plan, organize and coordinate, so as to guarantee independence of quality management.

II. Amendment of New Drug GMP

- **Chief of Production Management**

  At least possess bachelor's degree of pharmacology or related majors (or intermediate titles or practice pharmacist license), more than 3 years of practical experience in drug production and quality management, more than 1 year experience of drug production management, and received professional training related to produced products.

  Major responsibilities：6

  Joint responsibilities：10

II. Amendment of New Drug GMP

- **Chief of Quality Management**

  At least possess bachelor's degree of pharmacology or related majors (or intermediate titles or practice pharmacist license), more than 5 years of practical experience in drug production and quality management, more than 1 year experience of drug production management, and received professional training related to produced products.

Major responsibilities： 15

Joint responsibilities： 10

II. Amendment of New Drug GMP

- Quality Licensee

  At least possess bachelor's degree of pharmacology or related majors (or intermediate titles or practice pharmacist license), more than 5 years of practical experience in drug production and quality management, experience of drug production process control and quality test.

  Quality licensee should possess necessary professional knowledge , receive product release related training and undertake its responsibility independently.

  Major Responsibilities： 3

II. Amendment of New Drug GMP

- Enterprise should be equipped with certain amount of management and operation personnel of appropriate qualifications (including educational background, training and practical experience) , and explicitly define responsibility of each department and position. The position responsibility should not be omitted and crossed responsibility should be explicitly defined. Each person should not assume too much responsibilities.
- All staff should definitely know about their own responsibility, be familiar with related requirements and receive necessary training, including pre-job training and continuing training.

II. Amendment of New Drug GMP

- **Annex of Sterile Drug：**

  The cleanliness degree is categorized as A, B, C and D for production environment of Sterile Drug. Detailed definition and explanation of suspended particles' static state, dynamic monitoring, airborne viable particles, colony forming unit , surface microbial and observation condition have been formulated.

  The requirement for medium simulation filling, sterilization verification and management has been refined, added detailed requirement for asepsis operation and strengthened measures to ensure asepsis.

II. Amendment of New Drug GMP

- **Annex of raw material：**

The major reference is the Q7a of ICH, in addition, the special requirement of raw material is also enclosed.

The annex strengthens software requirement, increases requirement of controlling classic fermentation technique, and defines requirements of raw material recycle, remake and reworking.

II. Amendment of New Drug GMP

- **Annex of TCM Preparation:**

  Strengthen the management requirements for quality control, distill technique control and storage of distilled material of TCM and TCM decoction, raise thoroughly requirements for quality control of Chinese medicinal plant and TCM preparations, and also raised requirements for controlling of recycled solvent under distill process.

II. Amendment of New Drug GMP

- Added the content of contact manufacture and contract test

Contract manufacture and contract test are extensively adopted manufacture method for pharmaceutical manufacturers home and abroad currently. Its production management and standardization level directly affect on safety, efficiency and controllable quality of drug.

The chapter of contract manufacture and contract test is added, which raise detailed requirements for consigner, consignee and contract, so as to ensure the contract manufacture and contract test are eligible fore GMP requirement.

II. Amendment of New Drug GMP

- Relevant content of drug production and registration is added

  Requirements for registration technique reflected in many chapters, such as, enterprise must manufacture according to approved and registered recipe and technology, must undertake tests according to approved and registered quality standard and test methods, must adopt registered and approved quality standard for raw material and packaging material whose origin must be in accordance with what have been registered. Only eligible for each Article of requirements approved by registration can the drug be released and distributed into market.

II. Amendment of New Drug GMP

- Fortify the management requirement of launched drug of enterprise:

  Every year, must undertake product quality retrospective analysis and continuous product stability inspection.

  Refine drug recall requirement, regulate enterprise in establishing product recall system, appoint special person in charge of recall implementation and coordination, formulate written recall disposal procedure, and clarify responsibility of enterprise during recall process.

  In order to effectively link up with Drug Adverse Reaction Report and Monitoring Regulation, enterprise should establish drug adverse reaction and monitoring system, and appoint special institution and personnel to take charge of it.

II. Amendment of New Drug GMP

- The feedback of WHO clearly points out, the revised Drug GMP level is equivalent to GMP standard of WHO and other countries with strict regulations on supervision.
- Comments from FDA: it is similar to international GMP standard, covering sterile standard, active drug ingredients and biological products. The announcement of new GMP regulation display breakthrough progress of China, the integration of ICH and standard of European union, and in harmony with American laws.

III. Implementation Schedule of New Drug GMP Supervision

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Announcement on Thoroughly Implementation of Good Manufacture Practice, GMP (2010 revised)

SFDA [2011] No.101

SFDA

Feb.25, 2011

III. Implementation Schedule of New Drug GMP Supervision

State Food and Drug Administration Announcement

No. 19, 2011

Announcement on Implementation of Good Manufacture Practice, GMP (2010 revised)

SFDA

Feb.28, 2011

III. Implementation Schedule of New Drug GMP Supervision

- Since March 1st , 2011, any newly registered pharmaceutical manufacturer, newly built (renovated or enlarged) workshop should be eligible for requirement of Good Manufacture Practice, GMP (2010 revised) .
- Current pharmaceutical manufacturers will be give a 3-year or 5-year transitional period.
- The production of Sterile Drug including blood products, vaccine, and injection, etc, should reach the requirement of Good Manufacture Practice, GMP (2010 revised) by the end of Dec.31, 2013.

III. Implementation Schedule of New Drug GMP Supervision

- Drug production of other categories should fulfill the requirement of Good Manufacture Practice, GMP (2010 revised) before the end of Dec. 31, 2015.
- Expired the above regulated date, enterprises which does not fulfill the requirement of Good Manufacture Practice, GMP (2010 revised), will be not allowed to proceed the manufacturing.

III. Implementation Schedule of New Drug GMP Supervision

- In accordance with Good Manufacture Practice, GMP (2010 revised), drug manufacturer should establish and improve quality management system, build up and update various kind of management software and verify and undertake pilot run, and organize staff training.

  Those above mentioned work should be accomplished before Dec.31, 2013.

III. Implementation Schedule of New Drug GMP Supervision

- Since March 1st, 2011, food and drug administrative department began to receive certification application in accordance with Good Manufacture Practice, GMP (2010 revised), and issue new coded Drug GMP Certificate.
- Those application received before March 1st, 2011, the certification continue to follow original regulations and issue drug GMP certificate, with longest expiry date to the limitation stipulated in Article 1 of this announcement.

III. Implementation Schedule of New Drug GMP Supervision

- The expiry date of Drug GMP Certificate of drug manufacturer has reached but is not eligible for Good Manufacture Practice, GMP (2010 revised), should undertake self-inspection according to Good Manufacture Practice, GMP (1998 revised) and report the results to local provincial food and drug administrative department within 6 months before the expiry date.

III. Implementation Schedule of New Drug GMP Supervision

- Provincial food and drug administrative department should undertake supervision to enterprises' self-inspection. The expiry date of drug GMP certificate of those eligible fore requirement, Sterile Drugs including blood product, vaccine and injection, etc, manufacturers shall be postponed to Dec. 31, 2013. the expiry date of Drug GMP Certificate of drugs of other categories shall be postponed to Dec. 31, 2015.
- Drug GMP Certificate of those not eligible fore requirements shall be withdrawn by provincial food and drug administrative department during reform period.
- SFDA shall post the announcement of postponed Drug GMP Certificate on its website.

III. Implementation Schedule of New Drug GMP Supervision

Strengthen international exchanges and cooperation

- Cultivate senior inspectors with English communication capability and GMP knowledge, so as to meet the necessities of imported drug supervision and inspection.
- Study on and discuss about joining in international organizations such as PIC/S, etc.

Conclusion

Enhancing drug GMP implementation level and strengthen drug quality and safety supervision in china is the fundamental demands for ensuring medication safety for the public.

The adjustment of pharmaceutical economic structure and facilitating the upgrade of industry in China is sure to play an active role in promoting domestic pharmaceutical manufacture enterprises marching into international mainstream market.

Thanks !