WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

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(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Shanghai Dahua Pharmaceutical Company
Unit number	Not Applicable
Production Block	Not Applicable
Physical address	3503 Changzheng Farm Road, Chongming County Shanghai, China GPS ID number: Latitude: 31.76564687051916 Longitude121.40976190567016 Telephone: 86-21-5931-1132 Fax: 86-21-5931-1132
Contact address	Mr Markus Steiner, fhi360 MSteiner@fhi360.org
Date of inspection	08 to 12 June 2015
Type of inspection	Routine re-inspection
Dosage forms(s) included in the inspection	Sterile sustained release implant
WHO product categories covered by the inspection	RH028 Sino-implant (II) 150mg (75x2) Levonorgestrel Implant
Summary of the activities performed by the manufacturer	Manufacture and packaging and associated QC activity

Part 2: Summary

General information about the company and site

Shanghai Dahua Pharmaceutical Co., Ltd (Dahua) was established in 1991, as an enterprise designated by National Population and Family Planning Commission (NPFPC) and State Food and Drug Administration (SFDA) for the manufacture of birth control products.

The Dahua manufacturing facility is a located in Chongming County, a suburb of Shanghai, China. The facility covers an area of 24,642 m2, 70% of which is landscaped lawns and natural area. The current facility was completed in December 2003, and is GMP certified by China Food and Drug Administration (CFDA) every five years.

The Dahua corporate office and manufacturing site are located at:
3503 Changzheng Farm Road,
Chongming County
Shanghai, China
Telephone: 86-21-5931-1132
Fax: 86-21-5931-1132

The facility manufactures a single product, Sino-implant (II). Sino-implant (II) is an implantable depot hormonal contraceptive drug containing Levonorgestrel (LNG). Sino-Implant is indicated for the prevention of pregnancy and is a long acting (up to 4 years) reversible method of contraception.

Sino-implant (II) was initially approved by China State Food and Drug Administration (SFDA) on 8 December 1994. The current manufacturing authorization was issued by CFDA on 1 January 2011 and valid until 31 December 2015.

Sino-implant (II) is manufactured entirely at the inspected site. Dahua purchased Sino-implant (II) manufacturing and testing technology in early 1991, and has no R&D research facility. There has been no new product produced at this site over last ten years other than Sino-implant (II).

History of WHO and/or regulatory agency inspections

This was the third inspection of the site by WHO PQT.

To date, Sino-implant (II), has been registered and approved for sale under the brand names of Zarin®, Trust®, Femplant®, Simplant® and SUSUK KB II® in over 24 countries in addition to China.

Focus of the inspection

This was a routine surveillance inspection focused on the production and control of Sino-implant II. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

- Quality Assurance
- Qualification and validation
- Complaints
- Recalls
- Supplier qualification
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 QUALITY ASSURANCE

In general, pharmaceutical quality system (PQS) was implemented to ensure that pharmaceutical products fit for their intended use. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. The organisation chart was available and reviewed. Job descriptions of Quality Assurance (QA), Quality Control (QC) and Production personnel were reviewed.

The PQS is basic but currently fit for purpose except where comments were made in the observations section. In general, the documentation of systems and basic quality of documentation since the previous inspections had improved.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing processes were clearly defined and systematically reviewed. Qualification and validation were performed.

The observations raised from this section have been addressed satisfactorily and will be verified during future inspections.

2.3 SANITATION AND HYGIENE

In general, this area was found to be satisfactory.

2.4 QUALIFICATION AND VALIDATION

The key elements of a qualification and validation programme were defined and documented. Process validation document for Sino-implant was reviewed and some issues were noted.

The observations raised from this section have been addressed satisfactorily and will be verified during future inspections.

2.5 COMPLAINTS

The procedure was not checked during this inspection. The PQRs gave no cause for concern in regard of complaints.

2.6 PRODUCT RECALLS

The procedure was not checked during this inspection. There had been no recalls.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Manufacturing and Quality control operations of the inspected product were not contracted out.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspection was not checked during this inspection in detail. During the opening discussions and review the inspectors were informed that there had been extensive documentation reviews since the last inspection and during this visit improvements were noted in the quality of documentation seen.

2.9 PERSONNEL

Not checked during this inspection. There have been no changes in key operational level personnel. The site head had retired but was still working part time with the company on a consultative basis.

2.10 TRAINING

Not reviewed in detail during this inspection. There has been very little staff change since the previous inspection.

2.11 PERSONAL HYGIENE

Not checked during this inspection. The facilities seen and general levels of hygiene noted during the inspection were acceptable with no significant observations noted during the factory tour.

2.12 PREMISES

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Quality control laboratories were separated from production areas.

The new Microbiology area is a significant improvement of that seen previously but further improvement was suggested.

In QC microbiology it was noted that the sterility test is performed in a class A hood in a class C room. The manner in which items are transferred and disinfected into the test bench have not adequately considered ease of disinfection of the external surfaces of the items used and the risk of false positives. Also, procedures do not adequately deal with the issue of how a positive test might be handled especially in the instance where a clear root cause cannot be identified.

The observations raised from this section have been addressed satisfactorily and will be verified during future inspections.

2.13 EQUIPMENT

Production equipment checked during this inspection was found to be satisfactory for the product produced on site. Laboratory instrument/equipment HPLC, used for the stability study testing verification was checked and found generally satisfactory.

2.14 MATERIALS

See comments above concerning control of LNG from the two manufacturers. Receipt and control of the ethylene oxide sterilisation liquefied gas was inspected. It was noted that two batches of ETO received in 2013 were accepted based on certificate of analysis from the manufacturer/supplier. There was no further testing done on ETO upon receipt of this critical material used for the sterilisation of the finished product. In this respect it was also noted that manufacturer/supplier had not been assessed by on-site audit.

The observations raised from this section have been addressed satisfactorily and will be verified during future inspections.

2.15 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. In general, documents were approved, signed and dated by the appropriate responsible persons. Documents were laid out in an orderly fashion and were easy to check. Reproduced documents were clear and legible. Documents were regularly reviewed and kept up to date. There were some issues noted.

The observations raised from this section have been addressed satisfactorily and will be verified during future inspections.

2.16 GOOD PRACTICES IN PRODUCTION

In general the surfaces were smooth and free from cracks. Equipment and materials were orderly positioned to minimize the risk of confusion between different pharmaceutical products or their components.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The QC was independent from production department. The QC functions were independent of other departments and under the authority of a person with appropriate qualifications and experience. In general, adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out.

During inspection of the laboratory, some weaknesses were observed related to measures to assure data integrity. For more detail, refer to section on observation.

During the inspection a number of apparent discrepancies were noted between initial test results and certificate of analysis as included in the dossier. The company was eventually able to explain these to the satisfaction of the inspectors but it was clear that the history should have been better recorded in the QMS.

Retains of API were not stored in simulated packaging. LNG was stored only in double polyethylene bags and according to the relevant SOP stored for up to nine years. (Three years for FPP and up to 5 years for implementation plus a margin of one year)

The area was not monitored with an instrument with the capability of recording maximum and minimum conditions. (Note that this observation is also present for several other storage and processing areas that would benefit from similar monitoring).

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, **SHANGHAI DAHUA PHARMACEUTICAL CO. LTD** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.