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Prequalification Unit Inspection services
WHO Public Inspection Report (WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Shanghai Dahua Pharmaceutical Co.
Corporate address of manufacturer	3503 Changzheng Road Changzheng Farm, Chongming County Shanghai, China
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Shanghai Dahua Pharmaceutical Co. 3503 Changzheng Road Changzheng Farm, Chongming County Shanghai, China
Unit / block / workshop number	Production Block
Inspection details	
Dates of inspection	10 to 14 October 2022
Type of inspection	Routing re-inspection
Introduction	
Brief description of the manufacturing activities	Production, quality control and product release of Levonorgestrel Implant.
General information about the company and site	Shanhgai Dahua was established in 1991. The current facility is located in Chongming County of Shanghai, China. The company had 100 employees at the time of inspection. Dahua's product Sino-implant (II) is the only product manufactured at this site. The product was PQed in June 2017.
History	The site had been inspected by WHO several times. The last WHO inspection was held in March 2018. The site is regularly inspected by local authorities.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	• Quality management system • Production block • QC including chemical and microbiological laboratories • Warehouse for stating materials and finished products • Water system
Restrictions	N/A

Out of scope	N/A
WHO products numbers covered by the inspection	RH028 Levonorgestrel Implant 75 mg per rod (150 mg in total)
Abbreviations	**Meaning** add additional ones if needed)
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original, and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation, and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance

PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
QP	Qualified person
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
RH	Relative humidity
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
SMP	Standard management procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection
EtO	Ethylene oxide

Part 2	**Summary of the findings and comments**

1. Pharmaceutical quality system

The quality management system was generally well established, documented and implemented. The quality assurance department was independent from production. The persons authorized to release products were specified.

Principle

The PQS was defined and documented in the Quality Manual which contained a description of the quality management system including the responsibility of senior management to the attainment of quality objective.

Product Quality Review

The PQR was managed according to an approved written procedure included statistical analysis and processes capability evaluation tools. The timeline for the finalization and approval of the PQR was specified in the procedure. Several APQRs for Levonorgestrel Implant RH028 were reviewed during the inspection.

APQR for 2021:

This APQR was covering the manufacturing period ranging from January to December 2021. No batch of finished product was rejected. No out of trend or process capability failure was recorded. No OOS recorded for API and excipients. The OOS test results were recorded for the finished products.

APQR for 2020

This APQR was approved for the review period from January to December 2020. Batches produced were released as per WHO specifications. There were OOS reported but all was invalid after investigation. No return and recall were reported. The complaints reported were closed. Change control, deviation and CAPAs were reviewed in the APQR. Stability study of batches under conditions of 25^0C/RH60% and 30^0C/RH75% was reviewed.

Management review

The SOP for management review was in place. The management review meeting is conducted once every year with participation of senior management team. Meeting minutes of the last MR and the list of participants were reviewed.

Quality Risk Management

The QRM procedure was not reviewed in detail in this inspection. Some risk assessments e.g., risk assessment for data integrity related to computer system were evaluated and discussed during the inspection.

Deviations

Deviations were handled according to an approved SOP. They were classified into three levels: significant, major and minor. The deviation logbook was checked. Several deviations were reviewed, or spot checked. Root cause analysis was described in an approved SOP which applied to all GMP topics, such as deviation, OOS and audits with the methodology described in the procedure.

Corrective actions and preventive action (CAPA)

The standard management procedure for CAPA was in place. The evaluation form for CAPA effectiveness report was reviewed and discussed.

Change control (CC)

Change control was managed according to an approved SMP. CCs were classified into three levels based on criticality. The CC logbook was checked. Several major changes occurred at the company since the last inspection were checked. The CCs such as addition of a new production line in the production building was ongoing at the time of this inspection.

Batch Review and final disposition

The finished product batch release was described in an approved SOP. The qualified person or his delegated sub-authorized person was responsible for approving a batch for release. The release of a selected batch was reviewed and discussed.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were generally implemented. Necessary human and physical resources with premises, equipment and utilities were provided for the current operational level of the levonorgestrel implant manufacturing activities. The manufacturing processes followed procedures as defined and documented in the BMRs.

3. Sanitation and hygiene

Premises and equipment in the FPP production area were maintained at an acceptable level of cleanliness at the time of inspection. Sanitation of clean areas was performed frequently in accordance with approved procedure. Personal and the facilities for sanitation and hygiene established on the site appeared acceptable.

4. Qualification and validation

Validations and qualifications performed according to the site policy, validation master plan, and documented procedures.

Validation master plan

Based on the project implementation matrix and the standard management procedure for validation, the annual validation master plan was established and was checked during the inspection.

Process validation and qualification

The process validation from March 2020 to January 2021 was reviewed. The data of a PV batch was checked and found within the established limits by the company. The qualification reports of key equipment were spot checked and discussed.

Cleaning validation

The production facility and equipment were dedicated to the levonorgestrel implant product. The cleaning validation protocol, cleaning validation report and the SOP for equipment cleaning and disinfection were reviewed. Residue limit of the cleaning solvent was specified and validated. Equipment clean holding time was validated with supportive data. A thorough cleaning is required to be performed at specified intervals.

Qualification of HVAC

The manufacturing facility was supplied with the clean air by HVAC systems. The annual qualification reports approved were checked, and the results were found within the established specifications. The OQ report for HVAC systems and approved qualification reports were spot checked. Viable and non-viable particles at rest and in operation were considered. The integrity test of the HEPA filters was performed by a third party.

5. Complaints

The SOP for customer complaint handling was in place. The QA department was responsible for dealing with complaints. A QA responsible person for handling the complaints was designated. The QP must be informed in case of important or critical complaints. Competent authorities should be informed in case of serious quality problems with the product. The complaint registers were available and checked. Several selected complaints were reviewed and discussed.

6. Product recalls

The SOP for product recalls was briefly reviewed. Recalls were classified as three levels with action initiation time specified. The company informed that they have never conducted any recall of the product. Simulated recall shall be performed regularly. Last mock recall record conducted was presented.

7. Contract production, analysis and other activities

No manufacture was contracted out. Several QC testing for API and FPP were contract out. The contract testing laboratories were documented with quality agreement.

8. Self-inspection, quality audits and suppliers' audits and approval

The SOP for material suppliers was in place. The SOP was applicable to suppliers of raw materials, excipients and packaging materials. Incoming materials were defined as the critical and non-critical. The site audit of material suppliers, qualification and disqualification of a qualified supplier described in the procedure and their practice in records were reviewed and discussed.

9. Personnel

There was adequate number of personnel suitably qualified by education and training to perform and supervise the manufacture of the implant product. The personnel met during the inspection appeared to be knowledgeable about GMP.

An organization chart was available and reviewed. Key personnel responsibilities were required to be defined in job descriptions. Production, Job description and responsibility of Quality VP, Production VP, QA, and QC manager was reviewed and discussed.

10. Training

The human resources department planned and conducted annual employee training. The quality assurance department performs training assessment. Each department conducted its own specific training related to the job skills, standard operating procedures, GMP guidelines and applicable regulations.

11. Personal hygiene

Personnel hygiene requirements were documented in SOP. The requirements for entry cleanrooms were documented, including pictorial drawings in change rooms. Staff observed in these areas were dressed in appropriate protective clothing.

12. Premises

The site consisted of several independent buildings used for warehouses for stating materials and finished products, production block, quality control laboratories, utilities etc.

Storage areas

The storage areas were adequately clean, dry and maintained within acceptable temperature and humidity limits. Temperature and humidity were controlled, monitored and recorded. Segregation and restricted access were provided for the storage of rejected, recalled, or returned materials or products. Sampling rooms were located inside the warehouse.

Production areas

The production block and line were dedicated to the product in the inspection scope. The room classification in the production block was documented. The temperature, RH and pressure differentials appeared adequately controlled at the time of inspection.

Quality control areas

QC Laboratories were in a separate building. Sufficient space was given to avoid mix ups and cross-contamination. Storage space was provided for samples, reference standards, solvents, reagents and records. Microbiological laboratory was separate from chemical laboratory.

Water system

The water systems including PW and WFI were inspected. The PW and WFI system appeared designed and maintained under acceptable control, and suitable to produce PW for FPP production. The SOP for production of WFI was reviewed.

Nitrogen

The filtered Nitrogen was used in the product processing steps. Nitrogen system's P& ID, specifications, sampling and testing were reviewed and discussed during the inspection.

13. Equipment

Design and construction

Equipment installed in the production block was dedicated to the levonorgestrel implant and each piece of equipment had a unique identification number. The equipment viewed appeared to be of suitable design and construction for the allocated process in general.

Equipment maintenance and cleaning

The equipment viewed during the inspection appeared maintained in good condition. The cleaning procedures and records were available for each item of equipment. The SOP for use and cleaning of equipment was spot checked.

Equipment qualification

Equipment qualification of production equipment spot checked was considered generally acceptable.

14. Materials

Materials were received, sampled and tested according to written procedures. Warehouses for starting materials, packaging materials and finished products were inspected. Starting materials and primary packaging materials were sampled in controlled environment. The material suppliers were checked according to the approved supplier list. The SOP for acceptance, warehousing, storage and distribution of raw materials was reviewed.

15. Documentation

The documentation system was paper based manual system and controlled by QA department. The documentation management followed an approved SMP. The approved, signed and dated testing procedures and specifications were available for starting, packaging materials and for finished products.

Batch numbering system

A Batch numbering system was in place and managed according to an approved SOP. Batch manufacturing records (BMRs) were retained for each batch processed. BMRs were briefly reviewed during the inspection.

16. Good practices in production

The production of the levonorgestrel implant was in operation at the time of inspection. The production blocks and production operations were inspected for all non-sterile processing steps and for sterilization process. The manufacturing processes were performed and recorded according to instructions in the batch manufacturing records. Reprocessing was managed according to an approved SOP. Reworking was not allowed.

17. Good practices in quality control

The QC function was independent from other departments. Adequate resources were available to ensure that all QC arrangements were carried out in a timely and orderly fashion.

Out of specification (OOS)

The SOP for handling out of specification investigations was in place. The investigation of OOS was reviewed and discussed.

Analytical methods and their validations

The company provided the list of analytical methods for API and finished product for review.
Most of the validations of key test methods were reviewed recently by the company with referenced validation reports. The validation documents for the tests of finished product were reviewed.

Microbiological laboratory

The microbiological laboratory was visited, there were no activities going on at the time of inspection. The media for testing and environmental monitoring were in-house prepared. Sterility test was carried out in isolator with hydrogen peroxide for decontamination. No sterility test failure was reported.

Environmental monitoring

The SMP for clean areas monitoring and test results for January, February 2021 was spot checked. No excursion was recorded.

Computerized system

The SMP for computer systems was available for review. The chromatography systems and equipment in QC were standalone stations. The upgrade of the working software to network the GC\HPLC in the QC laboratory has been addressed by the manufacturer in the CAPA at a satisfactory level.

Part 3	Conclusion – Inspection outcome

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, ***Shanghai Dahua Pharmaceutical Company*** located at ***3503 Changzheng Farm Road, Chongming County Shanghai, China*** 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.

Part 4	List of GMP Guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
   https://digicollections.net/medicinedocs/documents/s21467en/s21467en.pdf

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO TRS No. 957, Annex 2***
   untitled (digicollections.net)

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3
   9789240020900-eng.pdf (who.int)

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   https://digicollections.net/medicinedocs/documents/s21440en/s21440en.pdf

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
   https://digicollections.net/medicinedocs/documents/s23455en/s23455en.pdf

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4.
   Short name: WHO TRS No. 937, Annex 4
   https://digicollections.net/medicinedocs/documents/s20108en/s20108en.pdf

7. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1.
   Short name: WHO TRS No. 961, 957), Annex 1
   https://digicollections.net/medicinedocs/documents/s18681en/s18681en.pdf

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
   Short name: WHO TRS No. 957, Annex 3
   https://digicollections.net/medicinedocs/documents/s22358en/s22358en.pdf

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.
   Short name: WHO TRS No. 961, Annex 6
   https://digicollections.net/medicinedocs/documents/s19959en/s19959en.pdf

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7.
    Short name: WHO TRS No. 961, Annex 7
    https://digicollections.net/medicinedocs/documents/s18677en/s18677en.pdf

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. ***Short name: WHO TRS No. 961, Annex 9***
    https://digicollections.net/medicinedocs/documents/s18683en/s18683en.pdf

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3***
    https://digicollections.net/medicinedocs/#d/s21438en

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2.
Short name: WHO TRS No. 961, Annex 2
https://digicollections.net/medicinedocs/documents/s18682en/s18682en.pdf

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2.
Short name: WHO TRS No. 981, Annex 2
https://digicollections.net/medicinedocs/#d/s20177en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3.
Short name: WHO TRS No. 981, Annex 3
https://digicollections.net/medicinedocs/#d/s20175en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14.
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***
https://digicollections.net/medicinedocs/documents/s23697en/s23697en.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. ***Short name: WHO TRS No. 992, Annex 4***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. ***Short name: WHO TRS No. 992, Annex 5***
Essential Medicines and Health Products Information Portal (digicollections.net)

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
https://www.who.int/publications/m/item/who-recommendations-for-quality-requirements-when-plant-derived-artemisinin-is-used-as-a-starting-material-in-the-production-of-antimalarial-active-pharmaceutical-ingredients---trs-992---annex-6

21. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS No. 1033, Annex 4***
9789240020900-eng.pdf (who.int)

22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditionning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://digicollections.net/medicinedocs/documents/s23699en/s23699en.pdf

25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. **Short name: WHO TRS No. 1033, Annex 2**
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26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. **Short name: WHO TRS No. 1025, Annex 6**
9789240001824-eng.pdf (who.int)

27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***
https://www.who.int/publications-detail/978-92-4-000182-4

28. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. ***Short name: WHO TRS No. 1025, Annex 4***
https://www.who.int/publications-detail/978-92-4-000182-4