



**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)**

**Active Pharmaceutical Ingredient Manufacturer**

**Part 1: General information**

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| Name of Manufacturer                                           | <b>Shanghai Desano Chemical Pharmaceutical Co., Ltd.<br/>- Binhai Road</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Unit number                                                    | NA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Production Block                                               | Five workshops: <ul style="list-style-type: none"> <li>• <b>Workshop A16</b></li> <li>• <b>Workshop B14</b></li> <li>• <b>Workshop B16</b></li> <li>• <b>Workshop C16</b></li> <li>• <b>Workshop C18</b></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Physical address                                               | <b>No. 417 Binhai Road</b> , Binhai Town, Nanhui, Shanghai, 201302, China.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| Date of inspection                                             | <b>9, 10 and 11 September 2009</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Type of inspection                                             | Routine Inspection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| WHO product categories covered by the inspection               | <b>Products against HIV/AIDS (HA)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Active Pharmaceutical Ingredient(s) included in the inspection | Active Pharmaceutical Ingredients against HIV/AIDS (HA) and Malaria (MA)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |



|                                                         |                                                                                                                       |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Summary of the activities performed by the manufacturer | Manufacturing, packaging, control and release of Anti-Retroviral and Anti-Malarial active pharmaceutical ingredients. |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|

## Part 2: Summary

### *General information about the company and site*

The site inspected was **Shanghai Desano Chemical Pharmaceutical Co., Ltd. No. 417 Binhai Road, Nanhui, Shanghai 201302, China**, hereafter called **Shanghai Desano Binhai Site**. The company corporate office was located at Plot No.1479, Zhangheng Road, Zhangjiang High Tech Park, Shanghai, China.

According to the Site Master File Version No. 03 effective August 2009 and the presentation given at the opening meeting, **Shanghai Desano Binhai Site** was established in 2007. It belonged to **Shanghai Desano Chemical Pharmaceutical Co., Ltd** which was established in 2002 and which was in turn owned by **Shanghai Desano Pharmaceutical Investment Co., Ltd** which was established in 2005. **Shanghai Desano Binhai Site** had sister companies involved in the chemical, pharmaceutical and nutritional areas. It was, however, stated that **the sister site located at 9125 Huinan Road, Nanhui, Shanghai 201300 China, stopped production of ARV APIs in mid 2007 and was sold to another company under DESANO holding..**

The site of **Shanghai Desano Binhai Road** was about **46km from Shanghai City centre** and about **17 km from Pudong International airport**. The total size of the site was 102,840m<sup>2</sup> with a built up area of 50,441m<sup>2</sup>.

**Shanghai Desano Binhai Road** had 5 production Workshops in separate blocks with separate air handling systems:

- 1. Building A16: for synthesis, purification and packing of certain Active Pharmaceutical Ingredients (APIs).** This building had three independent modules:
  - a. Module A16-C where one API was synthesized
  - b. Module A16-B where two APIs were synthesized.
  - c. Module A16-A where the purification and packing of the 3 APIs took place.
- 2. Building B14: newly constructed and dedicated for synthesis of one API.** Purification and packaging of this API were still being done in A16. A new workshop was under construction for the purification of this API. Once completed, the purification and packing of this API in A16 will be stopped.
- 3. Building B16: dedicated to the synthesis, purification and packing of one API.**
- 4. Building C16: dedicated to the synthesis, purification and packing of one API.**
- 5. Building C18: for the synthesis, purification and packing of two APIs. It had also been validated for another API.** This building had three independent modules:
  - a. Module C18-A where one API were synthesized using two alternative solvents.
  - b. Module C18-B where two APIs were synthesized.
  - c. Module C18-C where the purification and packing of the 3 APIs took place.

There were separate warehouses for solid starting materials (A12), liquid starting materials (A11 and B11), finished APIs (A15-2) and empty drums (C19). The QC laboratory was located in the administration block (A18). The water purification plant was located in separate

block (A15-1) and there were facilities for effluent treatment and waste management, generation of compressed air, steam and chilled water.

According to the presentation by the company, as of 31 August 2009 the Binhai site employed 474 people distributed as follows:

| S/No. | Department                                 | No. of Employees |
|-------|--------------------------------------------|------------------|
| 1     | Production                                 | 294              |
| 2     | Engineering/Maintenance/Utilities          | 44               |
| 3     | Warehouse                                  | 25               |
| 4     | Quality control Laboratories               |                  |
|       | ⇒ Chemistry laboratory                     | 38               |
|       | ⇒ Microbiology Laboratory                  | 2                |
| 5     | Quality Assurance                          | 17               |
| 6     | Others (HR, Administration, Security, etc) | 54               |
|       | <b>Total Workforce</b>                     | <b>474</b>       |

### *History of WHO and/or regulatory agency inspections*

According to the SMF version No. 03 and company presentation, Shanghai Desano Binhai Site was on August 10, 2007 granted a **License No. Hu Ha20060081** for manufacturer of drugs by Shanghai Food and Drug Administration. It was stated that it was inspected and **approved by USFDA in April 2009 for three APIs**. This site was previously inspected and approved by WHO-PQ in October 2007. It had since applied for several Active Pharmaceutical Ingredient Master Files (APIMFs).

### *Focus of the inspection*

The inspection focused on the production and control of **ARV APIs and Anti-Malarial APIs**. The inspection covered all the sections of ICH Q7, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

### *Inspected Areas*

#### **Day 1**

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards. They explained the procedure for WHO Prequalification Programme, the procedures and standards used for inspection including the newly introduced Notice of Concern (NOC), Notice of Suspension (NOS) and elaborated on the tentative inspection plan. After confirming the inspection plan, the company made a presentation about the company activities and the site to be inspected. The presentation highlighted the capacities, Quality Management System and inspection history of the site. A copy of the presentation was obtained and will be filed in the company file.

The presentation also highlighted the following change since the previous WHO inspection:

⇒ Construction of building B14.

The company presented the manufacturing process of each of the API due for inspection. The key starting materials and their suppliers plus the process critical parameters were highlighted.

The warehouses for solid starting materials, intermediates, liquids and primary packaging materials were inspected together with the associated, quarantine areas, rejected goods areas, sampling and dispensing areas. The warehouse for finished APIs, cold room for finished APIs and storage areas for returned goods, retention samples were also inspected. The records for temperature and relative humidity monitoring were reviewed together with the associated balance calibration records.

The tank farms together with associated delivery records were inspected.

The inspection ended late in the day so the review of the progress of the activities of the day, and giving the day's feed back were differed to the next day.

## **Day 2**

The inspectors started by reviewing the areas inspected the previous day and gave feed back on the observations made.

The production activities were inspected in workshops A16, B14, B16, C16 and C18. Workshop C16 was under maintenance and cleaning so no production activities were going on. Other areas inspected included:

- ⇒ HVAC system for the purification area of Building A16.
- ⇒ IPQC for A16 and related testing records.

The inspection ended late in the day so the review of the progress of the activities of the day, and giving the day's feed back were differed to the next day.

## **Day 3**

The inspectors started by reviewing the areas inspected the previous day and gave feed back on the observations made.

The inspectors proceeded to inspect the following areas:

- ⇒ Water purification and distribution system
- ⇒ QC laboratory
- ⇒ Stability chambers
- ⇒ Primary and Working standards

This was followed by review of documentation in the following areas:

- ⇒ Annual product quality review for the years 2007 and 2008.
- ⇒ SOPs for SOPs
- ⇒ SOP for Batch release
- ⇒ SOP for product recall
- ⇒ SOP for complaints
- ⇒ SOP for handling deviations
- ⇒ SOP for handling OOS results

- ⇒ SOP for change control
- ⇒ Personnel issues including training records, job descriptions.
- ⇒ Internal audit programme and records.
- ⇒ Cleaning validation protocols and reports of:
  - A dryer in C18 for a product change over between two APIs.
  - Protocol and report for cleaning after synthesis of one specific API.
- ⇒ Process validation for one API: Protocol and Report.

## **2.1 QUALITY MANAGEMENT**

Shanghai Desano Binhai site had an acceptable documentation system consisting of procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance. The responsibilities of the Quality and production units were defined. There was a system and records for Annual product quality review.

## **2.2 PERSONNEL**

It was established that Shanghai Desano Binhai Site had adequate number of qualified, experienced personnel to carry out the tasks in accordance to the applicable GMP. Individual responsibilities were generally defined in the organograms and individual job descriptions.

The heads of production and quality control were independent of each other.

Personnel interviewed and records checked reflected that they were aware of the principles of GMP although the routine GMP training could be strengthened further. Entry to critical production, storage and quality control areas was restricted to only authorized personnel.

## **2.3 BUILDINGS AND FACILITIES**

The building and facilities were designed to facilitate logical flow of production activities and to avoid cross contamination. The building and facilities were in a good state of repair and were adequately cleaned.

The clean areas for purification stage were separate from those for the synthesis stages. There were smooth, were supplied with separate AHU and purified water. Temperature and relative humidity were regularly monitored.

## **2.4 PROCESS EQUIPMENT**

The process equipment were designed and installed to facilitate containment and logical flow of production. They were regularly cleaned and maintained according to approved procedures and records were maintained. There was a system to indicate the status of the equipment although its implementation needed to be consistently implemented.

## **2.5 DOCUMENTATION AND RECORDS**

There was a system for documentation in form of SOPs, manufacturing procedures, log books, specifications, testing procedures. These were designed, approved and controlled according to

established SOP. Some weaknesses were observed in the reference or numbering of the documents and cross referencing related documents and records, but these were consequently addressed.

## **2.6 MATERIALS MANAGEMENT**

Materials were sourced from approved suppliers. On receipt they were quarantined, sampled and tested before acceptance into approved stores for subsequent use. The storage of starting materials, intermediates and finished APIs was generally adequate and the storage conditions were regularly monitored.

Materials at different stages processing were identified with a unique batch numbers and stage of processing.

## **2.7 PRODUCTION AND IN-PROCESS CONTROLS**

Production processes were guided by documented procedures and detailed instructions. Production processes were either conducted in dedicated facilities or on campaign basis. There were in-process controls conducted at appropriate stages of synthesis to monitor the quality of the intermediates and APIs. The processes used were generally similar to those outlined in the dossiers submitted to WHO. The cleaning procedures, design of the buildings and equipment, plus the planning of production facilitated prevention of possible cross-contamination

## **2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

Materials at different stages processing were identified with a unique batch numbers and stage of processing. Intermediates and finished APIs were packed using packaging materials meeting the relevant specifications. Packaging operations took place in segregated areas and were preceded with appropriate line clearance. There was appropriate reconciliation of packaging materials at the end of each packaging operation.

## **2.9 STORAGE AND DISTRIBUTION**

Shanghai Desano Binhai Site had appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. Conditions of storage were monitored and appropriate records for stock and distribution were maintained.

## **2.10 LABORATORY CONTROLS**

The main QC laboratory was situated on the first floor of the administration block. The premises, facilities and utilities were separate from production and were in a good state of repair. There were dedicated rooms for activities like sample receipt and storage, wet chemistry, instrumentation, hot areas and balance room. There were adequate pieces of equipment with up to date calibration status.

Records of sample receipt and allocation, analysis were maintained. Records of analysis could facilitate traceability of the reagents, standards and equipment used.

The microbiology laboratory was separated from the chemical laboratory.

There were stability chambers for the different storage conditions and records of charging and withdrawal of samples for testing were available and consistent with the protocols and regulatory requirements.

## **2.11 VALIDATION**

Validation of manufacturing processes and cleaning procedures had been done and the relevant protocols and reports were available.

## **2.12 CHANGE CONTROL**

There was a procedure for change control which included evaluation on the validation status of the system and prescribed appropriate control measures to preserve the validated status. There was a change control register and appropriate records were maintained.

The introduction of new products in a workshop (e.g. one API in A16) was not done through a well documented change procedure.

## **2.13 REJECTION AND RE-USE OF MATERIALS**

Recovery of solvents and materials at different stages of synthesis was done according to documented instructions and were tested to meet predefined specifications. Solvent recovery was either done on site or off site at the facilities of a sister company which was located across the road (No. 418 Binhai Road). The in house recovery processes were validated as part of the process validation. Recovered solvent were used at different stages of synthesis. Due to time constraints, this area was not assessed in detail.

## **2.14 COMPLAINTS AND RECALLS**

There were procedures for handling customer and market complaints and product recall. Only few market complaints had been encountered since the last inspection and none had resulted into a recall.

## **2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

The contract with the vendor used to recover solvents was reviewed. It had been audited and approved by QA and production before the agreement was executed.

## **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 Desano Chemical Pharmaceutical Co., Ltd. No. 417 Binhai Road, Nanhui, Shanghai 201302, 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.