

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**

Part 1: General information

Name of Manufacturer	Shanghai Desano Chemical Pharmaceuticals Co., Ltd
Unit number	No. 417 Binhai Road
Production Block	Six workshops: <ul style="list-style-type: none"> • Workshop A16: • Workshop B14: • Workshop B15: • Workshop B16: • Workshop C16: • Workshop C18:
Physical address	No. 417 Binhai Road, Binhai Town, Nanhui, 201302 Shanghai, China.
Contact person and email address.	Ms. Zheng Yuqing, Plant Manager Tel. Office: +86-21-5805 3300 - 2001 Mobile: +86-136-1196 5863 Fax: +86-21-5805 3311 e-mail: zhengyuqing@desano.com
Dates of inspection	15 - 18 March 2011
Type of inspection	Routine inspection
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 201203, China. The site was about **46km from Shanghai City centre** and about **17 km from Pudong International airport**. The total size of the site was 102,840m².

According to the Site Master File Version No. 05 authorized on 16 February 2011 and the presentation given at the opening meeting, **Shanghai Desano Binhai Site** was established in 2006. 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 1996 (owned by 14 private owners, 45% by Desano Holdings and 21% by Shanghai Government).

Shanghai Desano Binhai Road had 6 production Workshops in separate blocks with separate air handling systems:

1. **Building A16:** for synthesis, purification and packing of Anti-HIV/AIDS and Anti-Malarial APIs. This building had three independent modules:
 - a. Module A16-C where an Anti-Malarial API was synthesized
 - b. Module A16-B where Anti-HIV/AIDS APIs were synthesized.
 - c. Module A16-A where the purification and packing of the APIs took place.
2. **Building B14:** for synthesis of one Anti-HIV/AIDS API. Purification and packaging were done either in B15B or A16. The purification and packing of this API in A16 will be stopped once the process in B15B is approved. Trial batches of another Anti-HIV/AIDS API have been synthesized in this block.
3. **Building B15:** A newly constructed workshop for the purification of several Anti-HIV/AIDS APIs.
4. **Building B16:** dedicated to the synthesis, purification and packing of one Anti-HIV/AIDS API.
5. **Building C16:** dedicated to the synthesis, purification and packing of one Anti-HIV/AIDS API.
6. **Building C18:** for the synthesis, purification and packing of Anti-HIV/AIDS and Anti-Malarial APIs. This building had three independent modules:
 - a. Module C18-A where one Anti-Malarial API (using 2 purification routes/solvents) was synthesized.
 - b. Module C18-B where Anti-HIV/AIDS APIs were synthesized.
 - c. Module C18-C where the purification and packing of the 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 28 February 2011 the Binhai site employed 592 people (2 production shifts of 12 hours for 7 days a week) distributed as follows:

S/No.	Department	No. of Employees
1	Production	383
2	Engineering/Maintenance/Utilities	58
3	Warehouse	29
4	Quality control Laboratories	
	⇒ Chemistry laboratory	58
	⇒ Microbiology Laboratory	3



5	Quality Assurance	19
6	Others (HR, Administration, Security, etc)	48
	Total Workforce	592

Shanghai Desano Binhai Site was under expansion to construct new blocks A19 (power house), B19 (one Anti-Malarial API), C19 (Multipurpose), A20 (Multipurpose) B20 (one Anti-HIV/AIDS API) and C20 (one Anti-HIV/AIDS API). There were sister companies involved in the chemical, pharmaceutical and nutritional areas. For example, a sister company on Plot No. 418 Binhai Road (hereafter called Desano Synthesis site) was involved in solvent recovery for use at Plot No. 417 and the synthesis of:

- Intermediates for some Anti-HIV/AIDS and Anti-Malarial APIs for use at Plot No. 417 and for sale.
- Some Anti-HIV/AIDS and Anti-Malarial APIs for non-WHO/USA markets.

This company also served as a scale up plant from R&D. It was still operated as a chemical plant but work had started to upgrade it to a GMP plant to manufacture API for the WHO market.

History of WHO and/or regulatory agency inspections

According to the SMF version No. 05 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 which was renewed on 01 January 2011 with a new **No. Hu Ha20110059**. It was stated that it was inspected and approved by USFDA in April 2009 for 3 Anti-HIV/AIDS APIs. This site was previously inspected and accepted by WHO-PQ in October 2007 and September 2009. It had applied for several APIMFs:

Focus of the inspection

The inspection focused on the production and control of 5 ARV APIs and 3 Anti-Malarial APIs. The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients, including Quality Management; Personnel; Buildings and Facilities; Process Equipment; Documentation and Records; Materials Management; Production and In-Process Controls; Packaging and Identification Labelling of APIs and Intermediates; Storage and Distribution; Laboratory Controls; Validation; Change Control; Rejection and Reuse of Materials and Complaints and Recalls.

Inspected Areas

Day 1: 15 March 2011

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards with the key staff of the company. The inspectors explained the procedure for the WHO Medicines Prequalification Programme, the procedures and standards used for inspection and timelines for the processing the report and company responses to the inspection observations. The recently developed WHO guidelines and the procedures for prequalification of APIs were explained. The tentative inspection plan was discussed and confirmed. The company made a presentation about the company and the site to be inspected. The presentation highlighted the company profile, the description of the site, a summary of manufacturing capacities and annual sales, location of production of the various APIs, the site inspection history, key issues and changes since the last WHO inspection. The major issues and changes highlighted include the following:

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- 4 complaints, 4 returns and no recalls since the last inspection.
- A new manufacturing process for one Anti-HIV/AIDS API was introduced, validated and approved by WHO assessors.
- A new workshop (B15) was built, process validation was completed and variation applications for 3 Anti-HIV/AIDS and Anti-Malarial APIs submitted to WHO.
- A new production manager appointed on promotion.

It was agreed that a visit would be made to plot No. 418 Binhai Road to review the solvent recovery and manufacture of some of the intermediates that were used synthesis of API on plot No. 417.

The inspection of the following followed:

- Organograms and the job descriptions of the key personnel: Production Manager, Quality Assurance Manager, Deputy Quality Assurance Manager and QC Manager.
- Product quality review reports for 4 APIs:
- Product codes and batch numbering system: SOP-B-PM-000-11.
 - The formats for the codes were as follows:
 - For intermediates: DBC PPP SS where D = Desano, B = 417 Binhai Road, C = Category (H = HIV, M = Malaria), PPP = Product code, SS = serial number of the process stage.
 - For APIs: DBC PPP-G where D = Desano, B = 417 Binhai Road, C = Category (H = HIV, M = Malaria), PPP = Product code, G = grade of API.
 - For recovered solvents: BHYRRR-PPP-SS where BHYRRR = Recovered solvent at 417 Binhai, PPP = Product code, SS = serial number of the process stage.
 - The format of the batch number was: DBC PPP-G-BBBB-YYMMNNN where D = Desano, B = Binhai Road, C = Category (H = HIV, M = Malaria), PPP = Product code, G = grade of API, BBBB = block number, YY = last 2 digits of the year of manufacture, MM = 2 digits representing the month of manufacture and NNN = serial number of the batch per month.
- Receiving, quarantine, sampling and storage of the following:
 - Solvents and liquid reagents in drums in A11.
 - Acids and reagents in B11.
 - Solid raw materials in A12.
 - Solvent tank farm.
- Failure investigation FIR DBM86B-2010 006
- Out Of Specification report OOS-DBMI-86B02-1002
- CAPA DBMI86B02-C18A-101124
- Deviation DEV-DBMI86B02-201 0001
- Self inspection procedure SOP-B-QA-014-01 + the related 2011 self inspection schedule + the cover page of the last two reports (IQAP-2010-003 dated 06 Dec 10 and IQAP-2011-001 dated 08 Mar 11)

At the end of the day, the team reviewed progress of the activities of the day. Feedback was deferred to the following day.

Day 2: 16 March 2011

After providing the company with a summary of the observations from the previous day, the inspectors proceeded to inspect the following areas:

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- Approval and qualification of supplier: SOP-B-QA-022-01 effective 18.02.2011.
- Approved vendor list version No. 021
- Evaluation and site audit reports for suppliers of key API starting materials.
- Evaluation, site audit reports and quality agreements with the contractor for solvent recovery.
- Deviation procedure SOP-B-QA-015-02 and deviation DEV-DBH010-2010004
- Change control procedure SOP-B-QA-009-02, change controls CA-QC-10001 and CA-QA-10011
- Procedure for cleaning of solvent drums SOP-B-MM-022-02
- Procedure for material receipt SOP-B-MM-001-05 and procedure SOP-B-MM-022-02 for annual cleaning of solvent drums
- Calibration procedure SOP-B-EM-203-02, the Feb. 2011 and March 2011 calibration schedules, and a number of calibration records
- Product release procedure SOP-B-QA-025-1 and release records for batch DBH010-4-A16A-100601b
- Recall procedure SOP-B-QA-028-02
- Complaint procedure SOP-B-QA-026-01 and the complaint number CC-DBH021-2011001 for the Stavudine batch DBH021-4-C18C-110202
- Review of the production and supply of HA and MA APIs by Shanghai Desano plot 417 Binhai Road in 2010

Plant tour: the B15 workshop for the latest manufacturing stages of two Anti-HIV/AIDS APIs. Particularly, the manufacturing process of one Anti-HIV/AIDS API was followed.

At the end of the day, the team reviewed progress of the activities of the day. Feedback was deferred to the following day.

Day 3: 17 March 2011

After providing the company with a summary of the observations from the previous day, the inspectors proceeded to inspect the following areas:

- Preventive Maintenance procedure SOP-B-EM-002-04
- 2010 equipment list
- 2010 maintenance record for the drier D10501-2 drier used in one Anti-Malarial API process
- Log book for precision filter No. X15103-1 in block B15.
- Pressure gradient P&ID No. TDB-B15-003-00 for block B15.
- Tour of the Desano Synthesis plant (Plot 418 Binhai Road): warehousing, solvent recovery for the Shanghai Desano plot 417 Binhai site, Workshop K18 for manufacturing an intermediate for an anti-malarial API delivered to Shanghai Desano plot 417 Binhai, Workshop K17-2 for purification of several Anti-HIV/AIDS and Anti-Malarial APIs for non-WHO/USFDA markets, L18 for synthesis of one intermediate and one Anti-HIV/AIDS APIs.
- Tour of Workshop C16 in Shanghai Desano plot 417 Binhai Road for the manufacture of one Anti-HIV/AIDS API and related solvent recovery facilities.
- A full set of batch records for one Anti-HIV/AIDS finished API, including the requisition and issuance of shipping labels.

- One Anti-HIV/AIDS API process change validation protocol (BVP-027-2010001), report (BVR-027-2010001), BMRs of the batches used in the process validation study plus the related analysis raw data.

At the end of the day, the team reviewed progress of the activities of the day. Feedback was deferred to the following day.

Day 4: 18 March 2011

After providing the company with a summary of the observations from the previous day, the inspectors proceeded to inspect the following areas:

- Purified water system P&ID drawing, TDB-US-000-J-02.
- Process water specifications, SOP-B-QC-220-01.
- Purified water specifications, SOP-B-QC-300-03
- Tour of the water treatment plant.
- Cleaning, sanitisation and maintenance of the water treatment system: carbon filters: back flushed regularly; UV lamp changed after a set number of hours; RO cleaned with regularly; mixed bed filter regenerated with HCL and NaOH when conductivity exceeds asset amount; purified water tank and loop sanitised frequently.
- SOP-B-EM-126-00: How to use the purified water.
- Review of trends of results of water monitoring and chemical and microbiological analysis from several sampling points: 1-1 for source water from city supply; PW01 after mixing carbon filtered water and RO1 water (process water); PW02 on distribution line for process water; 1-5 on distribution loop for purified water; 1-3 in the return loop for distribution water.
- Deviation No. DEV-PW-2011003 related to OOS of TOC on 25 February 2011.
- Inspection of the QC laboratory: receipt, recording, storage and allocation of samples for analysis; review of raw and electronic records of sampling and testing of selected batches of key starting materials, fresh and recovered solvents, intermediates and APIs; preparation and qualification of selected batches of working standards;
- Inspection of microbiology laboratory: Premises and equipment; glassware cleaning; waste management; receipt, storage and control of purchased media; purchase, storage, sub-culturing and control of reference culture; handling and testing of water samples.
- Tour of finished product warehouse, including sampling area and cold storage of some anti-malarial intermediates/APIs.
- One Anti-HIV/AIDS API repacking master record BPR-B-PM-307-03
- Change control CA-DBH010-A16-10001 for replacement of the double cone drier D 10501-2, as well as the qualification documents:

	Protocol number	Report number
Installation Qualification	BQP-012-201-0005	BQR-012-201-0005
Operation Qualification	BQP-012-201-0006	BQR-012-201-0006
Performance Qualification	BVP-098-201-0003	BVR-098-201-0003

- Process deviation DEV-DBM098A02-2010002
- Training record of one of the production operators on a TLC IPC test
- Training record of one of the analysts on GC testing for residual solvents
- Validation procedure SOP-B-QA-033-01

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- 2011 validation master plan VMP-B-2011001
- Cleaning validation protocols and reports for the drier D 15115-1 as follows:

	Protocol number	Report number
Cleaning after Lamivudine	BVP-CL-010-2010001	BVR-CL-010-2010001
Cleaning after Efavirenz	BVP-CL-012-2010001	BVR-CL-012-2010001

At the end of the day, the team reviewed progress of the activities of the day and the entire inspection, gave feed back and wrap up for the inspection and received reactions from the management of the company.

2.1 QUALITY MANAGEMENT

Generally QMS procedures were well executed. The 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 self inspection and annual product quality reviews. The Quality Assurance department was particularly strong, which resulted in a high level of control but shall not exonerate other departments from assuming their responsibilities in ensuring compliance.

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 organisation charts 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 training evaluation system could be strengthened further. Entry to critical production, storage and quality control areas was restricted to 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. The surfaces were smooth and the areas were supplied with separate AHUs and purified water.

The neighbouring Desano Synthesis site (Plot 418 Binhai Road) was still operated as a chemical plant but work had started to upgrade it to a GMP plant to manufacture API for the WHO market.

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. The system used to perform batch to batch cleaning, and particularly the status labelling, needed to be improved.

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 an established SOP. The comprehensiveness and maintenance of the documents needed to be strengthened.

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 manufacturing stages were identified with a unique batch number and stage of processing.

The fact that Desano Binhai plot 417 purchased advanced intermediates requires a particular attention on starting material controls.

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 in multipurpose workshops and equipments. There were in-process controls conducted at appropriate stages to monitor the quality of the intermediates and APIs. The cleaning procedures, design of the buildings, equipment and the planning of production facilitated prevention of 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. The labelling of finished API's before the shipping label is applied needed improvement.

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.

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.

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.

Improvements were needed in the way Out of Specification results are investigated. Also, the use of detergent for glassware cleaning in the microbiology laboratory needed to be reviewed.

2.11 VALIDATION

Validation of manufacturing processes, cleaning and analytical methods were extensively documented but evaluation of the collected data needed improvement.

2.12 CHANGE CONTROL

The control of changes was reviewed and found deficient in several areas. The approach to change management needed to be strengthened.

2.13 REJECTION AND RE-USE OF MATERIALS

Recovery and use of solvents and materials were generally well documented but some solvent recovery was carried out at the Desano Synthesis site (plot 418 Binhai Road) where a program to upgrade its standards had started.

2.14 COMPLAINTS AND RECALLS

Procedures were in place but the effectiveness of the recall procedure has not been established.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The contractor for solvent recovery was evaluated and there was a quality agreement in place but this agreement did not clearly specify how labelling and traceability of recovered solvents would be handled.

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**

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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 and in particular, WHO Good Manufacturing Practice for Active Pharmaceutical Ingredients.

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.