

WHO PUBLIC INSPECTION REPORT API Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**
Part 1: General information

Name of Manufacturer	Hetero Drugs Ltd								
Unit number	Unit 1								
Production Block	1. Block D (line 2): Ritonavir Form I (code RT) 2. Block E (line 2): Levofloxacin Hemihydrate (code LF) 3. Block I (line 2): Moxifloxacin Hydrochloride Monohydrate (code MX)								
Physical address	Survey Nos. 213, 214, and 255, Bonthapally Village, Jinaram Mandal, Medak District, Andhra Pradesh, India								
Contact person and email address.	Mr. C. Raghunath, Vice President – QA & RA Hetero Drugs Limited • Telephone: o Office : 0091 40 23704923/24/25, extension 2089 o Mobile : 0091 9849455560 • Email : Raghunath@heterodrugs.com								
Date of inspection	26 to 28 November 2012								
Type of inspection	Initial routine inspection.								
Active Pharmaceutical Ingredient(s) included in the inspection	<table border="1"> <thead> <tr> <th>Reference</th><th>Name of API</th></tr> </thead> <tbody> <tr> <td>1. APIMF27</td><td>Ritonavir Form -I</td></tr> <tr> <td>2. APIMF162</td><td>Levofloxacin Hemihydrate</td></tr> <tr> <td>3. APIMF188</td><td>Moxifloxacin Hydrochloride Monohydrate</td></tr> </tbody> </table> <u>NB:</u> Hetero stated that the following APIs are not manufactured on this site and therefore they are not covered by this inspection report: Lamivudine, Nevirapine, Ritonavir, Stavudine, Tenofovir Disoproxil Fumarate, Zidovudine	Reference	Name of API	1. APIMF27	Ritonavir Form -I	2. APIMF162	Levofloxacin Hemihydrate	3. APIMF188	Moxifloxacin Hydrochloride Monohydrate
Reference	Name of API								
1. APIMF27	Ritonavir Form -I								
2. APIMF162	Levofloxacin Hemihydrate								
3. APIMF188	Moxifloxacin Hydrochloride Monohydrate								
Summary of the activities performed by the manufacturer	Production, quality control, packaging, distribution of APIs and intermediates								

Part 2: Summary

General information about the company and site

The facility inspected was **Hetero Drugs Ltd, Unit 1, Survey Nos. 213, 214, and 255, Bonthapally Village, Jinnaram Mandal, Medak District, Andhra Pradesh, India**, here after referred to **Hetero Drugs Ltd, Unit 1**. Hetero Drugs Ltd was established in 1993 with a focus to manufacturer intermediates and Active Pharmaceutical Ingredients (APIs).

According to the site master file SMF-001-10 effective 20/06/2012 and the presentation made by the company at the opening meeting, Hetero Drugs Ltd, Unit 1 was located on a plot of land 30 acres with 50% built up area including 13 production blocks, each with an intermediate zone and Pharma zone.

The site had a licence 9/MD/AP/96/B/R, valid up to 31.12.2016 issued by Drug Control Administration, Andhra Pradesh, India. The site manufactures various organic intermediates and APIs.

The following categories of APIs are not manufactured on the site: steroids, beta lactam antibiotics (e.g. penicillins and cephalosporins), hormones, and cytotoxics and non-pharmaceutical products.

According to the company presentation and Site Master File (SMF), the site operates 24 hours in 3 + 1 (General Shift) shifts and employed a total of 736 people:

1. Production	419
2. Quality control (QC)	125
3. Quality assurance (QA)	41
4. Warehouse	41
5. Engineering	42
6. EHS	18
7. Others	50

History of WHO and/or regulatory agency inspections

This was the first inspection of this site by WHO Prequalification of Medicines Programme (WHO/PQP). According to the company presentation, the site has been inspected and approved by the following agencies:

S. No	Audit	Audit Date	Reported Date	Audit Out come
01	1 st USFDA	27 – 29 Nov 2001	22 Feb. 2002	Facility is acceptable
02	2 nd USFDA	24 – 27 Jan. 2005	19 April 2005	Facility is acceptable
03	3 rd USFDA	27 – 31 March 2008	25 July 2008	Facility is acceptable
04	4 th USFDA	8 – 11 Nov. 2010	8 March 2011	Facility is acceptable

05	1 st TGA	2 – 3 Nov. 2007	---	Facility is acceptable
06	2 nd TGA	7 – 9 May 2011	---	Facility is acceptable
07	1 st DMA	5 – 8 Nov. 2007	---	Facility is acceptable
08	2 nd DMA	28 – 30 Nov. 2011	10 Jan. 2012	Facility is acceptable
09	PMDA-JAPAN	17 – 20 May 2011	---	Facility is acceptable
10	KFDA-Korea	26 – 27 Sept. 2011	---	Facility is acceptable
11	Romania	15 – 17 Nov. 2011	---	Facility is acceptable
12	Berlin	30 July – 1 Aug. 2012	---	Facility is acceptable
13	DCA-AP, India	7 Nov. 2012	---	Facility is acceptable
14	ISO 9001:2008	17 – 18 Aug. 2012	---	Facility is acceptable

Focus of the inspection

The inspection focused on the production and control of **Ritonavir Form-I (APIMF27), Levofloxacin Hemihydrate (APIMF162) and Moxifloxacin hydrochloride monohydrate (APIMF188)** APIs. The inspection covered all the sections of WHO GMP for APIs (equivalent to ICHQ7), including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1: 26 November 2012

The first day of inspection covered the following:

- Opening meeting which covered the following:
 - Introduction of the inspectors and WHO/PQP.
 - Scope of the inspection and confirmation of the inspection schedule.
 - Introduction of the company staff.
 - Company presentation highlighting the company overview, site description, production and QC capacities, quality management and assurance systems, summary of manufacturing processes, major equipment and product range, inspection history.
- Personnel Policies: Organization charts, Job descriptions (JDs) and personnel training
 - Organogram for QA and Job descriptions of Deputy General Manager-QA, Manager-QA, Deputy manager-QA, Assistant manager-QA, Officer-QA.

- Organogram for QC and Job descriptions of GM/HOD-QC, Manager-QC, Deputy Manager-QC, Executive-QC:
 - The personnel to deputise key personnel were not specified in the job descriptions of key personnel.
 - The designations of the QC staff were not mentioned in their job descriptions.
- Production Department Responsibilities.
- Production Department Job Descriptions.
- Maintenance Department Responsibilities.
- Maintenance Department Job Descriptions.
- Training policies, procedures and records.

The outcome of the review of personnel issues is summarised in section 2.2 below.

- Good Document Practices
 - Documentation Requirements
 - Preparation of Master Formulae and Batch Production Records

The outcome of the review on documentation system is summarised in section 2.5 below.

- Quality management system (QMS) and related activities
 - Standard Operating Procedures (SOP) on Quality Assurance and Regulatory Affairs (RA) department responsibilities
 - SOP for QA release of products for dispatch.
 - SOP for label inspection, issue and reconciliation
 - Annexure referring to SOPs on issue and retrieval of product labels and QA product release.
 - SOP on preparation of certificate of analysis (CoA).
 - There was contradiction between the SOP on product release and the JDs of Deputy Manager-QA and Officer-QA on their exact roles in product release.
 - There was contradiction between the SOP on preparation of CoA and the JDs of selected staff on their role in preparation and approval of CoA.

The outcome of the review on QMS is summarised in section 2.1 below.

- Product Quality Reviews (PQR)
 - SOP on preparation of annual review report.
 - Annual Product Review for Ritonavir (Form-1) for 2011.
 - Annual Product Review for Ritonavir (Form-1) for 2010.
 - Product Quality Review for Moxifloxacin Hydrochloride for 2011.

The outcome of the review on PQR is summarised in section 2.1 below.

- The X-RPD for one batch of Ritonavir that had been produced from an intermediate with out-of-trend (OOT) results was reviewed and found concordant with that of working standard, although records showed that the refractogram of the WS was acquired in January 2010 while that of sample was acquired in June 2010.
- Hold time studies for intermediates: Result supported hold-time of 12 months for each of the intermediates DIS-I, DIS-II and DIS-III.
- Visit of the storage facilities (including outdoor storages) for:
 - Solid starting materials reception, sampling, storage, dispensing and related records. The key starting materials for the Ritonavir and Levofloxacin were out of stock but those for Moxifloxacin were in stock. Material dedicated scoops were used for dispensing and solvents to be used for cleaning were specified in an SOP available in the washing area.
 - Packaging materials reception, sampling, storage, dispensing and related records.
 - Intermediate products storage areas, temperature monitoring and related records.
 - Drum store for liquid raw materials in drums - sampling, storage, dispensing and related records.
 - Solvent Tank Farm for bulk solvents: Receiving (transport tankers), sampling and storage (tank farms). Fresh solvents were tested before addition into tanks but the mixture was not tested immediately for a new reference, but only on monthly basis. Solvent were pumped into day tanks in the production areas from which required amounts were dispensed into reactors.
 - For finished products (APIs): packaging, labelling, storage and release plus related records. The three API under the inspection scope were in stock approved by QC and waiting for QA release. The location of one of the batches of Levofloxacin was wrongly indicated to be in location 2 but was actually in location 3. Serially numbered drum (metallic) and bag (PVDC) seals with Hetero's name and logo were in place.

Day 2: 27 November 2012

Feedback was given on the previous day's inspection and the company was given an opportunity to provide any preliminary response.

The inspection of the following issues and areas followed:

1. Annual Product Review for Levofloxacin Hemihydrate (LEO) for 2011. Observation are summarised in section 2.1 below.
2. Water treatment system:
 - Raw water was supplied from the Municipality Water Supply System, chlorinated and treated through a Multi-Grade Filter (MGF), Softener, 5µ filter, Ultrafiltration and Reverse Osmosis (RO). This was pumped to the workshops and used as process and washing water.

- Purified water was then prepared by dosing with SMBS, antiscalant and pH adjustment, through 1µ filter, RO-01, TOC reduction UV, TOC on line monitor, and UV, RO-02, EDI, UV and stored in a steam jacketed tank.
 - The distribution of purified water included a mother tank and 5 sub-distribution tanks for 5 distribution loops:
 - i) A tank for blocks A, B and E.
 - ii) A tank for blocks C, D and H.
 - iii) A tank for blocks F and PB-II.
 - iv) A tank for blocks G and I.
 - v) A tank for blocks J, K and PB-I.
 - The system was sanitised once every 15 days and monitored on line and offline.
3. Visit of the manufacturing facilities for synthesis, purification, powder processing and packaging of:
- Block I: including controlled areas: used for the manufacture of Moxifloxacin hydrochloride.
 - Block E: including controlled areas: used for the manufacture of Levofloxacin.
 - Block D: including controlled areas: used for the manufacture of Ritonavir Form-I.
 - Two Intermediate drying areas.
 - All these were multipurpose facilities (premises and equipment).

Day 3: 28 November 2012

Feedback was given on the previous day's inspection and the company was given an opportunity to provide any preliminary response.

The inspection of the following issues and areas followed:

1. Review of documents
 - Cleaning, see summary in sections 2.4 and 2.11 below.
 - Vendor Qualification, see summary in section 2.6 below.
2. Inspection of the Quality Control Department
 - Sample inward registers for raw materials, In-process control, finished goods (APIs) and stability.
 - SOP on sampling procedures.
 - Reviewed records of qualification, operation, calibration and maintenance of HPLCs, IRs, GCs and XRPDs.
 - Review of analysis is of the representative batches of API starting materials for Ritonavir, Moxifloxacin HCL and Levofloxacin Hemihydrate.
 - Records of preparation, storage and use of working standards for Levofloxacin Hemihydrate (LFWS), Moxifloxacin HCL (MXWS) and Ritonavir Form I (RTWS).
 - Review of analysis is of the representative batches of APIs.
 - Stability chambers of various conditions.

The outcome of the review of quality control facilities and activities is summarised in section 2.10 below.

At the closing meeting, the inspectors gave feedback on the inspection observations of the day and the entire inspection. The company was informed about the procedures and timelines for the report, Corrective and Preventive Actions (CAPAs) and WHO Public Inspection report (WHOPIR).

2.1 QUALITY MANAGEMENT

The company had established and documented a system for managing quality supported by an organisation structure and job descriptions, policies, procedures and relevant records.

The quality unit was divided into QA and QC departments. Quality Assurance and Regulatory Affairs department responsibilities were defined in an SOP. Procedures were in place to handle changes, deviation and evaluation of materials before they are released or used. The responsibility for QA release of products/APIs for dispatch was described in an SOP. The systems in place were generally adequate and the observations noted were subsequently adequately addressed and confirmed through written CAPAs.

Details of responsibility for production were given in an SOP on “Production department responsibilities”. Aspects defined in WHO GMP for APIs (ICHQ7), clause 2.3, were covered. Responsibilities were described in job descriptions for each job position from Junior Chemist to Senior Manager. Completed Job Descriptions for each employee were held in the QA Department. There were some observations noted which were subsequently adequately addressed.

Product quality reviews were performed based on SOP on preparation of annual review report. Product Quality Reviews were conducted in two parts. One was concerned with API-specific issues, Annual Review Report, whereas other details such as cleaning, equipment were covered in the General Review Report.

The following PQRs were reviewed:

- Annual Product Review for Ritonavir (Form-1) for 2011: Ritonavir Form-I was produced in a multiproduct block D under Ph.Eur and USP standards with specified range of output batch size, storage conditions and defined shelf life. The process had been validated and commercialised in 2005 but no batch had been produced in 2011. Four batches were under stability, with only one under 30°C/75%RH and all under 25°C/65%RH. The only production related changes was revision of the cleaning procedure following periodic review and there were no changes in QC. Three analytical methods had been validated. There were no complaints, returns, recalls, incidences, deviations, OOS and reprocessing. No new vendor of key starting materials was added although the performance and audit status of the existing one was not discussed. Five regulatory inspections had been conducted on the site but none had specifically covered Ritonavir Form-I. There was no provision for review of recommendations of the previous APR and effectiveness of the CAPAs.

- Annual Product Review for Ritonavir (Form-1) for 2010: Several batches of specified output batch size were manufactured at each of the 5 stages of synthesis and production in a multiproduct block D. There were 6 planned deviations, 7 changes (1 in production and 6 in QC). There were no complaints, returns, recalls or OOS. Two new vendors had been added for key starting materials. The block had been inspected by local authorities and one foreign agency. Data was trended and some OOT results were noted but not discussed and no recommendations were made.
- Annual Product Review for Levofloxacin Hemihydrate (LEO) for 2011. Levofloxacin Hemihydrate was produced in a multiproduct Block E under USP + In-house specifications with a specified range of output batch size. The retest period was extended during the year. The process was validated and commercialised in 2009. Several batches had been produced at each of the 4 stages. Cleaning validation in relation to Rabeprazole Sodium and several analytical validations were conducted. Four batches were on stability including one placed on on-going stability. There were no complaints, returns, recalls, incidences, OOS and reprocessing. The DMF had been submitted to several countries, while the block was also inspected by several foreign agencies, but none had specifically covered Levofloxacin.
- Product Quality Review of Moxifloxacin Hydrochloride Form 1. Production of material made in 2011 was reviewed. There were no recalls, OOS results, reprocessed batches, incidents or deviations. There was one complaint, which resulted in the batch being returned. Investigation did not uphold the complaint. There were four Change Controls. Three referred to analytical methods and the fourth to Production. Stability data reported indicated that the API was stable under the defined conditions.

The observations made during this review were subsequently adequately addressed by the company through written CAPAs.

2.2 PERSONNEL

Training was conducted according to an SOP on “Training”. Content was thorough and all departments were included. Training records were kept. Lists of attendees were kept in a database.

The effectiveness of training was assessed, at the end of each session, by means of a question paper. Selected examples were reviewed and found to be adequate.

An example of On-the-Job training was the introduction of the process to make Levofloxacin. This was initiated by raising a Planned Deviation under the Change Control procedure.

Training records for one staff of the QC department indicated that his training covered induction, GMP, SOP and specific QC related topics and records of its evaluation were available.

In order to ensure adequate hygiene, personnel donned protective clothes appropriate to the required level of product and personnel protection. Dining facilities were separate from manufacturing areas.

2.3 BUILDINGS AND FACILITIES

The site manufactured API in multipurpose facilities (blocks and equipment).

Ritonavir was produced in Block D with 2 equipment lines which produced on line 1: 2 variants of Pantoprazole Sodium Sesquihydrate and Esomeprazole magnesium dihydrate on **line 2**: Citalopram Hydrobromide and **Ritonavir**.

Levofloxacin was produced in Block E with 2 equipment lines which produced on line 1: 4 Omeprazole variants and **on line 2**: 5 variants of Rabeprazole Sodium and **Levofloxacin**.

Moxifloxacin was produced in Block I with 4 equipment lines which produced on line 1: Aprepitant, Felbamate and 2 variants of Montelukast Sodium; **on line 2**: Cyclobenzaprine Hydrochloride, Riluzole and 2 variants of **Moxifloxacin** (*anhydrous and monohydrate*); on line 3: 2 variants of Dorzolamide and Ziprasidone; and on line 4: Atovaquone, Solifenacin and Proguanil.

Overall, the design and construction of buildings were appropriate to the activities conducted. Pest control systems (insectocutors and traps) were installed as required.

Lighting levels appeared to be adequate.

There were two water purifications systems, one to produce potable water and the second to provide Purified Water USP. Installations appeared adequate and some observations regarding the operation noted were subsequently adequately addressed through written CAPAs.

There were several examples of inadequate standards of cleaning and maintenance. The premises used for drying intermediates for Levofloxacin intermediates were particularly in a very poor state of repair. These observations were subsequently adequately addressed by the company and evidence submitted through written CAPAs.

2.4 PROCESS EQUIPMENT

Overall, process equipment was of a suitable design using satisfactory product – contact materials. Construction was generally adequate. In some cases, process equipment were not adequately installed and maintained to suit the operations carried out. Throughout the factory there were examples of pipework inadequately supported, or held in place with string instead of correct supports being used, although these were subsequently adequately addressed and evidence provided through written CAPAs.

The equipment cleaning procedure was described in "Cleaning of Equipment", SOP.

The cleaning procedures had been adequately validated. For Block I, "Protocol for Cleaning Validation of Multiple Product Cyclobenzaprine Hydrochloride to Riluzole to Moxifloxacin Hydrochloride", gave details of requirements, drawings of equipment and where swabs should be taken. Details included surface areas of equipment. Criteria included visual checks and reference to therapeutic daily dose (TDD).

For Block E, the equipment line used to make Levofloxacin was used also to make Rabepazole Sodium of different specifications. Therefore only Levofloxacin and Rabepazole Sodium were considered in the relevant protocol for cleaning validation. Details included calculation of maximum allowed carry over residues (MACO).

2.5 DOCUMENTATION AND RECORDS

The company had a comprehensive documentation system including master production instructions, batch production records, standard operating procedures, specifications and standard testing procedures, registers and log books. The system provided for their controlled distribution and regular review. Some lapses in the documentation practices and control were seen but these were subsequently adequately addressed.

2.6 MATERIALS MANAGEMENT

Materials were received into the Solids Raw Material Warehouse according to SOP on "Receipt, Verification Quarantine and Sampling of Raw Materials".

Several examples were reviewed. Documentation and records maintained could facilitate traceability to the approved vendor, analytical reports, storage location and use.

Packing Materials were stored on the first floor of the Raw Materials Warehouse.

There was a separate storage area for liquid raw materials packed in drums. These too were adequately handled.

The qualification of vendors of raw materials and packing materials was performed by QA and QC using "Vendor Qualification" SOP. Also included were outside contractors. External laboratories were audited every three years or as required. Suppliers of key raw materials were audited initially and then after three years. Critical raw materials were only audited on a need basis.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

The products were manufactured in multipurpose facilities (blocks and equipment) with clear instruction not to manufacture more than one product at a time in the same area (campaign basis). The manufacturing processes were guided by elaborate Batch

Manufacturing Records (BMRs) and were generally under control with adequate in-process checks (IPCs).

Ritonavir Form-I is manufactured in a multiproduct Block D in five stages namely: DIS-I, DIS-II, DIS-III, DIS-IV and DIS-V: Ritonavir Form-I (Wet material is dried in a tray drier, then milled, micronized and packed). The expected yield was specified with an allowed range.

Levofloxacin Hemihydrate is manufactured in a multiproduct Block E in four stages namely: LEO-I, LEO-II, LEO-III and Levofloxacin Hemihydrate (Wet material is dried in a tray drier, then pulverised, blended, sifted and packed). The output batch size was specified. Some issues were noted with pH adjustment and monitoring in stage I but these were subsequently adequately addressed.

Moxifloxacin Hydrochloride Monohydrate is manufactured in a multiproduct Block I in four stages namely: JAN-I, JAN-II, JAN-III and Moxifloxacin hydrochloride monohydrate (Wet material is dried in a tray drier, then pulverised and packed). Expected yield for Moxifloxacin Hydrochloride was specified with an allowed range. Concerns about the compatibility of the reaction mass with the reactors at some stages were subsequently addressed.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging operations were conducted in designated areas following standard procedures and adequate records were maintained.

Ritonavir Form-I is packed in double - transparent in black - polythene bags and into a High Density Polyethylene (HDPE) container.

Levofloxacin Hemihydrate is packed in double - transparent in black - polythene bags and into an HDPE container.

Moxifloxacin Hydrochloride Monohydrate is packed in double - transparent in black - polythene bags lined with Triple Laminate Medium Barrier (TLMB) bag and into an HDPE container with silica gel pouch.

Packaging materials including labels were approved by QC before use. Labelling and the records maintained could adequately facilitate traceability.

2.9 STORAGE AND DISTRIBUTION

There were warehousing facilities of adequate size for the materials stored. Storage conditions were regularly monitored and recorded.

Distribution records were detailed enough to facilitate traceability of batches especially in case of complaints and recalls.

2.10 LABORATORY CONTROLS

The Analytical Department was adequately equipped for the work being conducted. Sample inward registers were maintained for raw materials, in-process control, finished goods (APIs) and stability. Sampling was performed according to SOP on sampling procedures.

Records of qualification, operation, calibration and maintenance of HPLCs, IRs, GCs and XRPDs were reviewed. At the time of the inspection, the column used for the release of Moxifloxacin Hydrochloride was consistent with the requirements of the Ph.Eur monograph. The column approval details were recorded in the Column Performance Report, using form QC-112. The records regarding HPLC columns, and the storage of columns not in use were adequate.

Records of analysis of the representative batches of API starting materials were reviewed. For a batch of the API Starting Material (APISM) for Moxifloxacin Hydrochloride, all 20 containers were sampled and identified with IR. The spectra of the samples were compared with that of the standard scanned the same day. Raw data and results of chromatographic purity were reviewed and no concerns were noted. Raw data and results of chromatographic purity, chiral impurity and assay a batch of one of the APISM were reviewed and no concerns were noted.

For Levofloxacin Hemihydrate, raw data and results of chromatographic purity, piperazine impurity and assay of a batch of the APISM were reviewed and no concerns were noted.

Records of preparation, storage and use of working standards were reviewed. In case of Levofloxacin Hemihydrate: LFWS, 30 vials (one for each month and 6 as buffer stock) were prepared each time with a validity of 2 years. The lot reviewed was prepared from an approved lot of the API and standardized against USP standard GOJ406. The XRD results were obtained from the original results of the source batch. Other working standards reviewed included: Moxifloxacin Hydrochloride: MXWS and Ritonavir Form I: RTWS. This review indicated that reference and working standards were adequately prepared, stored and used.

Records of analysis of representative batches of APIs were reviewed. In case of Moxifloxacin, the raw data and results of analysis (assay and isomer impurity) of selected batches were reviewed and no concerns were noted.

The site had stability chambers of various conditions, including 25⁰C/60%RH; 30⁰C/65%RH; 40⁰C/75%RH and Standby. It was stated that the site uses the chamber at hetero Labs Unit I for conditions of 30⁰C/75%RH. The following batches were established to be under conditions 30⁰C/65%RH:

- Levofloxacin: 2 batches produced in September 2012.
- Moxifloxacin: 3 batches produced in October 2012.
- Ritonavir: 3 batches produced in September 2012.

2.11 VALIDATION

Policies of validation and qualification were outlined in the validation master plan. The manufacturing processes for the three APIs had been validated: Ritonavir Form-I in November 2005 (Block D: $51 \pm 1.5\text{kg}$ batch size), Levofloxacin Hemihydrate in May 2009 (Block E: $210 \pm 10\text{kg}$ batch size) and Moxifloxacin Hydrochloride Monohydrate in April 2010 (Block I: $46 \pm 2.5\text{kg}$ batch size).

Cleaning procedures had been validated and examples reviewed (see Part 2.4 above) did not raise any concerns.

2.12 CHANGE CONTROL

There was an established procedure for managing changes. These were documented evaluated and approved before implementation. Several examples were reviewed with no issues noted.

2.13 REJECTION AND RE-USE OF MATERIALS

The site did not use recovered solvents or materials for the APIs submitted to for WHO-PQ. The records reviewed also did not indicate that any materials related to the 3 APIs in focus had been reprocessed or reworked in the last 2 years. The policies for reprocessing and reworking were however in place and no concerns were noted.

2.14 COMPLAINTS AND RECALLS

There were adequate procedures for handling customer complaints and product recalls. No complaint had been received for the APIs in focus and no batch of these APIs had been recalled.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

According to the company, no manufacturing activity was contracted out. A total of 16 parties were listed as contracted to carry out various analytical work, but due to time constraints, this aspect was not reviewed.

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, **Ritonavir Form-I (APIMF27), Levofloxacin Hemihydrate (APIMF162) and Moxifloxacin hydrochloride monohydrate (APIMF188) manufactured at Hetero Drugs Ltd, Unit 1, Survey Nos. 213, 214, and 255, Bonthapally Village, Jinnaram Mandal, Medak District, Andhra Pradesh, India** were considered to be manufactured in compliance with WHO GMP 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.