

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

Name of Manufacturer	Signa, S.A. de C.V.
Unit number	NA
Production Block	Plant A, Plant C, Plant D and Plant E
Physical address	Signa, S.A. de C.V. Av. Industria Automotriz No. 301, Zona Industrial Toluca, Toluca, Estado de México, C.P. 50071, MEXICO Tel: (52) 722 226 1100 Fax: (52) 722 226 1101
Contact person and email address.	1. Mr. Oscar Vivanco, President & General Manager E-mail: ovivanco@signa.mx 2. Mr. Pedro Gorgonio, Director of Quality E-mail: pgorgonio@signa.mx
Date of inspection	26 – 28 March 2012
Type of inspection	Initial inspection
Active Pharmaceutical Ingredient(s) included in the inspection	WHOAPI-143, Lamivudine methanol solvate
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

Signa S.A. de C.V, here after known as Signa, is a privately owned company located at Av. Industria Automotriz No. 301, Zona Industrial Toluca, Toluca, Estado de México, C.P. 50071, MEXICO. It was established in 1961 while the manufacturing of active pharmaceutical ingredients (APIs) started in 1965. Although the initial focus was to supply the Mexican market, it reorganised in 1994/1995 to meet the requirements of the highly regulated market.

According to the SMF and company presentation at the opening meeting, the site is located on 10,112 acres of land with the following facilities:

- 4 production plants (Plant A, C, D & E) with total reaction capacity of 93,645 gallons
- 2 distillation column systems
- 21 finishing rooms, including 10 FP rooms with controlled environments
- 3 warehouses: raw materials, intermediates and Finished product
- Solvent storage tank farm
- Analytical operations/quality control laboratories
- R&D process and analytical laboratories
- Utilities like process water, cooling water, compressed air, steam, chilled water, nitrogen, etc.

The site employed 403 staff (*10 PhD, 35 Masters, 116 Bachelor and 100 Technicians*) distributed as:

- | | |
|-----------------------------------|-----|
| • General Management | 2 |
| • Technical Direction (R&D) | 38 |
| • Risk Engineering and Management | 12 |
| • Engineering Direction | 51 |
| • Logistics Direction | 25 |
| • Production Direction | 193 |
| • Quality Direction | 59 |
| • Comptrollership | 9 |
| • Human Resources Management | 10 |
| • Information Technology Mngt | 4 |

The company stated that 33 products (*SMF states over 40 products*) were currently manufactured in its multipurpose facilities and supplied to the domestic, American, Canadian, Japanese, European and South American markets. These were typically API intermediates and APIs for use in OSD formulations. None included antibiotics (including penicillin, cephalosporins), agrochemicals or cytotoxic materials although it was stated that cytotoxic products may be produced on campaign basis with appropriate control measures.

History of WHO and/or regulatory agency inspections

This was the first inspection by WHO-PQP. In México, the Food and Drugs Act sets out the legal requirements for the production and sale of Active Pharmaceutical

Ingredients, however, at present, no regulatory framework or licensing system is in place. The site had been inspected by USFDA (1995, 2000, 2004, 2009 and 19 – 23 March 2012), PMDA Japan (2008) and Mexico SSA (2000, 2003, 2004, 2008 and 2011). It had TGA pre-clearance expiring 30 January 2014.

Focus of the inspection

The inspection focused on the production and control of Lamivudine methanol solvate API in Plant C and A. The inspection covered all the sections of WHO Good Manufacturing Practices for Active Pharmaceutical Ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1: 26th March 2012

The following area and aspects were covered during the first day of inspection: covered introductions and presentation of the company and the site.

- The opening meeting attended by the top management and heads of departments of the site
 - Introductions
 - Update on the WHO Medicines Prequalification Programme
- Brief presentation of the company and of the activities carried out on the site:
 - Company overview, site description, production and QC capacities, quality management and assurance systems, major equipment and product range, inspection history.
- Personnel Policies: *Organization charts, Job descriptions.*
 - SOP for preparation of organisation charts and organisation charts for site, Production, Engineering, Quality control and Quality assurance.
 - SOP for preparation of job description (JD) and job descriptions of key personnel
 - SOP on quality management with a section on deputisation.
- The training programme and records of the coordinator of release and of two QC technicians were examined.
- SOP of batch release was examined and found sufficiently detailed with description of the several checks necessary to release the products.
- SOP of Complaints, returned materials and recalls were examined. They are considered sufficiently detailed.
- OOS SOP was examined and found sufficiently detailed. Two OOS of the starting material of lamivudine (LAM-10) were examined.
- SOP for management of deviations was examined and found sufficiently detailed.

- SOP on assigning of material codes was reviewed. There were specific prefixes for codes for the various categories of materials.
- SOP on preparation of the manufacturing code and batch number was reviewed.
- SOP on document control was reviewed and it provided for preparation, review, approval, training on new SOPs and retrieval, archiving and destruction of superseded SOPs.
- SOP on revision of specifications and analytical methods was reviewed and no issues were noted.
- SOP on Product quality review (PQR) was reviewed. As validation of Lamivudine was completed late in 2011, no PQR had been prepared so far.

The implementation and scale up report for Lamivudine was presented and reviewed. It covered two processes.

- SOP on supplier qualification was reviewed. It provided for 2 levels of approval: level I and. Level II.

The audit report of the supplier of the APISM on 09 – 10 November 2011, the responses were received on 13th January 2012 were reviewed.

Day 2: 27th March 2012

Feedback was given on the previous day's inspection and the company gave clarification on some outstanding issues:

- The various material codes used to identify Lamivudine from the different processes and the controlled according to different specifications for the different markets. The company clarified why the original process had material code (04903) later than the optimized process (04901).
- The supplier questionnaire filled by the supplier of LAM10 the APISM.
- A statement from the supplier of the APISM dated March 28, 2012 about its relationship with the one mentioned in the APIMF.
- Reviewed an example of planned deviation for reprocessing of an intermediate.

The following issues and areas were inspected:

- Change control management described in two procedures, one for change in documentation and another for changes to equipment.
- Warehouse for Starting materials, including receiving, sampling, storage and dispensing procedures. All materials used in the manufacture of Lamivudine were verified to be in stock with the exception of the APISM (last stock was received in November 2011).
- Tank farm for solvents and the procedures including receiving, sampling, storage and dispensing procedures.

- Plant A following the process scheme and the equipment, including the powder processing areas. Batches reviewed showed that some batches were processed in both plant A and C. Cleaning procedures were reviewed.
- Plant C to examine equipment listed as used for Lamivudine manufacturing process and the cleaning procedure for reactors.
- Plant D to review Reactor DR28 which was used for the purification step of the APISM.
- Finished Products Warehouse including procedures for labeling Lamivudine for commercial distribution. The procedures for final sampling, testing, sealing and labeling was reviewed.

Day 3: 28th March 2012

Feedback was given on the observations of the previous day inspection and clarification was received from the company.

Inspection proceeded with inspection of the following areas:

1. Quality control laboratory including:
 - Sample reception.
 - Analysis of methanol.
 - Analysis of succinic acid and its specifications.
 - Analysis of the APISM.
 - Sampling procedure.
 - IPC sampling and testing: examined TLC used to control completion of the first reaction of the APISM.
 - Release analyses of a Lamivudine batch.
 - Maintenance of GC and related SOP.
 - Maintenance of HPLC: examined logbook of one HPLC.
 - Maintenance of KF.
 - Equipment qualification: HPLC, GC, Malvern, KF etc.
 - Reagent storage: examined expiry and refrigerator.
 - Preparation of solutions: dedicated book for the preparation of the solution with the impurities mix used for the related impurities test of Lamivudine.
 - Standard management: qualification and refrigerator for their storage.
 - Stability: chamber conditions and presence of the samples and their packaging for the ongoing study.
 - Method validations: examined the validation of the HPLC method 1 for related impurities.
 - Retention samples storage and monitoring.
2. Other points examined:
 - Specifications for methanol
 - Warehouse for intermediate materials was visited. Noted records of storage of purified APISM.
3. Process validation of Lamivudine (Code 04903: original process) in plant C and Plant A:
 - Plant C. March 2011: Protocol No. PVP:C:LAMFA:01/11:

- Plant A. November 2011: Protocol No. PVP:A:LAMFA:02/11 and report No. RVP:A:LAMFA:02/11:
4. The HVAC system for Plants A and C.
 5. Water system was reviewed beginning with layout diagrams, followed by inspection of the physical installation, sampling and testing procedures plus 6 monthly trends.
 6. Records of recovered methanol were reviewed and confirmed to have either been sold or used in preparation of brine for chillers.
 7. Reviewed the controls in place to ensure that APIs of the approved material code and specification were selected and distributed as controlled under a SOP and checklist for product release by QA.
 8. SOP on Cleaning validation, general protocol and equipment chain verification report for Lamivudine for 2011 approved on 14.03.2012. These were provided via e-mail on request after the inspection.

At the closing meeting, the inspectors gave feedback on the inspection observations of the day and the entire inspection. Clarification was received on some observations and there was consensus on the observations including those that require urgent attention (maintenance of Plant C, qualification of suppliers, PQR). The company was informed about the procedures and timelines for the report, CAPAs and WHOPIR.

2.1 QUALITY MANAGEMENT

Organogram, Unit Responsibilities and Job Descriptions (JD)

The site was headed by a General Manager who supervises directors for Production, Engineering, Quality among others. This organisation was supported with an organisation chart.

The production department was headed by a director who supervises managers for each plant and the in-charge production planning (vacant). The organization chart had no reference to the SOP and the JD of the director of Production did not indicate who would deputize him in his absence. There was a JD for the plant C while there was another one jointly signed by the managers of Plants A, C and D. This duplication was an indication of inadequate change control and conflict in responsibility. These issues were adequately addressed with CAPAs.

QA unit had the following organogram: at the apical position there was the Director of Quality and then several managers who share the different QA functions: QA Manager; Validation Manager; QC Manager; Manager of analytical services; Manager of regulatory affairs.

In particular the QA Manager had several employees who share the release responsibility; Audit responsibility and documentation responsibility. Furthermore,

the responsible for release directed two other functions: the coordinator of release and the inspector of sampling. The Job descriptions of the QA head and the coordinator of release were reviewed and it was observed that the release was made by coordinator of release with the supervision of the responsible of release.

QC had responsibilities subdivided among several supervisors. The Manager of QC coordinates a supervisor of raw materials and intermediates; supervisor for finished product (APIs); supervisor of in-process controls; and a supervisor of equipment and analytical instruments.

The Job description of the QC responsible and the supervisor of finished products were examined. It was observed that the approval of the CoA was reported among the responsibilities of the supervisor of the finished products but this was not congruent with the SOP of CoA management which stated that the CoA are approved by QA functions and QC only carry out revision of the analytical results. The Job description was subsequently updated to be in line with the relevant SOP.

Beside this structure the delegation policy was reported in an SOP and there is a matrix for substitution where delegation authorizations are indicated. This matrix reflected in practice the organogram so that lower functions are authorized to substitute higher functions but specific tasks were neither indicated in this matrix nor in the job descriptions and therefore it was possible that personnel assigned to management of documentations could substitute personnel with more technical duties such as batch release. In fact during examination of a change control documentation regarding change to an analytical method the QA approval was done by the documentation responsible. The lack of tasks definition in the delegation matrix did not guarantee that personnel with adequate competence can accomplish the tasks when substituting higher functions. These issues were subsequently adequately addressed.

Batch Release

SOP of batch release was examined and found sufficiently detailed with description of the several checks necessary to release the products. This SOP incorporated also instruction for release of raw materials and intermediates. Further details of release operations such as input in the informatics system and change of status of the products were reported in detail in another SOP.

Product quality Review:

SOP on Product quality review (PQR) provided that PQR would only be prepared after validation and scale up and would cover the calendar year for all material codes under one report but with sub-analysis. It did not provide the period within which report should be completed. These issues were subsequently adequately addressed. As validation of Lamivudine was completed late in 2011, no PQR had been prepared so far.

The implementation and scale up report for Lamivudine was presented and reviewed. It covered 10 batches through the original process and 4 batches through the optimised process, 3 of which were reprocessed by either recrystallization or re-milling. All these batches were manufactured in Plant C. During the implementation

and scale up, a number of changes in process parameters and equipment were made in both process and some of the batches from the optimized process had to be reprocessed to comply with the specifications. A typographical error in the table comparing the impurity profiles from the two processes indicated that one of the optimised batches had an impurity inconsistent with this process which was included in the statistical analysis but was neither noted nor discussed. Data on some of the reprocessed batches was not included in the report even through the addendum. Despite these observations, the conclusion was the two processes were consistent. The site has however since then concluded that the improvements in the optimised process were not substantive enough to justify the change from the original process and only the original process has been validated in plant C and A (*see notes on validation below*).

The two processes in Plant C and the validation batches produced later in plant A used similar equipment and there was an equivalence report produced by Engineering department to confirm this.

2.2 PERSONNEL

The personnel met generally had the qualification and experience to perform assigned functions. There was training programme for staff. Records reported the programs and the actual training accomplished. For the technician it was foreseen training for new and experienced personnel. The training included theoretical and on the job training and its registration and effectiveness (declared by a supervisor or head) was reported in dedicated forms and in laboratory books for the two examined technicians.

The form for registration of training was also a document which could be used as reference for the list of the tasks which a single employee could accomplish. Beside this form, for each employee, there was a list of SOPs whose training had been done. This list was prepared by the human resource section but it was noted that its update was not controlled and for example for a technician several SOPs were lacking whilst the training was already completed several months ago. It is recommended to control in an adequate timely manner also this list prepared by HR section in order to avoid any incongruence. Measure to address this matter were put in place.

2.3 BUILDINGS AND FACILITIES

The premises were generally designed and maintained in an acceptable manner but there were issue noted in plants A, C and D as noted under production section.

HVAC system:

The HVAC system for Plants A and C was reviewed starting with layouts and design diagrams for pressure cascades followed by inspection of the units in the technical area and the last qualification reports.

The powder processing areas of plant C and A were each supplied by one AHU with no recirculation. The filtration included primary and secondary filters in the plenum and terminal HEPA filter and the areas were designed and qualified to ISO8 level. The qualification 6 monthly and annually covered ACPH, air flow volume, viable

and non-viable particles, temperature, RH and ΔP . It was noted that certain aspects of ISO14644 were not adequately followed (*number locations for particle counting and use of 95% confidence interval*) and the markings of the ducts and balanced manual control dampers needed to be improved. The filters were never cleaned but were monitored by magnehelic gauges (*NMT 1" WC*) and changed as required. Never-the-less, the HVAC system was generally adequate for the purpose used and in addition, adequate corrective measures were put in place.

Water system

The water system was reviewed beginning with layout diagrams, followed by inspection of the physical installation, sampling and testing procedures plus 6 monthly trends.

Water was sourced from a bore hole within the site, filtered via 20 μ and 5 μ filters before being stored in 2 tanks fitted with spray balls and hydrophobic vent filters. The distribution loop had 52 user points and there was a heat exchanger (60 $^{\circ} \pm 5^{\circ}\text{C}$) in the return loop. The water from the well was sampled monthly while the distribution, return and at least one user point were sampled weekly.

Water was tested according to specifications of potable water set by the relevant government agency although the water was sourced from an in-house bore hole. Never-the-less, the water was comprehensively tested by a contract lab in the USA once a year. It was recommended the results of the comprehensive testing should be used to evaluate the appropriateness of the specifications used for routine in-house testing.

2.4 PROCESS EQUIPMENT

Equipment used to produce Lamivudine included glass-lined and SS reactors, Centrifuges, crystallizers, portable sparkler and robo filters, dryers and mills.

The main pieces of equipment were fixed although some small pieces of equipment were portable and were moved between different plants (e.g. sparkler filter). Reactors had top or bottom fitted temperature sensors with range of -30 $^{\circ}$ to 150 $^{\circ}\text{C}$ which were labeled to be within their calibration status. The centrifuges were designed to discharge from the bottom and mounted with their own scrapers.

There were fixed drawing points for solvents and dedicated hoses together with portable flow meters used to transfer solvents to the various reactors as required. Issues were noted with status labeling, cleaning and use logs for portable equipment.

There were two general cleaning procedures for process equipment depending on whether it was batch or product change (*see more details under production procedures below*).

There was a maintenance programme for equipment.

2.5 DOCUMENTATION AND RECORDS

SOP on document control was reviewed and it provided for preparation, review, approval, training on new SOPs and retrieval, archiving and destruction of superseded SOPs. There was a clear designation and identification of master, controlled and uncontrolled copies. Whereas the distribution and retrieval of controlled copies was well documented, their destruction was not. The revision history of this SOP was not presented in a manner to facilitate following its history. These issues were subsequently adequately addressed.

2.6 MATERIALS MANAGEMENT

SOP on supplier qualification was reviewed. It provided for 2 levels of approval. In case of suppliers of key starting materials, it provided for evaluation of a supplier filled questionnaire, 3 samples, CoA, route of synthesis, BSE/TSE declaration, analysis and use test by R&D to get level I approval. Level II was achieved only after 3 successful plant trials.

It was noted that a physical site audit was not mandatory to achieve level II approval. The supplier of the APISM was only audited on 09 – 10 November 2011, the responses were received on 13th January 2012 and by the time of this inspection, not all the observations had been closed but it was on the current approved suppliers list effective 20.12.2011 as level II. Moreover, the supplier questionnaire filled by the supplier and the audit report did not indicate other materials handled on the site and whether the APISM was manufactured in a dedicated or multipurpose facility. Both documents did not clarify the relationship between supplier mentioned in the APIMF and the site inspected. A statement from audited supplier dated March 28, 2012 confirmed that the supplier mentioned in the APIMF was their subsidiary responsible for sales.

Other sources of APISM declared in the APIMF had not even achieved level I approval and there was no justification to include them in the APIMF. The company had no information on whether any of their material had been used to formulate and product used in bio-studies.

All the above issues were subsequently adequately addressed.

Material codes were used to differentiate Lamivudine produced from different processes and meeting different specification for the different markets. The history of the current codes in use was reviewed.

Warehouse for Starting materials:

The warehouse was inspected where inventory control was through an ERP (BPCS) and reviewed material receiving and sampling procedures. This involved verification of the approval status of the supplier and the condition of the containers. The 2 sampling/dispensing rooms had air and nitrogen supply while one had earthing for liquids. Air through these rooms was only exhausted through the dust extractor. The balances were of appropriate range, were calibrated and verified adequately. The logs books were issued by QA and page numbered with indication of total number of pages. The sampling tools were kept by QA while there was only one scoop for dispensing which was cleaned according to SOP. The cleaning solution Sulfocon 30

(Sodium lauryl sulfate 30%) was prepared with water (100ml: 10L), although the type of water was not defined and the tap in the cleaning room did was not labeled.

The temperature and RH in the WH had been mapped during different seasons (March, May and September), action points set (*NMT30°C and NMT80%RH, excursions NMT24 hours*) and were adequately monitored. Material were labeled with status and segregated according to reactivity.

All materials used in the manufacture of Lamivudine were verified to be in stock with the exception of the APISM (last stock was received in November 2011).

Tank farm for solvents:

Inspection of tank farm for solvents indicated that there was a designated place for sampling tankers with facility for earthing, although it had no shade. Fresh solvents were sampled, analyzed and approved before adding them to storage tanks but there was no practice of analyzing the mixed solvent. It was noted that there was planned schedule for cleaning the tanks. There were dedicated discharge hoses and pumps for the different solvents. The lot numbering of solvents was based on the month, e.g. MeOH-MAR-12. The quantity of solvent in the tank was calculated based on a pressure gauge but there was no conversion chart to facilitate the calculation. The solvents were directly filtered into the reactor by the production operator on demand.

Ware house for intermediate materials:

Warehouse for intermediate materials was visited because Company declared the possibility to purify the APISM if not in compliance with the specifications (company was invited to file this variation in the answer to the issues raised in the assessment report of the current submitted APIMF. If it would be used the purified APISM could be stored in the warehouse for intermediates.

In fact three batches of purified APISM had been stored in the past in this warehouse. The management of this warehouse was the same as the other two. Products were divided and identified for their status. Temperature and RH% was monitored and data loggers were found in the warehouse.

The Company had not yet defined specifications for this product being considered as a “reprocessed APISM”. From the examination of the data in the informatics system it was noted that the retest date of the purified APISM batches was one year. This retest date was based on the same retest date of the APISM assigned by the supplier.

Finished Products Warehouse

The warehouse was clean, neat and well controlled (T and RH). See more comments under the section on storage and distribution.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Plant A

The inspection of Plant A followed the process scheme and the equipment train. Final crystallizers, centrifuges, dryers and mills were located in controlled areas designed to ISO8 class under positive pressure (NLT 0.02”WC) with respect to the surrounding

environment. It was noted that portable equipment were moved between different plants (e.g. sparkler filter). Temperature sensors were labeled to be within their calibration status although one of those seen did not indicate the operating range. Batches reviewed showed that some batches were processed in both plant A and C.

A portable flow meter was presented without status label and there was no log book to record and monitor its use and cleaning.

There were two general cleaning procedures for process equipment depending on whether it was to batch to batch or product change (*see more details under Plant C below*). Cartridge filters were claimed to be changed after every batch but there was no instruction or record of the same. There was no limit of campaign (batches or duration) for which the cloth connecting the centrifuge and the dryer or centrifuge bags could be used before changing.

The batch record for Lamivudine did not specify how to take samples from reactors and there was no cross-reference to the SOP for sampling reactors. The sampling process described by the staff and in the SOP could not guarantee that the sample was representative of the reaction mass at the time of sampling and not contaminated with any residues retained between the two valves. These issues were subsequently adequately addressed.

The flow of process and level of segregation in the Pharma area was not optimal as the dried material awaiting milling was stored in the same room where milled materials (final product) were weighed and quantity adjusted in the final container.

Plant C

The visit was based on the examination of equipment listed which could be used for Lamivudine manufacturing process. Plant C was served with 7 points of “process water” all correctly identified except the two C4 points. The person interviewed was the Head of Plant C.

Cleaning procedure for reactors was a general procedure which is applied for all the reactors of the plants when there is a campaign change. It refers to a table of solvents for identification of the cleaning solvent and the final rinsing solvents. The table was attached in the plant and was a QA controlled/approved document. Volumes were indicated in another controlled list and were based on the equipment volume. Efficacy of the cleaning is verified by visual inspection and test of the rinsing solution.

SOP for the rinse of centrifuge specified a visual control of the centrifuge bag. Furthermore in the SOP it was stated that the centrifuge bag is discarded at the end of a production campaign but no limit of use was defined.

Several observations which were noted were subsequently addressed through CAPAs.

Plant D

The reactor in plant D was visited because it was used for the purification step of the APISM which should be submitted in the APIMF. It was noted that this reactor is in the upper part of plant D and the walls do not protected adequately the reactor during

charging of the solids. Based on the submitted CAPAs, measures were subsequently taken to protect the materials during charging.

Deviations:

SOP for management of deviations was examined and found sufficiently detailed. Deviations are investigated by relevant responsible functions and QA ensure their approval. Follow up is reviewed monthly during the meeting of the “Council of Quality” attended by all the main section heads.

Reviewed planned a deviation for reprocessing of a batch of LAMFB but batch number was not changed as per SOP. Other examples reviewed indicated that batch numbers were changed when they were reprocessed (remilled) under planned deviation following OOS with respect to particle size.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging and labelling procedures were in place and well controlled. See section on storage and distribution below for more details.

2.9 STORAGE AND DISTRIBUTION

Finished Products Warehouse was clean, neat and well controlled (T and RH). Batches of Lamivudine under different codes were seen in the warehouse. They were labeled with a retest period on 36 months put according to the APIMF a retest period of 12 months was claimed. The template for the commercial label for Lamivudine (*material codes 04907 and 04908 from original and optimized processes respectively for WHO*) indicated storage condition of “below 25⁰C” when the APIMF stated store between 15⁰ – 30⁰C and the WHO assessors had requested that it be changed to not more than 30⁰C.

The procedures for final sampling, testing, sealing and labeling was reviewed. Once a purchase order was prepared by the office of the General Manager and verified by QA for correct code, the commercial labels were prepared printed and fixed to the drums by warehouse with unique traceable material codes and serial numbers for the seals and drums.

The controls in place to ensure that APIs of the approved material code and specification were selected and distributed as controlled under SOP and checklist for product release by QA were reviewed and no serious issues were noted.

2.10 LABORATORY CONTROLS

The inspection of the quality control laboratory revealed generally adequate facilities and procedure.

- Starting materials were sampled following sampling procedure based on square root of N plus 1. This was confirmed by the sampling and analysis records for the APISM examined.

- The quality control of a sample of fresh methanol for approval before delivery in the tank farm was reviewed. It was noted that methanol had 3 different analytical codes and each code had different specifications. Fresh methanol and recovered methanol from lamivudine process had the same code. Other two codes were for methanol for brine and for methanol recovered from other processes. The analysis of methanol by GC for purity was reviewed including chromatograms, GC equipment and relevant logbook.
- The review of analysis of a batch of succinic acid included assay test by acid-base titration and the balance and burette used. The burette was grade A whose certificate from the supplier had been provided. The specifications were identical to those supplied in the APIMF.
- Review of analysis of a batch of the APISM. The raw data of impurity test were examined. The specifications were in compliance with those submitted in the APIMF.
- An example of the IPC was the control of completion of the first reaction of the APISM by TLC. Data in the BMR was congruent with the duration of reaction. An observation was raised on the raw data.
- Release analyses of a Lamivudine batch. Raw data were present (examined chromatograms of related impurities method 1). The specifications were in compliance with those submitted in the APIMF.
- Maintenance of GC: Verified SOP versus actual last maintenance of GC 6980 including chromatograms and capillary column for control test. Maintenance frequency was 4 months and noted the last three maintenances in the logbook.
- Maintenance of HPLC: examined logbook of HPLC 20 and the frequency was 6 months which was in agreement with the relevant SOP.
- Maintenance of KF: There was a daily check for control of titrant solution assay and weekly check of the precision control with sodium tartrate. No issues were noted.
- Equipment qualification. All the main pieces of equipment (e.g. HPLC, GC, Malvern, KF, etc.) were qualified by the instrument manufacturer generally on a yearly basis.
- Reagents storage: These were stored in a dedicated room without temperature control: The expiry date on the label for sodium tartrate was examined. Reagents which need to be refrigerated were stored in a refrigerator. No issues were noted.
- Preparation of solutions: This was reported in a dedicated book. The preparation of the solution with the impurities mix used for the related impurities test of Lamivudine was reviewed and no issues were noted.
- Standard management. Standards were stored in the refrigerator. Working standards were retested every year. The presence of the impurities standards for related impurities test was verified and examined the certificate of the assay standard for Lamivudine (in-house standard) and its raw data (ID by IR versus Pharmacopoeial standards and related substance analysis.).
- Stability: 5 chambers were present: 2 chambers for 25°C/60%RH and one chamber for each of the following conditions: 30°C/65%RH; 40°C/75%RH; 30°C/75%RH (region IV). The presence of the samples and their packaging for the ongoing study required by WHO at 30°C/65%RH was verified and the batches included were noted. The raw data of the 6 months points for this study

was examined plus the raw data for one batch at 36 months (25°C/60%RH) point related to the stability study submitted in the APIMF.

- Method validations: examined the validation of the HPLC method 1 for related impurities. The method was validated by Apotex and Signa carried out a co-validation to verify the transfer in its QC lab (precision and accuracy were the tested parameters).
- Retention samples were stored in a dedicated room whose temperature and RH% were monitored. Presence of retention samples and adequacy of packaging was checked for last manufactured three lamivudine lots.

Other points examined included the following:

- Methanol specifications did not include benzene test as per issue raised by the assessors. The Company will provide justification for this point in the answer to the APIMF assessment.

Out-of- Specifications (OOS):

OOS SOP was examined and found sufficiently detailed. Two OOS of the starting material of lamivudine were examined. These two batches were received from the approved supplier. The specific OOS investigation was found satisfactory, but it was noted that the supplier had not notified Signa of a change in the final crystallization step of the APISM production therefore showing a lack in GMP agreement which should demand a clear responsibility of the supplier to inform Signa of any possible change to the manufacturing process.

Furthermore as preventative action Signa implemented an alternative process of lamivudine including the possibility of purification by recrystallization in case of problem related to the OOS examined. This is not acceptable until the Company has included this alternative purification steps in the APIMF provided for examination to WHO and included clear indications of when this purification step should be carried out.

2.11 VALIDATION

Process validation of Lamivudine (Code 04903: original process) in plant C and Plant A has been performed

- Plant C. March 2011: Protocol No. PVP:C:LAMFA:01/11:
The Master Processing File used was 04903-Rev-01-0311, following incorporation of changes noted during the implementation plan. The process neither included use of recovered solvents nor recovery of 2nd crop, though these were included in the APIMF.

The batches used, their sizes and yield were noted. .

The major pieces of process equipment were identified although no statement on their qualification status was shown to inspectors even after repeated requests.

Critical parameters were identified and their importance discussed.

The polymorphism is controlled by PXRD in the final API.

The API was tested against specifications for material of code 04903 (for USA market) and 04905 (for the Canadian market).

Apart from the final product where 3 more samples were taken, there was no extra sampling and testing to confirm consistency of the process and adequacy of the in-process controls at the commercial production scale.

The acceptance criteria was set as compliance and demonstration of consistency with respect to raw materials used, final API (4 sets of results), IPCs, critical parameters and yield.

The report No. RVP:C:LAMFA:01/11 indicated that in some cases different equipment was used but the equivalent reports reviewed by the inspectors indicated that these were equivalent.

The TLC results in one step indicated that the first batch took markedly longer time for one reaction to be completed compared to other batches. It was noted that there were errors in reading and interpretation of the TLCs for the first batch which was addressed for the next batches. It was noted that the results were signed only by the IPC analyst.

The second batch required more pH adjustment to bring it within the limits, but this was anticipated in the procedure.

Errors in the calculation of water added resulted in differences in water content, damp weight, dynamic drying time and yield.

The deviations were recorded and adequately discussed and recommendations were made to update the BPCR and monitor the yield in the subsequent PQRs. The results of final products of the pre-validation batches were compared with the validation batches.

- Plant A. November 2011: Protocol No. PVP:A:LAMFA:02/11 and report No. RVP:A:LAMFA:02/11:

The Master Processing File used was 04903-Rev-03-1111 and the batches used, their sizes and yields were noted.

Similar issues related to pre-validation meeting and verification of qualification of equipment were noted. The first batch, again, took markedly longer time for the same reaction to be completed compared to other batches. The fact that the same error in reading and interpreting the TLCs was allowed to continue for 36 hours indicated weakness in the QA system.

Deviations were adequately discussed and recommendations included improvements in the BPCR, inclusion of milling parameters and change of the TLC procedure to improve on the precision of determination of completion of the reaction.

2.12 CHANGE CONTROL

Change control management was described in two procedures, one for change in documentation and another for changes to equipment. All the other changes were managed according to relevant SOPs (e.g. change of supplier is managed by supplier management SOP). All the SOPs which should be used for different changes were listed in the SOP for changes in documentations. Follow up was carried out through the monthly “Council of Quality” meeting.

2.13 REJECTION AND RE-USE OF MATERIALS

APIs were reprocessed by either recrystallization in a specific solvent (*to remove foreign materials or improve residue on ignition*) or re-milling (*to improve particle size*). The process neither included use of recovered solvents nor recovery of 2nd crop, though these were included in the APIMF

Records of one recovered solvent were reviewed and confirmed to have either been sold or used in preparation of brine for chillers.

2.14 COMPLAINTS AND RECALLS

SOP of Complaints, returned materials and recalls were examined. They are considered sufficiently detailed.

No recalls were declared by the Company in the last two years.

The returned materials and complaints were reported in an informatics register based on the MS Excel program. These register could be accessed only by authorized personnel for input of data based on password access.

A returned material for foreign matter was examined and it was noted that in one case the rationale for sampling of the several containers returned was not registered in a proper way being present only in a communications by email from a QA responsible (responsible of release) without indication of personnel consulted for decision and a rationale for the sampling itself which as explained by QA responsible was accomplished choosing the most contaminated container.

A complaint for trace of unexpected contamination of an API was examined and the investigation was found satisfactory.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

According to the SMF, some intermediates (not related to Lamivudine) could be outsourced and it was stated that some tests (e.g. water microbiology testing, PXRD) and services (e.g. calibration, pest control) too were outsourced. This area was not reviewed in detail.

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, **WHOAPI-143, Lamivudine methanol solvate** manufactured at **Signa, S.A. de C.V. Av. Industria Automotriz No. 301, Zona Industrial Toluca, Toluca, Estado de México, C.P. 50071, MEXICO** was 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.