



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	RH039 (Misoprostol 200 µg tablets, from Cipla Ltd.) HA563 (Ritonavir 100 mg tablets, from Cipla Ltd.)
Study number	1. Study No. ARL/11/104 (RH039) 2. Study No. ARL/11/228 (HA563)
Title of the study	1. Study No. ARL/11/104: To demonstrate the bioequivalence between Misoprostol 200 mcg tablets of Cipla Ltd., India, with Cytotec® (Misoprostol 200 mcg) tablets of Pharmacia Ltd., UK, under fed conditions in normal, healthy, adult, male human subjects in a randomized crossover study. 2. Study No. ARL/11/228: A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Ritonavir 100 mg Tablets of Cipla Ltd., India with Norvir® Tablets (containing Ritonavir 100 mg) of Abbott Laboratories, USA, in normal, healthy, adult, male and female human subjects under fed conditions
Clinical Part of the study: Name and address of the organization	The clinical parts of both studies were not covered by this inspections, as they were performed by another CRO.
Bio-analytical laboratory: Name and address	Sitec Labs Pvt Ltd Pee-Dee Info Tech. Plot No Gen 40, TTC, MIDC, Behind Millennium Business Park, Near Nelco, Mahape, Navi Mumbai 400 701, INDIA
Date of inspection	31 January & 1 February 2014

Part 2: Summary

General information about the site(s)

Sitec Labs started its clinical and bio-analytical operations for bioavailability / bioequivalence studies in December 2004. According to the opening meeting presentation, it had over 350 full time and contract staff. It has performed over 290 biostudies and 1000 NDA/ANDA (pharmaceutical analysis to support the ANDA and NDA submissions). In addition to BA/BE studies, Sitec also performed testing of

pharmaceutical products. It included 3 divisions, Analytical Research, Bioequivalence and Impurity Synthesis.

The bio-analytical studies for HA563 and RH039 were conducted between July 2011 and June 2013 at Sitec Labs Pvt Ltd Pee-Dee Info Tech. Plot No Gen 40, TTC, MIDC, Behind Millennium Business Park, Near Nelco, Mahape, Navi Mumbai 400 701, India. This location was in use for bioanalytical testing since September 2010. The clinical activities of this site were not inspected since the clinical portion of the above-mentioned studies had not been conducted there.

History of WHO and/or regulatory agency inspections

Sitec Labs Pvt Ltd was previously inspected by WHO in 2006 at Building No. 14, CTS No. 82,82 (1 to 17) Village Hariyali, L.B.S. Marg, Vikhroli(W), Mumbai-400 083. At this time both the analytical and clinical site were located at the same site. Later Sitec was inspected in 2008 and 2009 at bioanalytical site Building No. 14, CTS No. 82,82 (1 to 17) Village Hariyali, L.B.S. Marg, Vikhroli(W), Mumbai-400 083 .Clinical site by then had shifted to Jayashree Plaza, 1st Floor, L.B.S.Marg , Opp. R.R.Paints , Bhandup (W).

Sitec was then inspected in February 2012 .At the time of this inspection the analytical site had shifted to the current site ie., Pee-Dee Info Tech, Plot No. Gen 40, TTC, MIDC, Behind Millennium Business Park, Near Nelco, Mahape, Navi Mumbai and clinical site was at Jayashree Plaza, 1st Floor, L.B.S.Marg, Opp. R.R.Paints, Bhandup (W).

Hence this is the fifth WHO inspection of Sitec Labs Pvt Ltd but only the 2nd inspection of this new site. Both the analytical and clinical site are now located at the same site.ie Pee-Dee Info Tech, Plot No. Gen 40, TTC, MIDC, Behind Millennium Business Park, Near Nelco, Mahape, Navi Mumbai

Overall, Sitec had been inspected 5 times by the US FDA. The EMA inspected the company twice, in January 2007 and January 2011, and the MHRA inspected it once in November 2013. The latest US FDA inspection did not result in any 483 observations. The MCC had also inspected the company.

Focus of the inspection

The inspection focused on the bio-equivalence studies conducted for the RH039 and HA563 products. The inspection covered several sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies and other associated guidelines.

Inspected Areas

Day 1

On arrival, an opening meeting was held with key personnel The CRO made a presentation and it highlighted various activities carried out including a brief presentation on BE studies for HA563 and RH039. A copy of the presentation was obtained and saved in the company file.

After the presentation, the WHO inspector proceeded with a tour of the bio-analytical laboratory which included sample preparation, storage, reference standard weighing areas and balances, as well as the rooms which housed the various HPLC-MS/MS systems in use at the laboratory. This was followed by a review of relevant study documentation and standard operating procedures (SOPs).

Day 2

On the second day of the inspection, the WHO inspector gave a summary of the observations of day 1 and received clarifications where deemed necessary. The inspector also reviewed the following:

- instrument audit trails (uploaded on a computer).
- info regarding backup of the instrument audit trails.
- qualification of Analyst and documentation of hot fixes , security patches, etc...
- procedure for manually selecting data to be backed up (to be shown in the form of an example as the procedure for this does not exist).
- other miscellaneous documentation.

Summary of the misoprostol study:

- This study was performed using a AB Sciex Triple Quad API 5500[®], linked to a Shimadzu UFLC LC[®] system. Extraction was performed with a Waters Oasis MAX[®] cartridge (1 cc/30 mg). Method validation was started on 13 July 2012 and ended on 23 July 2012. Validation addendums were made afterwards for stability and to cover all instruments.
- There were 4 QC levels in the study.
- The aliquots were received in duplicate from the clinical site. The first sample was collected on 19 June 2012 and was received by Sitec on 9 July 2012.
- The total storage duration was 59 days, while the long term stability was done on 204 days.
- The method of analysis was method number BIO AM 08/12 (version No. 2).
- There were 83 re-injected samples and 7 repeat analysis samples.
- Two instruments were used for the bioanalysis, instruments No. I-BA-96 and I-BA-113 (both API 5500). Analyst 1.5.1 was used for these studies.

The information seen during the inspection generally matched that submitted in the dossier. Verifications were performed on the data and it was found to be reliable and satisfactory overall.

Summary of the ritonavir study:

- The internal standard was isotope labelled ritonavir (D6).
- The extraction procedure was done on a 96 well SPE plate (automated).
- There were 2 different contamination markers (doxazocine and indinavir) used.
- The method was performed on a MDS Sciex API 3000[®], linked to Shimadzu UFLCXR[®].
- The post preparative solution stability was of 48 hours. Some partial stability studies such as carry-over were repeated again for the 2nd LC-MS/MS system in 2013.

- There was a total number of 1819 samples. The 1st sample collection was on July 16, 2011, Sample transfer was done on 26 July 2011 and 3 August 2011. The total storage duration was 41 days at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$.
- Sample analysis took place between 16 August 2011 and 25 August 2011.
- Only 6 samples were re-injected, and 14 were reanalysed.
- There were no deviations during sample analysis. There were 99.34% samples that met the acceptance criteria. The chromatogram for the 13 subject samples that were repeated were shown for Subject 3/X/T04. The DI LCM-5 (limit contamination marker) exhibited poor chromatography (this was injected prior to the calibration curve) and hence was re-injected after following the filing of a deviation.

The information seen during the inspection generally matched that submitted in the dossier. Verifications were performed on the data and it was found to be reliable and satisfactory overall.

Laboratory equipment: There were 12 HPLC-MS/MS systems in the laboratory, 12 ultra-low temperature deep-freezers set at a target temperature of -80°C and one freezer which was set at a target temperature of -25°C . Temperatures were continuously monitored using a ThermoClient software system via data loggers. The software had an indication of “21 CFR 11” as “Disabled” in orange colour. A query had already been sent further to previous inspections regarding the meaning and impact of “Disabled”. The system provider had communicated an explanation to the company before, along with p. 112 of the manual, which stated that the “Disabled” option would be shown in blue if the 21 CFR 11 option was actually disabled. This is acceptable.

Method development and validation: Method development and validation was acceptable overall. It is noted that the laboratory had sufficient expertise and resources to validate and execute methods with LLOQs of less than 1 pg/mL for oral contraceptives and for antiretroviral drugs as well. These included methods for risedronate sodium from plasma, estradiol and cortisol which present specific analytical challenges since they are endogenous compounds. Chiral assays were also performed for analytes such as bicalutamide and for light sensitive compounds, for a total of 160 bioanalytical methods up to date. Levels of detection ranged from the µg/mL to the fg/mL.

Quality Assurance (QA): Study data was reviewed in the following manner by QA bioanalytical:

- The concentration values were verified with the raw data on paper before the data was sent to clinical (evaluated by their internal assessment group). After this step, it was sent to QA for review. The data was checked before the report was sent out. This was done in teams of 3.
- QA verified the printouts of the sequences for:
 - time gaps in between analysis,
 - file names
 - analytes
 - internal standard area (an Excel® spreadsheet was used for this purpose)
 - analyte concentration

- accuracy
- absence of concentrations beyond level 8, or below level 1.
- The presence of interference, if any, was recorded by analysts both in their laboratory notebooks and in sequence/data printout sheets. The observation data sheet was filled for each and every subject and pasted in a logbook. The pasted copy was signed and dated at its edge, so that if it was removed or replaced, a trace would remain on the logbook.
- 100% data checks were done by the internal assessment team. Internal assessment performed checks following a standard list. Audit trails were reviewed, but only results audit trails were covered. Other types of audit trails, such as the project and instrument audit trails were never reviewed, due to the large amount of paper data. A suggestion was made to find means of reviewing this data in electronic format instead. The internal assessment team verified how many times data has been integrated in the results(quantitation) audit trail.
- It is noted that ranges for integration parameters were specified in the methods of analysis. If other parameters were used, these had to be authorized by the section head and would be documented as an “authorization for reintegration”.
- According to the SOP entitled “Evaluation of chromatographic data”, dated 03.01.2013, effective 14.01.2014, version 8, No. BA/BE-13, “if any given chromatogram is reprocessed more than 10 times, Analyst should report the same to section head/head operations”: This value which is considered high, especially in the case of routine bioanalysis, was explained to be necessary because of the difficulties that are encountered during high sensitivity assays. The laboratory committed to lowering this value as much as possible in the future, but should also consider lowering it for routine bioanalysis.
- Manual integrations had to undergo an authorization process and were rarely done in practice except to obtain baseline noise.

Computerized systems: There was only 1 IT administrator. Under his login, the data files were verified to be inaccessible.

The computerized system linked to instrument No. I BA96 was opened under both Head and IT administrator user profiles. The recycle bin was checked and the information that it contained (deletion of user profiles due to a bug) did not pose any concern.

The system was set up so that data could not be saved on the D drive, only on the server, except for a period in 2010/2011 where settings had to be changed further to avoid malfunction of Analyst[®] when saving directly to the server.

Network based acquisitions did not adequately function with Analyst[®]. Several communications were made in this regard and 3rd party service providers came to resolve this issue. The supplier of the software, AB Sciex, had developed the appropriate patch only for the 1.5.1 and 1.5.2 versions of Analyst[®] which was problematic because the laboratory was using an older version of the software. There was an installation report for the June 2010 hotfix. The Validation performed on Analyst for “Software validation for calculation of summary sheet and calibration curve parameters using Analyst software”, was reviewed. The protocol, dated 31. 12.

2010 was shown. It included calculation of summary sheet and calibration parameters as well as accuracy. The validation report was dated of 15 December 2011.

The report dated 26 April 2010 on the qualification of the workstation, as provided by Analyst®, for Instrument No. BA 113, was reviewed. IQ, OQ and PQ was done by AB Sciex on the Dell workstations which were also supplied by them.

The procedure entitled “Server Administration”, No. SAP/BE-36, version 5, effective 13 June 2013, was reviewed. It contained instructions on passwords (e.g., what constitutes a strong password, how to delete a user, etc.) and how to add a new user, among other elements.

The SOP entitled “Server make: IBM”, No. EOP E A131, Version 05, effective 22 November 2013, was reviewed. It mentioned 2 different type of backups that could be selected “Full-Backup files” and “Differential – Back up changed files since last full – using archive bit (does not reset archive bit)” It stated that differential backups would be done on a daily basis, but that full backups should be done on a weekly basis.

The SOP on Backup policy and up-keep of tapes, No. SAP/BE-34, version 11, effective 1 February 2013, was also reviewed. Its purpose was to provide a guideline for taking backup and retrieving the data stored in the server. It did not identify the responsibility (only “designated person” was stated which is too vague as it could be anybody) and did not provide any information on the nature of the data to be backed up from the server or on how completeness of the backup would be verified. The IT administrator was requested to clarify how backups were performed. He explained that differential backups were being done but that he manually selected which folders should be backed-up. Such manual selections may be prone to human error. See observation under “Part 5”.

There was no specific training mentioned on current guidelines for computerized systems. Training on the most recent guideline (WHO, CFR 21 Part 11, and EMA Annex 11), was recommended.

Preparations:

For the misoprostol study:

- Subject 25 was seen as an example. Samples were removed from ultra-deep freezers, thawed and centrifuged – the time and duration of these steps was in a different logbook. Sample processing was started at in the case of this subject at 16:57 on 31 July 2012. Bulk spiking and ultra-deep freezer logbooks recorded the specific information related to this step and removal of samples.
- Subject No .25 Period X, Y, Z W was stored in E BA8. The time of withdrawal and time of storage was shown for each subject, but there was no mention of the aliquot. The requirement to record whether Aliquot 1 or 2 was taken out of the deep freezer was implemented just recently and was not yet set in procedure.
- All of the sample labels were coded in order to blind the analyst to the fact that a sample would contain the test or reference.
- Blank plasma was collected from the clinical unit at Sitec.

- 4 sources of blank plasma was used for this study. These were screened on 26 July 2012. Their chromatograms were briefly reviewed and no interference was seen (lots No. 9948, 2529, 3525, 3379).
- Pooled plasma chromatograms were also shown for 3 different sources that was pooled together. The pooled plasma was analysed in triplicate on 26 July 2012 as well.
- The M/Z ratio was of 367.4/249.200 Da for the analyte and of 372.2/249.1 Da for the reference standard.
- The aliquot was not indicated in the ultra-deep freezer logbooks or other documentation related to preparations for this study, but the company had an unwritten procedure of taking only the main aliquot. This procedure is now in SOP.
- A vacuum manifold (20 positions from Waters), was used to extract samples for the study . A layout on how the samples were kept was reviewed. It was not dated or signed off since it was prepared in view of the inspection but was based on the order or recording of other studies. It showed that there were 6 batches. There were no QC failures in this run, so that fact that each sequence could not be processed in a single batch is not seen to be a significant issue.
- Deviations were recorded consistently. Random verifications were done by the inspector. In one instance, the initial run for subject 7 was interrupted after 4 injections due to the fact that subject samples were wrongly named. This was not found out during in process QA due to the fact that the names had been changed to subject 7 without saving, hence the printed sequence did not match the sequence that was finally submitted and started (it returned to Subject 5). The events were verified by the inspector as true and correct.
- For subject 25, there were differing trends for the final subjects vs. the rest of the run (lower IS response). This was not noted during review. From 25/W/T12 to T20, ISR values varied from -17 to -35% relative to the average of CCs and QCs. The laboratory should note that such issues are expected to be noted and investigated since they could potentially impact accuracy of test results.

Miscellaneous: A list of failed/passed studies was provided upon request. The 2 studies under review were not included in this list.

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, the bioanalytical portion of studies No. **ARL/11/104 (RH039)** and **ARL/11/228 (HA563)**, was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at *Sitec Labs Pvt Ltd, Pee-Dee Info Tech. Plot No Gen 40, TTC, MIDC, Behind Millennium Business Park, Near Nelco, Mahape, Navi Mumbai 400 701, INDIA.*

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 CRO, 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.