



Prequalification of Medicines Programme

WHO PUBLIC INSPECTION REPORT

Bioequivalence Study

Part 1: General information

WHO product numbers covered by the inspection	Sulphadoxine/Pyrimethamine 500/25mg tablets
Study number	C081117-B21
Title of the study	An Open Label, randomized, single dose, 1 sequence, 1 period parallel bio-equivalence study to compare Sulphadoxine/Pyrimethamine 500/25mg tablets with the reference drug Fansidar (500/25mg) in healthy male volunteers in China.
Clinical part of the study: Name and address	Phase I Clinical Research Unit, Shanghai Xuhui Central Hospital 966 Huai Hai Zhong Rd, Shanghai China 200031
Bio-analytical laboratory: Name and address	Bio-analytical Laboratory of Shanghai Xuhui Central Hospital 966 Huai Hai Zhong Rd, Shanghai China 200031
Date of inspection	15 to 17 June 2010

Part 2: Summary

The purpose of the inspection was to inspect the bio-equivalence study performed at Phase I Clinical Research Unit, Shanghai Xuhui Central Hospital, 966 Huai Hai Zhong Rd, Shanghai, China 200031 (hereafter referred to as "Xuhui", to assess compliance with GCP, GMP and GLP (as appropriate) and to verify the related source data for the above mentioned study.

General information about the site

Shanghai Xuhui Central Hospital, located at 966 Huai Hai Zhong Rd, Shanghai was inspected on the above-mentioned dates. The clinical part of the study was done at the Phase I Clinical Research Unit of the hospital, and the bio-analysis at the bio-analytical laboratory of the hospital. The unit was established in 2000. It had 2 clinics with 28 beds each.

Between 2006 to 2009 Xuhui performed 13 clinical studies (mostly BE studies).

History of WHO and/or regulatory agency inspections

This site was not previously inspected by WHO. It was previously inspected by the Shanghai SFDA in 2007 and 2009; and by the Guangxi SFDA in 2009.

Focus of the inspection

The inspection focused on the bio-equivalence study performed on behalf of the sponsor, for the abovementioned product. The inspection covered the relevant sections of the WHO GCP, GLP and related texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

A total of 80 volunteers were screened about two weeks before the study. 48 male volunteers were enrolled for the study. The study was conducted in two parts. Group 1 (subject 1 to 26) were dosed on 12 May and group 2 on (subject 27 to 48) on 18 May 2009.

Test product:

Manufactured by: [REDACTED]

Batch number: [REDACTED]

Date of manufacture: [REDACTED]

Reference product: Fansidar (Purchased from Carlsbad Technology INC)

Manufactured by: F Hoffman La Roche Ltd

Batch number: B1500-50

Expiry date: October 2009

Inspected Areas

Day 1

After arrival at the Shanghai Xuhui Central Hospital, the inspectors were taken to the Clinical unit where they were introduced to staff members of Vivo and Shanghai Xuhui Central Hospital Clinical Unit I.

The study director made a presentation of the company and study introduced the staff after which business cards were exchanged. The inspectors made a presentation on the prequalification program and the parties agreed on the inspection plan.

The inspectors were informed that the government had changed the weekend and that it was actually public holidays. However, the inspection proceeded.

It was further explained, that the three organizations involved in the study were the sponsor which had delegated responsibility for the study (by means of a contract) to Vivo (CRO) which in turn had contracted the conduct of the study activities to Shanghai Xuhui hospital Clinical Unit I.

Vivo specialized mainly in phase I clinical studies and was founded in 2005. It formed an alliance with the hospital in 2008.

Xuhui received a certificate in 2006 from the SFDA to conduct clinical trials. The old facility (where the study was done) was established in 2000, was located on the 13th floor - and started clinical activities in 2006.

According to the CROMF there were various areas including a 28 bed clinical unit, a screening area, drug administration area, blood sample collection and storage area and an emergency room.

28 people were employed in the unit. Although the CROMF stated that there was no quality management system - documentation supporting a quality management was available including SOPs, an organization chart, job descriptions, training records. The CROMF was updated in the corrective actions to reflect the current quality management system at Xuhui.

At the time of the inspection, the laboratory had 4 LCMSMS instruments.

For the study inspected, Dr Kanyin Zhang was the Scientific Director (Vivo), Yuquan Ren (QA - Vivo), Yanmei Liu (Clinical investigator) and Gangyi Liu (BAL) responsible person.

The clinical part of the study was conducted between 12 - 25 May 2009 and the sample analysis was done between March and May 2009. PK and Biostatistics was done between June to July 2009.

The inspectors reviewed various documents which included:

- Contract between the sponsor and Vivo (study specific), dated 5 December 2008 - which specified that Vivo would also be monitoring the study, and could delegate activities to another party
- SOPs (Vivo and Xuhui)
- Contract between Vivo and Xuhui (signed in April 2009) which defined the role and responsibilities of clinical investigators and delegation
- Training record: Yanmei Liu (PI), Chen Yu (Administrator, Sub-Investigator), Jingying Jia* (Sub-Investigator), Gangyi Liu (BAL Study Director)

* Ms Jia held the position of QA Supervisor in Xuhui. However, in this study, she performed the role of a sub-investigator for the clinical phase and the role of QA for bioanalytical. This aspect was addressed in the corrective and preventive actions.

A clinical monitor from Vivo was present from time to time during the study

Ethics committee approval:

Documents were submitted to IEC on 10 March 2009 included:

- SFDA approval
- Investigator brochure
- Protocol
- ICF
- Certifications of CRO and sponsor

The trial master file (TMF) was briefly reviewed for the contents of the following documents

- Regulatory authorization SFDA
- Ethics committee approvals
- Approval for importation and invoice (reference product)

- Protocol and amendment
- ICF
- Subject identification numbers
- Sample CRF
- Investigators Brochure
- IMP information
- Drug administration
- Dispensing
- Dosing
- Environmental records (IMP)
- Meal records
- Laboratory certificates, normal ranges
- Monitor log
- QA audit plan and report
- Study initiation visit report
- CVs and training records
- Minutes and study related training/meeting
- SAE report from
- Statement for GLP compliance
- Sample collection sheet
- Sample transfer sheet
- Deep freezer temperature log (no record over weekends or extended times)
- Analytical reports (reference standards)
- Method validation report.
- Protocol deviations
- Randomization
- Contracts
- Compensation paid
- Clock calibration
- Blood sample bar code
- ECG record

On the second day of the inspection, the inspectors reviewed selected documents and source data from the TMF. Then the documentation relating to the acquisition, storage and transport of the IMPs was reviewed.

The products were transported from sponsor to Vivo on 20 March 2009, Vivo to Xuhui on 7 and 13 April 2009.

In total, 25 packs of Fansidar (packed as 25 tablets) were purchased, and transferred 90 tablets (one pack was dispensed 15 tablets).

It was explained how the dispensing was done according to the randomization (A vs B). The product was then administered the day after dispensing.

The documentation relating to dispensing and reconciliation was inspected.

The SOP for vitals monitoring was inspected

- ICF for several subjects were verified.
- CRFs were reviewed for several subjects.

After the review of the above-mentioned documents, the clinical unit was inspected briefly. Various areas were visited including the screening area, emergency room, wards, offices, change rooms and pharmacy.

The inspectors visited the bio-analytical laboratory (BAL). The layout of the BAL was changed in February 2010.

They inspected various areas and reviewed documents and records including:

- Balance room
- Analytical balance calibration and verification
- Reference standard storage
- Refrigerators (e.g. nr 11)
- Deep freezers (e.g. nr 7, -30C)
- Centrifuge (nr 2)
- LCMSMS (nr 2)
- Columns and HPLC
- Sample preparation
- Temperature monitoring records
- Calibration of micro pipettes

On the third day, the inspectors continued inspecting documentation relating to the BAL and analysis. The organization chart was reviewed (dated 5 January 2009). The current organization chart (May 2010) was not signed, and the reporting lines from the analysts to the group leader (Meng-qi Zhang) was missing. Corrective actions were taken.

Job descriptions were general documents - however, this was addressed in the corrective actions.

Selected documents and source data (including selected chromatograms where appropriate) were reviewed including:

- Method development
- Method validation including preparation of stock solution, weighing of references standards, calculations,
- Preparation of internal standards
- Precision
- Accuracy
- Selectivity
- stability of stock solutions
- stability (freeze thaw, long term, short term)
- sample analysis
- QCs and CCs for all batches / runs

Short term and long term stability was determined - observations were addressed through corrective actions.

Freeze thaw stability was determined at three concentrations for both analytes in matrix.

Sample analysis was arranged in 9 batches / runs for the 46 subjects. Pre-dose samples for the 2 withdrawn subjects were also included resulting in a total of 784 samples having been analysed. The sample sequence and plans were inspected for both analytes in all runs with a focus on the acceptance of the runs (for CCs and QCs).

Electronic data (for selected runs/batches) for sample analysis (both analytes) and validation and stability were inspected including:

- audit trail settings (all runs)
- audit trail history (all runs)
- integration parameters

- retention times
- injection dates and times
- IS response

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection of the above-mentioned study - (C081117-B21) "an open label, randomized, single dose, 1 sequence, 1 period parallel bio-equivalence study to compare Sulphadoxine/Pyrimethamine 500/25mg tablets with the reference drug Fansidar (500/25mg) in healthy male volunteers in China, conducted at Shanghai Xuhui Hospital Clinical Unit I ,China, it was concluded that the study was conducted at an acceptable level of compliance with GCP, GMP (where appropriate) and GLP.

Part 4: Reference documents

1. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. *WHO Expert Committee on the Use of Essential Drugs. Sixth Report.* Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850), Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_850.pdf
2. OECD Principles of Good Laboratory Practice (GLP). [C(97)186/Final], 1997
http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html
3. Additional guidance for organizations performing in vivo bioequivalence studies. WHO Technical Report Series, No. 937, 2006, Annex 9
www.who.int/prequal