World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Contract Research Organization (CRO)

Part 1	**General information**	
Company information		
Name of Company	Bio Pharma Services Inc. (BPSI)	
Corporate address of Company	4000 Weston Road Toronto, Ontario M9L 3A2, Canada	
Inspected site		
Name & address of CRO	Same as above	
Unit/Block(s) and their activities	N/A	
Desk assessment details		
Date of review	7 November 2018	
Product and study information covered by this desk assessment	Study no. 1999 Single-dose fasting bioequivalence study of Lamivudine, Tenofovir Disoproxil Fumarate and Dolutegravir tablets (300 mg / 300 mg / 50 mg; Mylan) versus EPIVIR® tablets (300 mg; ViiV), VIREAD® tablets (300 mg; Gilead) and TIVICAY® tablets (50 mg; ViiV) in healthy adult volunteers Study no. 2118 A Single-Dose, Randomized, Open-Label, Two-Way Crossover Bioequivalence Study of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate 50 mg/300 mg/300 mg Tablets (Cipla Ltd., India) and Tivicay® (dolutegravir) 50 mg Tablets (ViiV Healthcare), Epivir® (lamivudine) 300 mg Tablets (ViiV Healthcare) and Viread® (tenofovir disoproxil fumarate) 300 mg Tablets (Gilead Sciences, Inc. USA) in Healthy Male and Female Volunteers under Fasting Conditions(Study title with removal of proprietary names, WHO PQ reference numbers, study number, name of study sponsor)	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
US FDA	Dates of inspections:	13-17 Aug 2018 28 Aug – 1 Sep 2017
	Type of inspections:	Routine
	Unit:	Clinical

	Type of study covered:	Bioequivalence Clinical bioresearch monitoring
Joint inspection by ANSM – French Medicines Agency & DKMA – Danish Medicines Agency	Dates of inspection:	24-28 April 2017
	Type of inspection:	Routine
	Unit:	Clinical and bioanalytical
	Type of study covered:	Bioequivalence
MHRA (UK Medicines Agency)	Dates of inspection:	25-29 April 2016
	Type of inspection:	System inspection
	Unit:	GCP inspection
	Type of study covered:	Bioequivalence studies
US FDA	Dates of inspection:	2-10 Nov 2015
	Type of inspection:	Routine
	Unit:	Clinical
	Type of study covered:	Bioequivalence study
US FDA	Dates of inspection:	30 Nov – 9 Dec 2015
	Type of inspection:	Routine - A high priority, CDER Pre-Approval Data Validation inspection was conducted.
	Unit:	N/A
	Type of study covered:	Bioequivalence studies
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	Not applicable. Site not previously been inspected by WHO.	
Part 4	**Introduction**	
Brief description of the site's activities	The site was responsible for both clinical and bioanalytical part of the study no. 2118, and only the clinical part of the study no. 1999. According to the CROMF, the facility consists of five clinical units, including four clinics (174 beds), a 14-bed Phase I (First-in-man) clinic and bioanalytical laboratory with all applicable equipment. The facility in Toronto is equipped with freezers (-20°C as well as -70°C), refrigerators, BP units, ECG machines, centrifuges, LC-MS/MS, and other equipment necessary for the conduct of clinical trials and related bioanalytical activities. Preparation of clinical study reports and statistical analysis are conducted on-site.	

Abbreviations	Meaning
CCs	Calibration Curve standards
CAPA	Corrective and preventive action
CROMF	CRO master file
GCP	Good clinical practices
GLP	Good laboratory practices
NC	Non-conformity
NRA	National regulatory agency
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
SOP	Standard operating procedure
SRA	Stringent regulatory authority

Part 4	Summary of the assessment of supporting documentation

a) Clinical trial license granted by the local authority:

Health Canada reviews clinical trial protocols to assess the protection and safety of the participants, as well as the quality of the drugs; assures review by Research Ethics Boards; verifies the qualifications of Principal Investigators and monitors and reviews Adverse Drug Reactions (ADRs). Sponsors must file a CTA (Clinical Trial Application) to Health Canada to conduct clinical trials in Phase I through III of drug development and comparative bioavailability trials. The authorization to conduct Clinical trials in Canada is granted on an individual trial basis.

b) CRO Master File:

An updated CRO master file CROMF approved on 31 Oct 2018 was provided. The Master File was arranged in accordance with the WHO guidelines for the preparation of a contract research organization master file, Annex 7, no 957, 2010.

c) List of all regulatory inspections performed in the last 3 years and their outcomes:

For details refer to Part 2; Summary of the assessment of SRA/NRA evidence considered.

d) Local NRA inspection report:

An inspection notification by Health Canada, stating that an inspection would be carried out on 9-10 Jan 2018 was provided. Subsequently, an inspection was carried out in Jan 2018 covering the clinical part of the trial conducted by Biopharma services and the bioanalytical part of the trial conducted by Pharmascience. The final signed CAPA, dated 14 Mar 2018 was available. The CRO's response was reviewed by Health Canada and the closing inspection letter was issued on 6 Nov 2018. No further action was required.

e) Copy of any warning letter, or equivalent regulatory action, issued by any authority for the site:

According to the company, no warning letter was issued.

f) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the studies conducted for WHO product(s) has been performed and all matters dealt with:

Quality Assurance statement for Study numbers 2118 and 1999 was provided to state that the respective clinical study reports were reviewed by the Quality Assurance Department of BioPharma Services Inc. in compliance with Good Clinical Practice (GCP), International Council on Harmonization (ICH) Guidelines, applicable regulatory guidelines, general and departmental SOPs, company policies, protocols and study designs. Additional procedural inspections were done for these studies and reports were archived within the QA Department files. The final report accurately presented the raw data, statistical analysis generated (as required) and clinical activities relevant to this study.

g) IRB/IEC clinical trial approval (including the approved protocol, the amended protocol and consent form):

A copy of trial approval from the Ethics Review Board of Optimum Clinical research Inc for following documentation was available:

- Protocol BPSI study number 1999, version dated June 17, 2016
- ICF dated July 14, 2016 pertaining to study no. 1999
- Protocol BPSI study number 2118, version dated March 10, 2017
- ICF dated April 5, 2017 relevant to study no 2118

h) Additional documents submitted:

None.

Part 5	**Conclusion – Desk assessment outcome**

Based on the GCP/GLP/BE evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site ***Bio Pharma Services Inc.; 4000 Weston Road Toronto - Ontario, M9L 3A2; Canada*** is considered to have performed the studies submitted to WHO PQT under an acceptable level of compliance with WHO guidelines.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 6	List of WHO guidelines referenced in this inspection report

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9. ***Short name: WHO BE guidance*** http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
Short name: WHO GCLP
https://www.who.int/tdr/publications/documents/gclp-web.pdf

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137). ***Short name: WHO GCP***
http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

4. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9. ***Short name: WHO TRS 1010, Annex 9***
https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1

5. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. ***Short name: OECD GLP***
http://www.who.int/tdr/publications/documents/glp-handbook.pdf

6. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011. ***Short name: WHO Ethics Committee Guidance***
https://www.who.int/ethics/publications/9789241502948/en/

7. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. ***Short name: WHO storage and transport guidance*** or ***TRS 961 Annex 9***
http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

8. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.
Short name: WHO CROMF Guidelines or ***TRS No. 957, Annex 7***
http://www.who.int/medicines/publications/44threport/en/

9. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised). ***Short name: Glove use information leaflet***
http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

10. WHO guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5.
Short name: Annex 5 WHO GDRMP guidance
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf