

Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
WHOPIR
Bio-Equivalence Study

Part 1	General information
Organization details	
Company information	
Name and Address of Clinical Research Site	Bio Pharma Services Inc. 4000 Weston Road Toronto Ontario, M9L 3A2 Canada
Name and Address of Bioanalytical Research Site	Bio Pharma Services Inc. 4000 Weston Road Toronto Ontario, M9L 3A2 Canada
Name and address Statistical Site	As above
Corporate address of Organization	HEAD OFFICE (Clinical and Bioanalytical Facility) 4000 Weston Road Toronto, Ontario, M9L 3A2, Canada T: +1 (416) 747-8484 F: +1 (416) 747-8480 Toll Free: +1 (844) 747-8484 E: info@biopharmaservices.com
WHO product number covered by the inspection	WHO application no. CV016 Bioequivalence Study of Nirmatrelvir Tablets
Inspection details	
Dates of inspection	10-14 July 2023
Type of inspection	Initial – Joint inspection with Health Canada
Introduction	
Summary of the activities	The facility had the capability to conduct bioequivalence/bioavailability and in-vitro studies involving both healthy subjects and patients.

Bio Pharma Services Inc., Toronto Canada, CRO

10-14 July 2023

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	<p>The specific types of studies that could be conducted by the CRO were outlined in section 1.5 of the CRO MF.</p> <p>Bio Pharma Services Inc. (BPSI) held a Licensed Dealer status granted by Health Canada’s Office of Controlled Substances. This license authorized BPSI to engage in activities such as ordering, possessing, distributing, transporting, delivering, and destroying controlled drugs/substances, subject to the license's terms and conditions.</p> <p>Additionally, the organization had established a clinical facility in Missouri, USA.</p>
<p>General information about the company and site</p>	<p>Established in 2006, BPSI has been conducting early-stage Clinical Trials since 2007, primarily based in Toronto, Canada. In 2011, BPSI launched its bioanalytical laboratory with LC-MS/MS platform. The expansion continued in 2014 with the establishment of a US clinical centre in Columbia, MO, later relocated to St. Louis, MO. In 2021, BPSI underwent acquisition by Think Research. However, Biopharma remained an independent entity in processes and procedures concerning clinical study conduct. The main facility remained situated in Toronto, Canada.</p> <p>Moreover, BPSI operates a separate Clinical Operations Phase I Clinical Facility in Creve Coeur, Missouri. This facility serves as a second site for conducting Phase I/IIa clinical trials and BE studies, complementing the company's existing clinical facility in Toronto, Canada.</p>
<p>History</p>	<p>The CRO underwent inspections by various regulatory authorities, including Health Canada, US FDA, ANVISA as well as Austrian, Danish, and Dutch Medicine agencies acting on behalf of EMA. A comprehensive list of these inspections was provided.</p> <p>In addition to these inspections, a desk assessment was conducted by WHO in November 2018</p>
<p>Brief report of inspection activities undertaken</p>	<p>The review encompassed the following scope and study-related activities:</p> <p>The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment</p>

	<p>calibration, employee training, computer controls, and a tour of the facility.</p> <p>Regarding analytical operations, the review provided coverage of practices, qualifications of personnel, and procedures used during method validations and analytical testing.</p> <p>A comprehensive examination was conducted, including a review of the clinical study data, analytical method validation, and analytical study data. This involved comparing the source data to the study reports to ensure accuracy and consistency.</p>
Scope and limitations	
Out of scope	Not applicable

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BA	bioanalytical
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis
	CSR	clinical study report
	DQ	design qualification
	ECG	electrocardiogram
	GAMP	good automated manufacturing practice
	GCP	good clinical practice
	GLP	good laboratory practice
GMP	good manufacturing practice	
HPLC	high-performance liquid chromatograph	
LC-MS/MS	liquid chromatography–mass spectrometry	
IB	investigator’s brochure	

ICF	informed consent form
ICH	International Conference on Harmonization
(I)EC	(Independent) Ethics Committee
IMP	investigational medicinal product
ISF	investigator study file
ISR	incurred sample reanalysis
IQ	installation qualification
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
MS	mass spectrophotometer
MVR	monitoring visit report
NRA	national regulatory agency
OQ	operational qualification
PIS	patient information sheet
PQ	performance qualification
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QRM	quality risk management
SAE	serious adverse event
SAR	serious adverse reaction
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
URS	user requirements specifications

PART 2	SUMMARY OF THE FINDINGS AND COMMENTS
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General section

1. Organization and management

An informative presentation was shared, providing a detailed overview of the organization's activities.

The CRO had an up-to-date organizational chart that depicted key positions and the responsible individuals. The chart was authorized and dated as of 16 Jun 2023.

BPSI held a Controlled Drugs and Substances License Permit issued by the Office of Controlled Substance. Furthermore, the bioanalytical laboratory of BPSI had obtained certification from the Standard Council of Canada, demonstrating compliance with the OECD Principles of Good Laboratory Practices.

The contract with the sponsor was available and reviewed.

Each employee had a defined job description outlining their respective responsibilities. Random verification confirmed that each job description was signed and dated by the corresponding staff member.

Furthermore, a comprehensive list of signatures from authorized personnel involved in conducting each study was readily available and duly verified.

The management took diligent measures to ensure the implementation and adherence to appropriate and technically valid SOPs. The maintenance of a comprehensive historical file containing all SOPs was effectively organized and managed through a relatively newly established digital system.

2. Computer systems

To ensure compliance with the principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP), as applicable, the CRO had established procedures for Computer System Validation. These procedures were designed to ensure that computerized systems were suitable for their intended purpose and underwent validation, proper operation, and performance qualification. Additionally, the CRO had SOPs in place for Computer System Registry and Decommissioning Computers and Equipment. These SOPs provided guidelines and protocols for the registration of computer systems as well as decommissioning and disposal of computers and related equipment.

An inventory of computerized systems was available. It included a clear identification of systems subject to GxP regulations. Any modifications made to the systems, including the temporary addition or removal, were diligently documented.

There were enough computers to enable personnel to perform data entry, and data handling required calculations and compilation of reports. Computers had the adequate capacity and memory for the intended use.

Access to the software systems containing trial-related information was controlled. The method of access control was specified, and a list of people who had access to the

database was maintained. Secure and unique, individual-specific identifiers and passwords were generally used.

The qualification and/or validation certificates were provided to ensure that the software was validated for its intended use and that it was developed in a controlled manner in accordance with a QA system. The qualification and upgrade of randomly selected systems was reviewed to be verified.

In the Performance qualification, consideration was given to the specific user requirements, regulatory/guideline requirements for BE studies, the operating environment in which the system was utilized, and the system's usage in the studies. Quality risk management principles were applied throughout the process. Moreover, the SOPs for each software program employed in conducting BE studies were accessible and utilized accordingly. Regular updates to key software programs, whenever required, following an appropriate risk assessment on the potential impact that it could have on current data and qualification or validation status, were carried out in accordance with the applicable SOP.

DATA MANAGEMENT

Data entry and data verification procedures were established in accordance with applicable Data Management SOPs to prevent errors, including transfer of the data from case report forms (CRFs), analytical data and any other data relevant to the reliability and integrity of a study, to the computerized system.

Electronic data was backed up in accordance with SOP for Backup and Retention of Data.

The specific details pertaining to Server Replication were outlined in their respective SOPs. However, during an interview with the IT staff, the inspectors were informed that the SOP was currently undergoing revision, and new systems had been implemented for the backup procedure. In order to ascertain the reliability and completeness of these backups, the restoration process was carried out, and virus testing was also performed as an added precaution.

If data were transformed during processing steps (such as in the example of re-integration of chromatographic data), it was possible to compare the original data with the processed data.

Observations related to the Computerized systems were addressed in the respective CAPA plan.

3. Quality management

The CRO had established QA and QC systems, supported by SOPs, to ensure the proper conduct of trials and the accurate generation, documentation, and reporting of data in accordance with the protocol, GCP, GLP, GMP, and relevant regulatory requirements. An electronic system was utilized as the software solution for managing these processes. Within the software system, Bio Pharma Services maintained a comprehensive list of SOPs that covered all study activities. This was demonstrated during the inspection. These SOPs were regularly updated. The applicable SOP outlined the procedures for writing, reviewing, approving, maintaining, and revising SOPs. The study related SOPs were provided during the inspection upon the inspectors' request.

The respective software system encompassed various modules that facilitated different QMS functions. These included the training module, which incorporated a training plan/matrix to, for example, notify relevant staff members of required training. Additionally, there were modules dedicated to SOP management, complaint handling, vendor qualification and assessment, as well as CAPA handling, among others.

The CRO had procedures in place for Clinical Quality Assurance and Bioanalytical Quality Assurance. These procedures ensured the presence of designated personnel responsible for implementing a QA program in accordance with the applicable principles. The BPSI Quality Assurance Unit was dedicated to upholding the quality of work and ensuring the following:

- All studies were in compliance with Protocols, Study Plans, BPSI Standard Operating Procedures (SOPs) and regulatory requirements.
- Providing Good Clinical Practices (GCP), Good Laboratory Practices (GLP) and Good Documentation Practices training to Bioanalytical Laboratory Staff.
- Inspection of laboratory processes, systems, and facilities for compliance with GLP, GCP and applicable regulatory requirements.
- Report findings to the Laboratory Management, Study Director(s) and/or Principal Investigator(s) as applicable.
- Promote, encourage, and educate BPSI staff in providing a quality service.

The Quality Assurance Unit (QAU) at BPSI was an independent department reporting directly to the Managing Director. It held the responsibility of auditing the execution of studies and related activities. The results of these audits were documented within the respective software system.

Both in-process and retrospective QA verifications (e.g., in bioanalysis, as the samples and standards were being prepared and tested) were performed.

The quality management system included root cause analysis, tracking for trends, ensuring data integrity and the implementation of appropriate corrective and preventive action (CAPA).

Observations related to the QMS were addressed in the respective CAPA plan.

4. Archive facilities

The CRO maintained a secure storage facility with controlled temperature, humidity, and pest measures for archiving trial-related documents. Effective drainage systems and flood barriers were in place to prevent flooding. Archiving activities followed the applicable SOPs.

Access to the archive storage areas was restricted to authorized personnel, and records of document access and return were maintained. A list of authorized personnel was recommended to be displayed at the facility.

The retention period for study documentation, including raw data, was defined in the respective SOP, and specified in the contract between the sponsor and the CRO. The CRO retained the documentation for 25 years to comply with authorities' requirement, exceeding the 15-year requirement of Health Canada. Provisions were also made for the retention of biological samples and IMP.

During the inspection, the archiving procedures were validated through successful retrieval and traceability of the documents.

5. Premises

During the inspection, a tour of the facility, including pharmacy was conducted on Day 2 and Day 3.

The facility consisted of five fully equipped clinics, including three BE clinic units with flexible design, and 2 Phase I intensive care units (ICU), along with a bioanalytical laboratory equipped with necessary equipment according to the presentation made at the opening meeting. The facilities were randomly visited.

The facilities were well-maintained, featuring clean floors, walls, and working benches that were easy to clean and decontaminate. There were sufficient lighting, ventilation, and environmental control.

Clinical trials were conducted under conditions ensuring subject safety, with appropriate site selection based on risk assessment.

The CRO had ample space to accommodate required personnel and activities for the studies, along with adequate facilities and equipment, including laboratories.

Access to the facility was restricted and controlled using keycards and/or locked doors, with camera surveillance to monitor subject exits. Entry and exit records were maintained, and emergency evacuation routes were included in the floor plans.

Clinical activities took place in designated areas, such as a pharmacy, where investigational products were stored under appropriate conditions. Access to the pharmacy was restricted, and entry/exit records were maintained.

Laboratory premises were designed to prevent mix-ups, contamination, and cross-contamination, with sufficient space for storage of samples, standards, solvents, reagents, and records. Safety measures were in place to protect personnel and ensure safe handling of chemicals and biological samples.

Staff had access to safety data sheets, and proper training was provided for handling firefighting equipment, wearing protective clothing, and using safety cabinets for handling highly toxic samples. Chemical containers were labeled appropriately, and electrical wiring and equipment were adequately insulated, and spark proofed.

Proper protocols were followed for handling compressed gases, and staff was knowledgeable about color identification codes. First-aid materials were available, and staff was trained in emergency care and antidotes.

Procedures were in place for the safe closure of containers containing volatile organic solvents, and certified fume hoods or air extractors were used for handling volatile organic chemicals. Additionally, safety and eye showers were provided in the laboratory.

The facility had systems in place to dispose of waste, treat fumes, and comply with local or national regulations to protect the environment.

To ensure uninterrupted power supply, the facility was equipped with a back-up generator operating on natural gas, along with UPS (Uninterruptible Power Supply) systems.

Observations related to the Premises were addressed in the respective CAPA plan.

6. Personnel

A sufficient and qualified team of medical, paramedical, technical, and clerical staff was available to support the trial and effectively respond to foreseeable emergencies. As of the time of inspection, there were 246 staff members. Throughout all stages of the trial, including at night, there were qualified and trained personnel in place to ensure the rights, safety, and well-being of the subjects were safeguarded, as well as to provide care in case of emergencies. In certain activities, contract workers were employed to complement the capabilities of the core team.

To verify this, a random selection of current curricula vitae and training records involved in trial activities was reviewed.

Clinical section

7. Clinical phase

The clinical phase of the studies took place at the CRO premises, utilizing a CPU with 180 beds across three units. Accommodation facilities were equipped with systems allowing subjects to easily alert CRO staff when needed. The facilities for changing, storing clothes, washing, and toilet purposes were clean, well-ordered, easily accessible, and suitable for the number of users. Additionally, the toilets and showers were lockable and equipped with alarms. During the inspection, the CRO modified the design of the restroom doors to allow them to be opened from the outside in the event of an incident.

The clinical site consisted of:

- subjects' registration and screening; obtaining informed consent of individual subjects without compromising their privacy;
- CPU;
- subjects' recreation;
- pharmacy;
- facility for the administration of the investigational products and sample collection;
- sample processing (e.g., plasma separation) and storage (freezer);
- archive facility in the basement;
- a dining hall;

In case of emergency, The CRO could call 911 for immediate assistance. There were two hospitals located in proximity.

The access to the randomization list was limited to the study's responsible pharmacist. The list was generated by the statistician upon the pharmacy's request, reviewed by the study director, and approved by the report writing group. It was then transmitted to the

pharmacist via email, while a printed copy was securely kept in the pharmacy binder under the pharmacist's supervision.

The equipment used was appropriately calibrated at predefined intervals. The adequate function and performance of emergency-use equipment (e.g., defibrillators) were verified at appropriate intervals.

8. Clinical laboratory

An external clinical laboratory was used for sample analysis. This laboratory was accredited by the Ministry of Health of Ontario.

Haematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol.

Sample labelling, receipt, storage, and chain of custody ensured full traceability and sample integrity.

The CRO received information about the analytical methods used in the laboratory, a dated list of laboratory normal ranges, and the accreditation certificate of the laboratory. However, the CRO had also provided a list of “Acceptable laboratory test ranges”, used for the inclusion and exclusion of volunteers.

The laboratory generated individual reports for each subject to be included in individual binders, together with the Case Report Forms (CRFs). The laboratory transmitted the reports to the clinical unit of the CRO via fax with specific number.

The observation related to the Clinical laboratory was addressed in the respective CAPA plan.

9. Ethics

The trial was approved by the independent ethics committee, on 21 Jul 2022, for the version dated 18 July 2022, prior to the commencement of the study. The independence of this committee from the sponsor, investigator, and CRO was confirmed by reviewing their respective member lists. Detailed minutes of the IEC meetings were maintained, documenting the discussions, recommendations, and decisions made. Sufficient time was provided to the IEC for the review of protocols, informed consent forms (ICFs), and other relevant documentation.

The studies were insured through the insurance company, based in Toronto, Canada, at the time of inspection.

Informed consent form

Information provided to study participants was communicated in English and presented at a level of complexity appropriate to their understanding. This information was conveyed orally, in writing, or through electronic formats such as electronic tablets.

Informed consent was obtained from each subject and duly documented either in writing or electronically via the respective database module before initiating any trial-related activities. The provided information was unambiguous, highlighting that participation in the study was voluntary, and the subject had the right to withdraw from the trial at any time without the need for justification.

Details regarding insurance coverage and procedures for compensation or treatment in case of injury or disability resulting from participation in the trial were made available through the insurance policy.

Volunteers or subjects were encouraged to discuss any concerns they had regarding potential side effects or reactions from the investigational products with a physician before deciding to participate in the trial.

10. Monitoring

The study was not monitored by the sponsor's representative/monitor. However, as per the internal procedures of the CRO, the study underwent both in-process and retrospective QA-verification. The detailed report of the audit program was stored in the respective system, containing information about the study, relevant statements, and the audits conducted.

The QA team performed various audits as part of the process. These audits included a sample processing audit, vital signs audit, a dispensing audit, and a general QA audit. The purpose of these audits was to ensure that the study was conducted in compliance with the applicable requirements, CRO's policies, protocols, SOPs, and other relevant guidelines.

Furthermore, additional procedural inspections were conducted specifically for this study, and the resulting reports were archived within the QA department. Any deviations from the specified requirements were thoroughly documented as part of the QA process.

11. Investigators

The principal investigator (PI) was responsible for the clinical conduct of the study, including clinical aspects of study design, administration of the products under

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investigation, contacts with local authorities and the ethics committee, and signing of the protocol and the final study report. The qualification of the PI was verified.

12. Receiving, storage and handling of investigational drug products

The trial recorded information on the receipt, storage, handling, and accountability of investigational products at each stage. Additionally, verification was conducted on the shipment, delivery, receipt, description, storage conditions, dispensing, administration, reconciliation, and return of the remaining pharmaceutical product. Details of the pharmaceutical product used, such as dosage form, strength, lot number, and expiry date, were also documented.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. The conditions were monitored through temperature monitoring system.

Randomization was performed in accordance with SOP for Randomization scheme creation and distribution and the respective records were maintained, including the randomization list and seed. The randomization list was accessible only to the person who generated it, and the pharmacists responsible for dispensing of the IMPs.

The IPs were properly labelled. Compliance of all labels with the randomization list was verified once they were printed and prior to labelling of the containers. The labels were affixed to the containers to prevent the loss of information when the lid was removed.

Adequate labeling and documentation systems were implemented to ensure accurate administration of the IP. Tear-off labels were utilized, with one portion affixed to the container and the second portion attached to the CRF during dosing, verifying that each subject received the appropriate product.

The empty containers were labelled separately for the test and the reference investigational products. They remained segregated in a secure area under lock and key to avoid the risk of any potential mix-ups until the dispensing stage.

Dispensing and packaging adhered to SOP for IP Dispensing. Prior to opening containers, the area was cleaned, and a second person verified the cleanliness. IMPs were handled with suitable utensils. Tablets were distributed into containers following the randomization list for the IMP. Test and Reference products were handled separately, including labeled containers. Detailed sequential documentation was recorded for each step.

Investigational product accountability and dispensing records were consistently upheld. All activities were documented promptly, including administered doses, returns, destructions, and second person verifications.

Dosing followed SOP for Drug Administration. The procedure was observed during inspection and deemed adequate. CRC, research coordinator, nurse, clinical research technician, and QC staff supervised the dosing. The label was verified prior to administration, and the exact time was recorded on the CRF. A mouth check was conducted using a spatula and penlight to confirm ingestion of solid oral dosage forms. Dosing details were directly recorded in the CRFs.

Investigational product reconciliation was conducted post-dosing and verified by a second responsible individual. Samples from the original container were preserved for potential confirmatory testing, following the relevant requirements. The procedure for sample retention was outlined in the respective SOP and specified in the contract between the sponsor and the CRO. Additionally, unused dispensed products were also retained.

13. Case report forms

Randomly selected CRFs from the study were reviewed.

The data collected on each volunteer was specified in the trial protocol. Subjects participating in the study underwent comprehensive assessments to ensure their health. These assessments included a review of medical history, physical examination, measurement of vital signs, ECG, and clinical laboratory tests (haematology, serum chemistry, serology, urinalysis, urine screening for drugs of abuse and cotinine, breath alcohol test, and serum pregnancy test for females). These evaluations were conducted during the screening phase, within 30 days prior to the initial drug administration, and all recorded in the respective CRFs.

The ECG machine and its software underwent inspection. The software included an audit trail that was linked to each subject. The technician was authorized to make edits limited to changing the Sub ID, which was documented in the audit trail. A screenshot of the audit trail, along with the corresponding ECG printout, was retained in the subject binder.

The observation related to the CRF was addressed in the respective CAPA plan.

14. Volunteers, recruitment methods

The procedures for volunteer recruitment, including the various methods employed by the CRO were outlined in the respective SOP. To prevent cross-participation and ensure a minimum time gap between study involvements, a database was maintained for

volunteers. This database served as a registration platform and optional electronic informed consent form (eICF). Access to the database was password-protected to maintain the confidentiality of volunteers' sensitive information. Volunteers and subjects were identified using their valid photo official ID, which included their signature. No biometric system was utilized for identification purposes.

Informed consent was obtained from potential subjects on a study-specific basis to assess their eligibility for participation. The clinical trial protocol outlined the criteria for subject selection (including inclusion and exclusion criteria) as well as the screening procedures. A software system named RSVP, which relied on fingerprint identification, was employed to identify if any subjects had previously participated in trials conducted by other CROs. Participation data was uploaded to this shared repository to prevent individuals from volunteering for multiple studies and was accessible to other CROs within the district.

15. Food and fluids

Meals were standardized and adequately controlled and scheduled during the study days. The CRO was able to arrange standardized meals, snacks, and drinks for the study subjects as described in the clinical trial protocol and according to the agreement with the catering service. The respective invoices were available and reviewed.

The timing, duration, and quantity of food and fluids consumed were documented. However, deviations from the planned protocol were not reported as it was not required by the study protocol. The CRO communicated the meal-related requirements specified in the protocol to the specialized catering service, which collaborated with CROs and employed qualified dietitians to design a menu tailored to the study protocol.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, performed, and monitored so that the safety profile was acceptable, including to the volunteers. A medical doctor was responsible for medical decisions in the case of adverse events and notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, specifically in the case of a serious adverse event.

First-aid equipment and appropriate rescue medication were available in the clinical unit and ready for emergency use at the study site. Any treatment given to a subject was documented and included in the CRF and the supporting documentation in the clinical unit. A qualified nurse was assigned the responsibility of ensuring the proper functionality of equipment and addressing urgent situations.

The CRO had adverse event and concomitant medication registration and reporting forms as part of the CRF.

Bioanalytical section

During the inspection, the data pertaining to the study and its associated validation projects were examined. Specifically, the following records and activities were investigated:

- Source documentation and raw data concerning the validation of bioanalytical methods.
- Analysis of subject plasma samples, including the corresponding electronic data.
- Audit trails associated with the electronic data capture and handling pertaining to the bioequivalence (BE) studies.
- Results obtained from calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs. Additionally, the chromatograms generated from these analytical runs were reviewed.
- Documentation regarding the preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents.

Furthermore, chromatograms and their integration, the absence of signals in the blank samples, and the absence of any unexplained interruptions in the injected sequences were randomly verified. The reason for the study sample repeat analyses and all instrument failures was reviewed. The provisions and the documentation of the ISRs were confirmed. The documentation and justification for the reinjection of the analytical runs were verified and compared to the provisions.

During the review of study documentation, the inspection team received sufficient support from knowledgeable and transparent personnel. The inspectors were granted access to the chromatograph software database and the corresponding raw data for examination during the inspection.

As the chromatograms in the chromatography data system did not display the sample concentration, and the data acquisition was performed using a software while regression calculations were carried out in a LIMS software system, random comparisons were made between the data in the LIMS and the original data to ensure the accuracy and data integrity.

17. Method development, Method validation & Analysis of study samples

The method development process was adequately described and documented, and the usage of IS was justified based on the relevant literature. A copy of the literature was available. After method development, an analytical plan/procedure was provided as a basis

for the method validation. A stable analogue internal standard was used in the MS method, and K₂EDTA was applied as an anticoagulant.

To evaluate trends over time within a single run, accuracy and precision were demonstrated using QC samples at LLOQ, LQC, MQC, and HQC levels. This assessment was performed in a Long Batch, which had a size equivalent to a prospective analytical run, following SOP for Bioanalytical method validation. The acceptance criteria for the Long Batch were the same as intra-run accuracy and precision, and the run size was calculated from the first to the last injection of the run. This helped to establish the maximum run size for analyzing study samples.

The sample processing was documented in the respective forms. A note to file was also provided to record any unexpected activity during sample processing, when applicable. Repeat analysis & reporting criteria for non-clinical (GLP) & clinical study samples were conducted in accordance with the applicable SOP.

Data to support the stability of the samples under the stated conditions and period of storage was available before the start of the studies, except for the long-term stability, which was performed before the issuance of the study reports. An addendum was provided dated 14 Oct 2022.

The method validation review encompassed several aspects, including precision and accuracy testing (P&A), sensitivity, selectivity, matrix effect, calibration curve, autosampler carry-over, and stability evaluations (such as freeze-thaw stability, stock solution stability, recovery, and reinjection reproducibility). Partial validation was conducted as per the applicable requirements. The matrix utilized for the analytical method validation matched the matrix of the study samples, including anticoagulants. The purchase documentation of the plasma, which included receipts, storage procedures, retrieval methods, preparation, and utilization of the pooled plasma, was thoroughly reviewed and discussed. The CRO had provided information about conducting all other necessary tests related to method validation, i.e., assessments of dilution integrity, reference standard storage stability, and the potential hemolytic effect.

In each analytical run, calibration curve (CC) standards, interspersed QC samples, and subject samples were simultaneously processed. A set of CCs was also employed for bracketing at the end of each run. The precise sequence of processing was defined and documented. All samples collected from a particular subject throughout the trial periods were analyzed within the same run.

The acceptance criteria for analytical runs were confirmed through a review of various factors, including analytes' retention time, accuracy of calibration standard and QC samples, peak integration, and internal standard (IS) peak areas, following the relevant SOPs. Calculations were performed using the LIMS software system, utilizing instrument response ratios. Sample concentrations were not available in the chromatography data system for sample analysis. However, for method validation calculations, information from the chromatography data system was used, and acceptance criteria were directly computed on the AP forms or available options within the chromatography data system were employed.

A system suitability test was conducted if there was a time gap exceeding 24 hours between consecutive runs. Prior to commencing each day's runs, a system check test, and an Equilibrium (stabilization) test were performed.

The number of samples selected for an Incurred Sample Reanalysis (ISR) test depended on the study size, with a minimum requirement of 20 ISR samples. In studies with fewer than 1000 samples, the ISR sample count should be 10% of the total number of samples. For studies with more than 1000 samples, the ISR sample count should be 10% of the first 1000 samples (i.e., 100), plus an additional 5% of the remaining samples. The chosen ISR samples should be representative of all subjects analyzed in the study. For each subject, at least two samples were selected for ISR testing. These samples included one at or near the C_{max} and another during the elimination phase. The acceptance criteria for ISR testing were clearly defined in SOP for both non-clinical and clinical Incurred Sample Reanalysis.

The system audit trail review was conducted during the study as part of the inspection process. The personnel responsible for the review had received appropriate training and possessed sufficient expertise in conducting such audits.

The observation related to the Method development was addressed in the respective CAPA plan.

18. Sample collection, storage and handling of biological material

The clinical trial protocol and information provided to the volunteers clearly outlined the specifications of the samples, including blood plasma, the sampling method, volume, and the required number of samples. The collection, preparation, transportation, shipping, and storage of the samples were performed following SOP for Receipt, Logging, Storage, Handling, and Disposal of non-clinical and clinical study samples.

Actual sampling times and deviations from the prespecified sampling times were recorded, and the respective deviations were to be considered when calculating the pharmacokinetic parameters.

The labelling of collected samples was done clearly to ensure accurate identification and traceability of each sample. All storage conditions, including freezer temperature, were carefully controlled, monitored, and recorded during both storage and transportation. Detailed records of sample storage and retrieval were maintained.

To ensure safe storage, samples were duplicated into two aliquots, which were then separately transferred between departments and stored in separate locations. Aliquot 1 samples were stored at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$, both before and after sample analysis. Aliquot 2 samples were similarly stored at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ in a different freezer, both prior to and following sample analysis.

19. Data processing and documentation

The integration settings employed were scientifically grounded and fully justifiable. The smoothing factor was maintained at a low level to avoid obscuring potential interferences and alterations in peak geometry. The recommended range for the smooth value was set from 0 to 3. If a higher factor was deemed necessary, the rationale behind it was required to be justified and documented in adherence to the applicable SOP.

The acceptance and exclusion criteria for calibration curve (CC) standards and quality control (QC) samples, as well as batch acceptance, were clearly outlined in the relevant SOP. The source data for all the analytical runs contained all information about the original first evaluation of runs (containing all calibration samples) when the analysis was repeated. To ensure accurate analysis, the calibration range was appropriately truncated. Variations in the internal standard were carefully tracked and utilized as part of the verification process to validate the results.

The CRO implemented a specific approach during the analytical runs, utilizing odd CCs at the beginning of each run and reserving the even CCs for bracketing purposes at the end of each run. Additionally, for each run, the CRO included two lower limit of quantification (LLOQ) and two upper limit of quantification (ULOQ) CCs to ensure accurate quantification across the entire concentration range.

All essential analytical raw data, such as calculations, chromatograms, and their associated audit trails, were recorded to ensure traceability. This documentation included details such as the sample number, equipment used, date and time of analysis, and the names of the technician(s) involved. Audit trail files, including the results table audit trail, project audit

trail, and instrument audit trail (excluding the instrument audit trail of MS08), were carefully retained.

Each data point was traceable to a specific sample, including sample number, time of collection of the sample, time of centrifugation, time when the sample was placed in the freezer, and time of sample analysis, to be able to determine whether any aberrant results might have been caused by sample mishandling.

20. Good laboratory practices

A tour of the facility was conducted on Day 3 to assess the suitability of the arrangement and safety measures. The bioanalytical part of the BE studies adhered to the general principles of Good Laboratory Practice (GLP), and an appropriate Quality Assurance (QA) system was in place.

The deep freezers for sample storage and refrigerators for reference standards were properly qualified, calibrated, and maintained. An alarm system connected to the digital temperature monitoring system was in place, triggering email notifications to the responsible custodians. During inspection, the automatic alarm system was tested to ensure it functioned correctly. Daily monitoring and alarm checks were electronically documented in the software application. The deep freezers, along with the storage facilities for reference standards, were securely locked in a separate room

The temperature mapping of randomly selected Deep Freezers was reviewed to verify the hotspots and sensor placement. The sensor, located in a container with ice beads, underwent testing. The temperature mapping for the freezer in the clinical unit's sample processing (used for all 5 units) was conducted on 1 Jan 2021, as per the regular 3-year interval which applied during the study. The mapping process was properly executed during inspection. The transfer of samples to alternative storage units was appropriately managed during maintenance and repairs. Deep freezers were defrosted as necessary.

Balances, measuring devices, equipment, and instruments utilized during the trial were regularly calibrated and verified to ensure their suitability for the intended purpose. Balances and pipettes underwent verification before each use.

The operation, use, calibration, checks, and preventive maintenance of equipment were outlined in the corresponding SOPs. Records were maintained to comply with relevant requirements. Random reviews were conducted to verify these activities on equipment used for study-related tasks. Equipment and its components were appropriately labelled with ID numbers, calibration dates, and the next calibration dates. Equipment usage was thoroughly documented in analytical sheets and templates designed for recording

instrument usage. The column usage was recorded in the analytical sheets. These templates were generated using the respective software under the supervision of the QA unit.

During the inspection, randomly selected qualification documentation was reviewed.

Chemicals, reference substances, reagents, solvents, and solutions were labelled to indicate identity, purity, concentration when appropriate, expiry date, and specific storage instructions. Information concerning the source, preparation date, and stability was available on the label or the CoA. Water for use in the laboratory was purchased from known suppliers.

Observations related to the Good Laboratory Practices were addressed in the respective CAPA plan.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

During the inspection, a review of the processes and procedures related to PK analysis and randomization list generation was conducted.

The randomization list process involved the pharmacy sending a request a few days before the dispensing began. The list was then shared with the medical writing team. After ensuring the absence of errors, the list was finalized and provided to the pharmacy. SAS software application was used for generating the randomization list.

Regarding PK analysis, timepoints from the clinical unit were stored in a designated folder on a Drive (storage location), accessible to statisticians and Clinical Research Coordinators (CRCs). BA-data was transferred to a separate folder in the Drive, managed by the laboratory, and once it was ready, the data was quality-checked, and approved.

The data was reviewed before being used in SAS software for PK analysis. Initially, the primary statistician performed the preliminary processing, followed by a review and verification of the modifications by a QC statistician. A copy of the processed data was saved, and a note was added to the folder to document the completion of data checks. The QC statistician ensured that the data aligned with the statistical model.

The inspection also addressed the data lock process, for which a specific SOP was available. Results of the PK analysis were stored in a designated folder, and a verification

was performed by the PK team, followed by random checks performed by the QA team. The inspection included a review and discussion of the access to the folders.

The medical writing team was responsible for writing the protocol and sharing it with the statistician for revisions to the statistical analysis, as necessary. The statistical model was specified in the protocol and/or a statistical analysis plan.

The statistician involved in the analysis was adequately qualified. A database of trial records was maintained and locked soon after the completion of the study. Once the data was locked, the study was unblinded, and statistical analysis was performed. Although the locking and statistical analysis dates were documented, they were not mentioned in the study report. The process for the review and control of bioanalytical laboratory documentation was outlined in the respective SOP.

22. Study report

The process of study report writing was verified during the inspection. Procedures were established to ensure the quality and integrity of the study report. No discrepancies were identified between the results stated in the report and the original (raw) data.

Miscellaneous	
<i>Samples taken</i>	N/A
<i>Assessment of the CRO master file</i>	The CRO master (CROMF) file was provided and reviewed.
<i>Annexes attached</i>	N/A

Part 3	Conclusion – inspection outcome
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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 study was considered to have been conducted at an acceptable level of compliance with WHO GCP/GLP/BE guidelines at **Bio Pharma Services Inc.**, located at **4000 Weston Road, Toronto, Ontario, M9L 3A2; Canada.**

All the non-compliances observed during the inspection that were listed in the complete 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 three years, provided that the outcome of any inspection conducted during this period is positive.

Part 4**List of guidelines referenced in the inspection report**

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
Short name: WHO BE guidance or TRS996 Annex 9
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
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
4. 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**
5. 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
6. 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
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
8. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
Short name: Glove use information leaflet
9. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO

Bio Pharma Services Inc., Toronto Canada, CRO

10-14 July 2023

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Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.

Short name: TRS 1003 Annex 6

10. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.

Short name: WHO TRS No. 1025, Annex 4

11. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.

Short name: WHO TRS 1033, Annex 4

12. Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical principles for medical research involving human subjects, Bulletin of the World Health Organization, 2001 (79(4)).

Short name: Declaration of Helsinki

13. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022

Short name: ICH M10

14. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.

Short name: WHO TRS No. 1019, Annex 3

15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Frothiest report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.

Short name: WHO No. 937, Annex 4