

SOLICITATION/CONTRACT/ORDER FOR COMMERCIAL ITEMS OFFEROR TO COMPLETE BLOCKS 12, 17, 23, 24, & 30				1. REQUISITION NUMBER 6809406		PAGE OF 1 6						
2. CONTRACT NO. 75N95024P00039			3. AWARD/ EFFECTIVE DATE		4. ORDER NUMBER		5. SOLICITATION NUMBER					
7. FOR SOLICITATION INFORMATION CALL:			a. NAME GIULIANA FALLER			b. TELEPHONE NUMBER (No collect calls) +1 301 480 9789		6. SOLICITATION ISSUE DATE				
9. ISSUED BY National Institutes of Health National Institute on Drug Abuse Bethesda, MD 20892-7511				CODE NIDA-EXEC		10. THIS ACQUISITION IS ☒ UNRESTRICTED OR ☐ SET ASIDE: % FOR: ☐ SMALL BUSINESS ☐ WOMEN-OWNED SMALL BUSINESS (WOSB) ☐ HUBZONE SMALL BUSINESS ☐ ECONOMICALLY DISADVANTAGED WOMEN-OWNED SMALL BUSINESS (EDWOSB) ☐ SERVICE-DISABLED VETERAN-OWNED SMALL BUSINESS (SDVOSB) ☐ 8(A)		NORTH AMERICAN INDUSTRY CLASSIFICATION STANDARD (NAICS): 541380 SIZE STANDARD: \$19				
11. DELIVERY FOR FREE ON BOARD (FOB) DESTINATION UNLESS BLOCK IS MARKED ☒ SEE SCHEDULE		12. DISCOUNT TERMS PROMPT PAY		13a. THIS CONTRACT IS A RATED ☐ ORDER UNDER THE DEFENSE PRIORITIES AND ALLOCATIONS SYSTEM - DPAS (15 CFR 700)		13b. RATING 14. METHOD OF SOLICITATION ☐ REQUEST FOR QUOTE (RFQ) ☐ INVITATION FOR BID (IFB) ☐ REQUEST FOR PROPOSAL (RFP)						
15. DELIVER TO CODE Redacted by agreement 9800 Medical Center Dr Redacted by agreement Rockville MD 20850				16. ADMINISTERED BY CODE NIDA National Institutes of Health National Institute on Drug Abuse Bethesda, MD 20892-7511								
17a. CONTRACTOR/ OFFEROR CODE L8NQAFSTPSY9 PHARMARON, INC.:1208250 201 E JEFFERSON STREET SUITE 304 LOUISVILLE KY 402021249		FACILITY CODE		18a. PAYMENT WILL BE MADE BY CODE NIH COMMERCIAL A NIH Commercial Accts Paid By: NIH Commercial Accounts Br 6701 Rockledge Drive 3rd Floor Bethesda, MD 20892-7784								
TELEPHONE NO. -				17b. CHECK IF REMITTANCE IS DIFFERENT AND PUT SUCH ADDRESS IN OFFER								
18b. SUBMIT INVOICES TO ADDRESS SHOWN IN BLOCK 18a UNLESS BLOCK BELOW IS CHECKED ☐ SEE ADDENDUM												
19. ITEM NO.		20. SCHEDULE OF SUPPLIES/SERVICES			21. QUANTITY		22. UNIT		23. UNIT PRICE		24. AMOUNT	
		UEI: L8NQAFSTPSY9 The purpose of this Purchase Order is to provide the National Center for Advancing Translational Sciences (NCATS) Pharmacokinetics assessment in Mice and Rats (40 Compounds) in accordance with the Statement of Work (SOW) and Pharmaron Inc. Quotation PH-NIH-PK-2023-043 dated November 20, 2023. FY2024 funds are obligated in the total Firm-Fixed Price amount of \$108,000.00 to fully fund this purchase order. (Use Reverse and/or Attach Additional Sheets as Necessary)										
25. ACCOUNTING AND APPROPRIATION DATA See schedule								26. TOTAL AWARD AMOUNT (For Government Use Only) \$108,000.00				
☐ 27a. SOLICITATION INCORPORATES BY REFERENCE (FEDERAL ACQUISITION REGULATION) FAR 52.212-1, 52.212-4, FAR 52.212-3 AND 52.212-5 ARE ATTACHED. ADDENDA								☐ ARE ☐ ARE NOT ATTACHED.				
☒ 27b. CONTRACT/PURCHASE ORDER INCORPORATES BY REFERENCE FAR 52.212-4. FAR 52.212-5 IS ATTACHED. ADDENDA								☒ ARE ☐ ARE NOT ATTACHED.				
☐ 28. CONTRACTOR IS REQUIRED TO SIGN THIS DOCUMENT AND RETURN COPIES TO ISSUING OFFICE. CONTRACTOR AGREES TO FURNISH AND DELIVER ALL ITEMS SET FORTH OR OTHERWISE IDENTIFIED ABOVE AND ON ANY ADDITIONAL SHEETS SUBJECT TO THE TERMS AND CONDITIONS SPECIFIED.						☒ 29. AWARD OF CONTRACT: REFERENCE PH-NIH-PK-2023-04 OFFER DATED 11/20/2023. YOUR OFFER ON SOLICITATION (BLOCK 5), INCLUDING ANY ADDITIONS OR CHANGES WHICH ARE SET FORTH HEREIN, IS ACCEPTED AS TO ITEMS: All						
30a. SIGNATURE OF OFFEROR/CONTRACTOR						31a. UNITED STATES OF AMERICA (SIGNATURE OF CONTRACTING OFFICER) Khurram M. Shaikh -S Digitally signed by Khurram M. Shaikh -S Date: 2023.11.28 16:21:03 -05'00'						
30b. NAME AND TITLE OF SIGNER (Type or print)				30c. DATE SIGNED		31b. NAME OF CONTRACTING OFFICER (Type or print) KHURRAM M. SHAIKH				31c. DATE SIGNED		

19. ITEM NO.	20. SCHEDULE OF SUPPLIES/SERVICES	21. QUANTITY	22. UNIT	23. UNIT PRICE	24. AMOUNT
1	PURCHASE ORDER ATTACHMENTS: 1. Statement of Work 2. Vendor (Pharmaron Inc) quotation PH-NIH-PK-2023-043 3. VAS Vertebrate Animals 4 FAR 52.212-4 Addendum (Dec 2022) 4. FAR 52.212-5 Contract Terms and Conditions Required to Implement Statutes or Executive Orders - Commercial Items (Sept 2023) 5. NIH Invoice and Payment Provisions. Please be advised that the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH) is a Federal agency. Your mass-market commercial sales and/or license agreement terms and conditions may include provisions that are customarily found in the commercial sector but which are not enforceable under a contract with a Federal agency. Delivery: 11/28/2024 Period of Performance: 11/28/2023 to 11/28/2024 Delivery: 11/28/2024 Period of Performance: 11/28/2023 to 11/28/2024 Pharmacokinetics Experiments, n=40, 2 ARM, rodent Catalog # : na Delivery To: Redacted by agreement Product/Service Code: Q301 Continued ...				108,000.00

32a. QUANTITY IN COLUMN 21 HAS BEEN

☐ RECEIVED ☐ INSPECTED ☐ ACCEPTED, AND CONFORMS TO THE CONTRACT, EXCEPT AS NOTED: _____

32b. SIGNATURE OF AUTHORIZED GOVERNMENT REPRESENTATIVE		32c. DATE	32d. PRINTED NAME AND TITLE OF AUTHORIZED GOVERNMENT REPRESENTATIVE	
32e. MAILING ADDRESS OF AUTHORIZED GOVERNMENT REPRESENTATIVE			32f. TELEPHONE NUMBER OF AUTHORIZED GOVERNMENT REPRESENTATIVE	
			32g. E-MAIL OF AUTHORIZED GOVERNMENT REPRESENTATIVE	
33. SHIP NUMBER	34. VOUCHER NUMBER	35. AMOUNT VERIFIED CORRECT FOR	36. PAYMENT	37. CHECK NUMBER
☐ PARTIAL ☐ FINAL			☐ COMPLETE ☐ PARTIAL ☐ FINAL	
38. S/R ACCOUNT NUMBER	39. S/R VOUCHER NUMBER	40. PAID BY		
41a. I CERTIFY THIS ACCOUNT IS CORRECT AND PROPER FOR PAYMENT			42a. RECEIVED BY (<i>Print</i>)	
41b. SIGNATURE AND TITLE OF CERTIFYING OFFICER		41c. DATE	42b. RECEIVED AT (<i>Location</i>)	
			42c. DATE REC'D (YY/MM/DD)	42d. TOTAL CONTAINERS

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REFERENCE NO. OF DOCUMENT BEING CONTINUED

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NAME OF OFFEROR OR CONTRACTOR

PHARMARON, INC.:1208250

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)
	Product/Service Description: MEDICAL- LABORATORY TESTING Project Data: 134176.2024.100.HN91 OD OFFICE OF THE DIRECTOR.25626 LAB&TESTING SERVICES.10/23/2023 Accounting Info: 08027520241RAD.2024.01.9100.HN91000000C.R.00301.90 2.9999.25626.61000001.9999.9999.NTR12008001 Funded: \$108,000.00 A monthly report shall be emailed to the following: Redacted by agreement ANIMAL WELFARE Animal Welfare Assurance Number: F16-00202 (A5844-01) All research involving live, vertebrate animals shall be conducted in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy). The PHS Policy can be accessed at http://grants1.nih.gov/grants/olaw/references/phspol.htm. In addition, the research involving live vertebrate animals shall be conducted in accordance with the description set forth in the Vertebrate Animal Section (VAS) of the Contractor's technical proposal, which was submitted to NIH on May 16, 2023 and is attached to this purchase order. CLAUSES The clause at FAR 52.252-2, Clauses Incorporated by Reference (Feb 1998). This contract incorporates one or more clauses by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. Also, the full text of a clause may be accessed electronically at www.acquisition.gov. The following clauses apply to this acquisition and are incorporated by reference: 1. The clause at FAR 52.204-13, System for Award Continued ...				

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NAME OF OFFEROR OR CONTRACTOR

PHARMARON, INC.:1208250

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)
	Management Maintenance (Oct 2018) 2. The clause at FAR 52.204-18, Commercial and Government Entity Code Maintenance (Aug 2020) 3. The clause at FAR 52.212-4, Contract Terms and Conditions ; Commercial Items (Dec 2022) 4. The clause at FAR 52.227-14, Rights in Data-General (May 2014)- In addition, the contractor must obtain approval from the contracting officer to assert copyright in any data first produced in performance of this contract and published in academic, technical or professional journals, symposia proceedings, or similar works. The contractor must also obtain approval from the contracting officer to use, release to others, reproduce, distribute, or publish any data first produced or specifically used by the contractor in the performance of this contract. 5. The clause at HHSAR 352.222-70, Contractor Cooperation in Equal Employment Opportunity Investigations (December 18, 2015) 6. The clause at HHSAR 352.223-70, Safety and Health (December 18, 2015) The clause at HHSAR 352.270-5b, Care of Live Vertebrate Animals (December 18, 2015). (a) Before undertaking performance of any contract involving animal-related activities where the species is regulated by the United States Department of Agriculture (USDA), the Contractor shall register with the Secretary of Agriculture of the United States in accordance with 7 U.S.C. 2136 and 9 CFR 2.25 through 2.28. The Contractor shall furnish evidence of the registration to the Contracting Officer. (b) The Contractor shall acquire vertebrate animals used in research from a dealer licensed by the Secretary of Agriculture under 7 U.S.C. 2133 and 9 CFR 2.1-2.11, or from a source that is exempt from licensing under those sections. (c) The Contractor agrees that the care, use, and intended use of any live vertebrate animals in the performance of this contract shall conform with the Public Health Service (PHS) Policy on Humane Care of Use of Laboratory Animals (PHS Policy), the current Animal Welfare Assurance Continued ...				

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NAME OF OFFEROR OR CONTRACTOR

PHARMARON, INC.:1208250

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)
	(Assurance), the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC) and the pertinent laws and regulations of the United States Department of Agriculture (see 7 U.S.C. 2131 et seq. and 9 CFR subchapter A, Parts 1-4). In case of conflict between standards, the more stringent standard shall govern. (d) If at any time during performance of this contract, the Contracting Officer determines, in consultation with the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health (NIH), that the Contractor is not in compliance with any of the requirements and standards stated in paragraphs (a) through (c) above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects the noncompliance. Notice of the suspension may be communicated by telephone and confirmed in writing. If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer's written notice of suspension, the Contracting Officer may, in consultation with OLAW, NIH, terminate this contract in whole or in part, and the Contractor's name may be removed from the list of those contractors with Animal Welfare Assurances. Note: The Contractor may request registration of its facility and a current listing of licensed dealers from the Regional Office of the Animal and Plant Health Inspection Service (APHIS), USDA, for the region in which its research facility is located. The location of the appropriate APHIS Regional Office, as well as information concerning this program may be obtained by contacting the Animal Care Staff, USDA/APHIS, 4700 River Road, Riverdale, Maryland 20737 (Email: ace@aphis.usda.gov; Web site: (http://www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalwelfare)). (End of clause) The Technical Point of Contact is Redacted by agreement Continued ...				

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NAME OF OFFEROR OR CONTRACTOR
PHARMARON, INC.:1208250

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)
	Redacted by agreement Invoicing will be a 3-way match and the primary point-of-contact for Invoice Payment Inquiries please contact The Office of Financial Management at ofm_customer_service@incontactemail.com or via phone at 301.496.6088. For additional assistance with invoicing, please contact the following NCATS personnel: Karen Elmore Phone: 301.435.0842 Email: karen.elmore@nih.gov				

WHITE COAT WASTE PROJECT



STATEMENT OF WORK (SERVICES) (SOW)

GENERAL INFORMATION

Title of Project:

Pharmacokinetics assessment in Mice and Rats

Statement of Need and Purpose:

This requisition is for the following:

1. Assessment of 40 novel compounds in a pharmacokinetics assessment

Background Information and Objective:

The National Institutes of Health (NIH) is the nation's leading medical research agency and the primary Federal agency whose mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability, conducting, supporting and making medical discoveries that improve people's health and save lives. The National Center for Advancing Translational Sciences (NCATS) is a translational science center that prides itself on its tremendously productive pipeline and is innovative in a number of ways. NCATS brings together a diverse range of scientists, including medicinal chemists, biologists, toxicologists, and engineers, in order to ultimately translate basic science into real products and services that help improve people's lives. Included in this process is the development of unique small molecules as potential anticancer agents or as potential for regenerative medicine.

Pharmacokinetics plays a critical role in determining the available drug in an living system for the target of interest, by determining the overall level of the drug. This parameter is key to assessing the potential in vivo efficacy of the drug.

Period of Performance:

1. Period of performance is within 12 months from the contract award and receipt of first batch of material

SCOPE OF WORK

General Requirements:

Independently and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government as needed to perform the Statement of Work below:

Specific Requirements:

1. 40 compounds in a Pharmacokinetics assay
 - a. The assay will have an N= 3 on the number of animals used
 - b. The animals to be used will be either CD-1 or C57 mice, or alternatively Sprague Dawley or Han Wistar rats

- c. 8 time points will be assessed over 24 hours
- d. Plasma levels of the given small molecule will be measured at each of these time points
- e. An excel spreadsheet will be provided as a report with the necessary information

LEVEL OF EFFORT:

1 Biologist, ~80 hours

GOVERNMENT RESPONSIBILITIES

Government has the responsibility to send the compounds, and review the data

DELIVERY OR DELIVERABLES

1 report and interim reports as needed.

REPORTING REQUIREMENTS

Monthly by e-mail

OTHER CONSIDERATIONS

Travel:

N/A

Key Personnel:

N/A

Information System Security Plan:

N/A

Data Rights:

All data will be considered confidential and property of the government

Section 508—Electronic and Information Technology Standards:

N/A

Publications and Publicity:

Data will not be published without permission of the government

Confidentiality of Information:

Data will be kept confidential

ATTACHMENTS

1. Independent Government's Cost Estimate
2. Evaluation / Selection Criteria



Redacted by agreement

WHITE COAT
WASTE
PROJECT



Addendum to FAR 52.212-4 Terms and Conditions – Commercial Items

(s) *Order of precedence.* Any inconsistencies in this solicitation or contract shall be resolved by giving precedence in the following order:

- (1) The schedule of supplies/services
- (2) The Assignments, Disputes, Payments, Invoice, Other Compliances, Compliance with Laws Unique to Government Contracts, Unauthorized Obligations, and Commercial Supplier Agreements – Unenforceable Clauses paragraphs of this clause.
- (3) The clause at 52.212-5.
- (4) Addenda to this solicitation or contract, including any commercial supplier agreements as amended by the Commercial Supplier Agreements – Unenforceable Clauses provision.
- (5) Solicitation provisions if this is a solicitation.
- (6) Other paragraphs of this clause.
- (7) The Standard Form 1449.
- (8) Other documents, exhibits, and attachments.
- (9) The specification.

(w) *Commercial supplier agreements–unenforceable clauses.*

(1) Definition. For the purpose of this contract, “Commercial supplier agreements” (referred to at FAR 12.216 as “Supplier License Agreements”) means terms and conditions customarily offered to the public by vendors of supplies or services that meet the definition of “commercial item” set forth in FAR 2.101 and intended to create a binding legal obligation on the end user. Commercial supplier agreements are particularly common in information technology acquisitions, including acquisitions of commercial computer software and commercial technical data, but they may apply to any supply or service. The term applies–

- (a) Regardless of the format or style of the document. For example, a commercial supplier agreement may be styled as standard terms of sale or lease, Terms of Service (TOS), End User License Agreement (EULA), or another similar legal instrument or agreement, and may be presented as part of a proposal or quotation responding to a solicitation for a contract or order;
- (b) Regardless of the media or delivery mechanism used. For example, a commercial supplier agreement may be presented as one or more paper documents or may appear on a computer or other electronic device screen during a purchase, software installation, other product delivery, registration for a service, or another transaction.

(2) When any supply or service acquired under this contract is subject to a commercial supplier agreement, and notwithstanding any other provision of this agreement, when the end user is an agency or instrumentality of the U.S. Government, the following language shall be deemed incorporated into the commercial supplier agreement. As used herein, "this agreement" means the commercial supplier agreement.

(i) *Applicability.* This agreement is a part of a contract between the commercial supplier and the U.S. Government for the acquisition of the supply or service that necessitates a license or other similar legal instrument (including all contracts, task orders, and delivery orders under FAR Part 12).

(ii) *End user.* This agreement shall bind the ordering activity as end user but shall not operate to bind a Government employee or person acting on behalf of the Government in his or her personal capacity.

(iii) *Law and disputes.* This agreement is governed by Federal law.

(A) Any language purporting to subject the U.S. Government to the laws of a U.S. state, U.S. territory, district, or municipality, or a foreign nation, except where Federal law expressly provides for the application of such laws, is hereby deleted.

(B) Any language requiring dispute resolution in a specific forum or venue that is different from that prescribed by applicable Federal law is hereby deleted.

(C) Any language prescribing a different time period for bringing an action than that prescribed by applicable Federal law in relation to a dispute is hereby deleted.

(iv) *Continued performance.* The supplier or licensor shall not unilaterally revoke, terminate or suspend any rights granted to the Government except as allowed by this contract. If the supplier or licensor believes the ordering activity to be in breach of the agreement, it shall pursue its rights under the Contract Disputes Act or other applicable Federal statute while continuing performance as set forth in subparagraph 52.212-4(d) (Disputes).

(v) *Arbitration; equitable or injunctive relief.* In the event of a claim or dispute arising under or relating to this agreement, a binding arbitration shall not be used unless specifically authorized by agency guidance, and equitable or injunctive relief, including the award of attorney fees, costs or interest, may be awarded against the U.S. Government only when explicitly provided by statute (e.g., Prompt Payment Act or Equal Access to Justice Act).

(vi) Updating terms.

(A) After award, the contractor may unilaterally revise commercial supplier agreement terms if they are not material. A material change is defined as:

- (1) Terms that change Government rights or obligations;
- (2) Terms that increase Government prices;
- (3) Terms that decrease overall level of service; or
- (4) Terms that limit any other Government right addressed elsewhere in this contract.

(B) For revisions that will materially change the terms of the contract, the revised commercial supplier agreement must be incorporated into the contract using a bilateral modification.

(C) Any agreement terms or conditions unilaterally revised subsequent to award that are inconsistent with any material term or provision of this contract shall not be enforceable against the Government, and the Government shall not be deemed to have consented to them.

(vii) *No automatic renewals.* If any license or service tied to periodic payment is provided under this agreement (e.g., annual software maintenance or annual lease term), such license or service shall not renew automatically upon expiration of its current term without prior express consent by an authorized Government representative.

(viii) *Indemnification.* Any clause of this agreement requiring the commercial supplier or licensor to defend or indemnify the end user is hereby amended to provide that the U.S. Department of Justice has the sole right to represent the United States in any such action, in accordance with 28 U.S.C. 516.

(ix) *Audits.* Any clause of this agreement permitting the commercial supplier or licensor to audit the end user's compliance with this agreement is hereby amended as follows:

(A) Discrepancies found in an audit may result in a charge by the commercial supplier or licensor to the ordering activity. Any resulting invoice must comply with the proper invoicing requirements specified in the underlying Government contract or order.

(B) This charge, if disputed by the ordering activity, will be resolved in accordance with subparagraph (d) (Disputes); no payment obligation shall arise on the part of the ordering activity until the conclusion of the dispute process.

(C) Any audit requested by the contractor will be performed at the contractor's expense, without reimbursement by the Government.

(x) *Taxes or surcharges.* Any taxes or surcharges which the commercial supplier or licensor seeks to pass along to the Government as end user will be governed by the terms of the underlying Government contract or order and, in any event, must be submitted to the Contracting Officer for a determination of applicability prior to invoicing unless specifically agreed to otherwise in the Government contract.

(xi) *Non-assignment.* This agreement may not be assigned, nor may any rights or obligations thereunder be delegated, without the Government's prior approval, except as expressly permitted under subparagraph (b) of this clause.

(xii) *Confidential information.* If this agreement includes a confidentiality clause, such clause is hereby amended to state that neither the agreement nor the contract price list, as applicable, shall be deemed "confidential information." Issues regarding release of "unit pricing" will be resolved consistent with the Freedom of Information Act. Notwithstanding anything in this agreement to the contrary, the Government may retain any confidential information as required by law, regulation or its internal document retention procedures for legal, regulatory or compliance purposes; provided, however, that all such retained confidential information will continue to be subject to the confidentiality obligations of this agreement.

(3) If any language, provision, or clause of this agreement conflicts or is inconsistent with the preceding paragraph (1), the language, provisions, or clause of paragraph (1) shall prevail to the extent of such inconsistency.

(End of clause)

52.212-5 CONTRACT TERMS AND CONDITIONS REQUIRED TO IMPLEMENT STATUTES OR EXECUTIVE ORDERS—COMMERCIAL PRODUCTS AND COMMERCIAL SERVICES (NOV 2023)

(a) The Contractor shall comply with the following Federal Acquisition Regulation (FAR) clauses, which are incorporated in this contract by reference, to implement provisions of law or Executive orders applicable to acquisitions of commercial products and commercial services:

(1) 52.203-19, Prohibition on Requiring Certain Internal Confidentiality Agreements or Statements (Jan 2017) (section 743 of Division E, Title VII, of the Consolidated and Further Continuing Appropriations Act, 2015 (Pub. L. 113-235) and its successor provisions in subsequent appropriations acts (and as extended in continuing resolutions)).

(2) 52.204-23, Prohibition on Contracting for Hardware, Software, and Services Developed or Provided by Kaspersky Lab and Other Covered Entities (Nov 2021) (Section 1634 of Pub. L. 115-91).

(3) 52.204-25, Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment. (Nov 2021) (Section 889(a)(1)(A) of Pub. L. 115-232).

(4) 52.209-10, Prohibition on Contracting with Inverted Domestic Corporations (Nov 2015).

(5) 52.232-40, Providing Accelerated Payments to Small Business Subcontractors (Mar 2023) (31 U.S.C. 3903 and 10 U.S.C. 3801).

(6) 52.233-3, Protest After Award (Aug 1996) (31 U.S.C. 3553).

(7) 52.233-4, Applicable Law for Breach of Contract Claim (Oct 2004) (Public Laws 108-77 and 108-78 (19 U.S.C. 3805 note)).

(b) The Contractor shall comply with the FAR clauses in this paragraph (b) that the Contracting Officer has indicated as being incorporated in this contract by reference to implement provisions of law or Executive orders applicable to acquisitions of commercial items:

[Contracting officer check as appropriate.]

- | | | | |
|-------------------------------------|------|-----------|--|
| ☐ | (1) | 52.203-6 | Restrictions on Subcontractor Sales to the Government (June 2020), with Alternate I (Nov 2021) (41 U.S.C. 4704 and 10 U.S.C. 4655). |
| ☐ | (2) | 52.203-13 | Contractor Code of Business Ethics and Conduct (Nov 2021) (41 U.S.C. 3509)). |
| ☐ | (3) | 52.203-15 | Whistleblower Protections under the American Recovery and Reinvestment Act of 2009 (June 2010) (Section 1553 of Pub. L. 111-5). (Applies to contracts funded by the American Recovery and Reinvestment Act of 2009.) |
| ☒ | (4) | 52.203-17 | Contractor Employee Whistleblower Rights (Nov 2023) (41 U.S.C. 4712); this clause does not apply to contracts of DoD, NASA, the Coast Guard, or applicable elements of the intelligence community—see FAR 3.900(a). |
| ☒ | (5) | 52.204-10 | Reporting Executive Compensation and First-Tier Subcontract Awards (Jun 2020) (Pub. L. 109-282) (31 U.S.C. 6101 note). |
| | (6) | | [Reserved]. |
| ☐ | (7) | 52.204-14 | Service Contract Reporting Requirements (Oct 2016) (Pub. L. 111-117, section 743 of Div. C). |
| ☐ | (8) | 52.204-15 | Contractor Employee Whistleblower Rights (Nov 2023) (41 U.S.C. 4712); this clause does not apply to contracts of DoD, NASA, the Coast Guard, or applicable elements of the intelligence |
| ☒ | (9) | 52.204-27 | Prohibition on a ByteDance Covered Application (Jun 2023) (Section 102 of Division R of Pub. L. 117-328). |
| ☒ | (10) | 52.209-6 | Protecting the Government's Interest When Subcontracting with Contractors Debarred, Suspended, or Proposed for Debarment. (Nov 2021) (31 U.S.C. 6101 note). |
| ☐ | (11) | 52.209-9 | Updates of Publicly Available Information Regarding Responsibility Matters (Oct 2018) (41 U.S.C. 2313). |
| | (12) | | [Reserved]. |

- ☐ (13) 52.219-3 Notice of HUBZone Set-Aside or Sole-Source Award (Oct 2022) (15 U.S.C.657a).
- ☒ (14) 52.219-4 (i), Notice of Price Evaluation Preference for HUBZone Small Business Concerns (Oct 2022) (if the offeror elects to waive the preference, it shall so indicate in its offer) (15 U.S.C. 657a).
- (15) [Reserved].
- ☐ (16) 52.219-6 (i) Notice of Total Small Business Set-Aside (Nov 2020) of 52.219-6 (15 U.S.C. 644).
- ☐ (ii) Alternate I (Mar 2020) of 52.219-6.
- ☐ (17) 52.219-7 (i) 52.219-7, Notice of Partial Small Business Set-Aside (Nov 2020) (15 U.S.C. 644).
- ☐ (ii) Alternate I (Mar 2020) of 52.219-7.
- ☐ (18) 52.219-8 Utilization of Small Business Concerns (Sep 2023) (15 U.S.C. 637(d)(2) and (3)).
- ☐ (19) 52.219-9 (i), Small Business Subcontracting Plan (Sep 2023) (15 U.S.C. 637(d)(4)).
- ☐ (ii) Alternate I (Nov 2016) of 52.219-9.
- ☐ (iii) Alternate II (Nov 2016) of 52.219-9.
- ☐ (iv) Alternate III (Jun 2020) of 52.219-9.
- ☐ (v) Alternate IV (Sep 2023) of 52.219-9.
- ☐ (20) 52.219-13 (i) Notice of Set-Aside of Orders (Mar 2020) (15 U.S.C. 644(r)).
- ☐ (ii) Alternate I (Mar 2020) of 52.219-13.
- ☐ (21) 52.219-14 Limitations on Subcontracting (Oct 2022) (15 U.S.C. 637(a)(14)).
- ☐ (22) 52.219-16 Liquidated Damages—Subcontracting Plan (Sep 2021) (15 U.S.C. 637(d)(4)(F)(i)).
- ☐ (23) 52.219-27 Notice of Service-Disabled Veteran-Owned Small Business Set-Aside (Oct 2022) (15 U.S.C. 657 f).
- ☒ (24) 52.219-28 Post Award Small Business Program Rerepresentation (Sep 2023) (15 U.S.C. 632(a)(2)). May require contractor completion.
- ☐ (ii) Alternate I (Mar 2020) of 52.219-28.
- ☐ (25) 52.219-29 Notice of Set-Aside for, or Sole Source Award to, Economically Disadvantaged Women-Owned Small Business Concerns (Oct 2022) (15 U.S.C. 637(m)).
- ☐ (26) 52.219-30 Notice of Set-Aside for, or Sole Source Award to, Women-Owned Small Business Concerns Eligible Under the Women-Owned Small Business Program (Oct 2022) (15 U.S.C. 637(m)).
- ☐ (27) 52.219-32 Orders Issued Directly Under Small Business Reserves (Mar 2020) (15 U.S.C. 644(r)).
- ☐ (28) 52.219-33 Nonmanufacturer Rule (Sep 2021)(15 U.S.C. 637(a)(17)).

- ☒ (29) 52.222-3 Convict Labor (June 2003) (E.O. 11755).
- ☐ (30) 52.222-19 Child Labor-Cooperation with Authorities and Remedies (Nov 2023).
- ☒ (31) 52.222-21 Prohibition of Segregated Facilities (Apr 2015).
- ☒ (32) 52.222-26 (i) Equal Opportunity (Sept 2016) (E.O. 11246).
(ii) Alternate I (Feb 1999) of 52.222-26. If this is checked, some terms have been waived.
- ☐ (33) 52.222-35 (i) Equal Opportunity for Veterans (Jun 2020)(38 U.S.C. 4212).
(ii) Alternate I (July 2014) of 52.222-35. If this box is checked, some terms have been waived.
- ☒ (34) 52.222-36 (i) Equal Opportunity for Workers with Disabilities (Jun 2020) (29 U.S.C. 793).
(ii) Alternate I (July 2014) of 52.222-36. If this box is checked, some terms have been waived.
- ☐ (35) 52.222-37 Employment Reports on Veterans (Jun 2020) (38 U.S.C. 4212).
- ☐ (36) 52.222-40 Notification of Employee Rights Under the National Labor Relations Act (Dec 2010) (E.O. 13496).
- ☒ (37) 52.222-50 (i) Combating Trafficking in Persons (Nov 2021) (22 U.S.C. chapter 78 and E.O. 13627).
(ii) Alternate I (Mar 2015) of 52.222-50 (22 U.S.C. chapter 78 and E.O. 13627). Alt I requires CO completion.
- ☐ (38) 52.222-54 Employment Eligibility Verification (May 2022). (Executive Order 12989). (Not applicable to the acquisition of commercially available off-the-shelf items or certain other types of commercial products or commercial services as prescribed in FAR 22.1803.)
- ☐ (39) 52.223-9 (i) Estimate of Percentage of Recovered Material Content for EPA–Designated Items (May 2008) (42 U.S.C. 6962(c)(3)(A)(ii)). (Not applicable to the acquisition of commercially available off-the-shelf items.) Requires CO completion.
(ii) Alternate I (May 2008) of 52.223-9 (42 U.S.C. 6962(i)(2)(C)). (Not applicable to the acquisition of commercially available off-the-shelf items.) Alt I requires contractor certification.
- ☐ (40) 52.223-11 Ozone-Depleting Substances and High Global Warming Potential Hydrofluorocarbons (JUN 2016) (E.O. 13693). Requires contractor completion.
- ☐ (41) 52.223-12 Maintenance, Service, Repair, or Disposal of Refrigeration Equipment and Air Conditioners (JUN 2016) (E.O. 13693).
- ☐ (42) 52.223-13 (i), Acquisition of EPEAT®-Registered Imaging Equipment (JUN 2014) (E.O.s 13423 and 13514).
(ii) Alternate I (Oct 2015) of 52.223-13.
- ☐ (43) 52.223-14 (i) Acquisition of EPEAT®-Registered Televisions (JUN 2014) (E.O.s 13423 and 13514).
(ii) Alternate I (Jun 2014) of 52.223-14.
- ☐ (44) 52.223-15 Energy Efficiency in Energy-Consuming Products (MAY 2020) (42 U.S.C. 8259b).
- ☐ (45) 52.223-16 (i), Acquisition of EPEAT®-Registered Personal Computer Products (OCT 2015) (E.O.s 13423 and 13514).
(ii) Alternate I (Jun 2014) of 52.223-16.
- ☒ (46) 52.223-18 Encouraging Contractor Policies to Ban Text Messaging While Driving (Jun 2020) (E.O. 13513).
- ☐ (47) 52.223-20 Aerosols (JUN 2016) (E.O. 13693).

- ☐ (48) 52.223-21 Foams (JUN 2016) (E.O. 13693).
- ☐ (49) 52.224-3 (i), Privacy Training (JAN 2017) (5 U.S.C. 552a).
- ☐ (ii) Alternate I (JAN 2017) of 52.224-3.
- ☐ (50) 52.225-1 (i) 52.225-1, Buy American-Supplies (Oct 2022) (41 U.S.C. chapter 83).
- ☐ (ii) Alternate I (Oct 2022) of 52.225-1.
- ☐ (51) 52.225-3 (i) 52.225-3, Buy American-Free Trade Agreements-Israeli Trade Act (NOV 2023) (19 U.S.C. 3301 note, 19 U.S.C. 2112 note, 19 U.S.C. 3805 note, 19 U.S.C. 4001 note, 19 U.S.C. chapter 29 (sections 4501-4732), Public Law 103-182, 108-77, 108-78, 108-286, 108-302, 109-53, 109-169, 109-283, 110-138, 112-41, 112-42, and 112-43.
- ☐ (ii) Alternate I [Reserved]
- ☐ (iii) Alternate II (Dec 2022) of 52.225-3.
- ☐ (iv) Alternate III (Nov 2023) of 52.225-3.
- ☐ (v) Alternate IV (Oct 2022) of 52.225-3.
- ☐ (52) 52.225-5 Trade Agreements (NOV 2023) (19 U.S.C. 2501, et seq., 19 U.S.C. 3301 note).
- ☒ (53) 52.225-13 Restrictions on Certain Foreign Purchases (Feb 2021) (E.O.'s, proclamations, and statutes administered by the Office of Foreign Assets Control of the Department of the Treasury).
- ☐ (54) 52.225-26 Contractors Performing Private Security Functions Outside the United States (Oct 2016) (Section 862, as amended, of the National Defense Authorization Act for Fiscal Year 2008; 10 U.S.C. 2302 Note).
- ☐ (55) 52.226-4 Notice of Disaster or Emergency Area Set-Aside (Nov 2007) (42 U.S.C. 5150). Requires CO completion.
- ☐ (56) 52.226-5 Restrictions on Subcontracting Outside Disaster or Emergency Area (Nov 2007) (42 U.S.C. 5150).
- ☐ (57) 52.229-12 Tax on Certain Foreign Procurements—Notice and Representation (Feb 2021)
- ☐ (58) 52.232-29 Terms for Financing of Purchases of Commercial Products and Commercial Services (Nov 2021) (41 U.S.C. 4505, 10 U.S.C. 3805).
- ☐ (59) 52.232-30 Installment Payments for Commercial Products and Commercial Services (Nov 2021) (41 U.S.C. 4505, 10 U.S.C. 3805).
- ☒ (60) 52.232-33 Payment by Electronic Funds Transfer—System for Award Management (Oct 2018) (31 U.S.C. 3332).
- ☐ (61) 52.232-34 Payment by Electronic Funds Transfer—Other than System for Award Management (Jul 2013) (31 U.S.C. 3332). Requires CO completion.
- ☐ (62) 52.232-36 Payment by Third Party (May 2014) (31 U.S.C. 3332).
- ☐ (63) 52.239-1 Privacy or Security Safeguards (Aug 1996) (5 U.S.C. 552a).
- ☐ (64) 52.242-5 Payments to Small Business Subcontractors (JAN 2017)(15 U.S.C. 637(d)(13)).
- ☐ (65) 52.247-64 (i), Preference for Privately Owned U.S.-Flag Commercial Vessels (Nov 2021) (46 U.S.C. 55305 and 10 U.S.C. 2631).

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(ii) Alternate I (Apr 2003) of 52.247-64.

☐

(iii) Alternate II (Nov 2021) of 52.247-64.

(c) The Contractor shall comply with the FAR clauses in this paragraph (c), applicable to commercial services, that the Contracting Officer has indicated as being incorporated in this contract by reference to implement provisions of law or Executive orders applicable to acquisitions of commercial products and commercial services

[Contracting Officer check as appropriate.]

☒

(1) 52.222-41

Service Contract Labor Standards (Aug 2018) (41 U.S.C. chapter 67).

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(2) 52.222-42

Statement of Equivalent Rates for Federal Hires (May 2014) (29 U.S.C. 206 and 41 U.S.C. chapter 67). Requires CO completion.

☐

(3) 52.222-43

Fair Labor Standards Act and Service Contract Labor Standards-Price Adjustment (Multiple Year and Option Contracts) (Aug 2018) (29 U.S.C. 206 and 41 U.S.C. chapter 67).

☐

(4) 52.222-44

Fair Labor Standards Act and Service Contract Labor Standards—Price Adjustment (May 2014) (29 U.S.C. 206 and 41 U.S.C. chapter 67).

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(5) 52.222-51

Exemption from Application of the Service Contract Labor Standards to Contracts for Maintenance, Calibration, or Repair of Certain Equipment—Requirements (May 2014) (41 U.S.C. chapter 67).

☐

(6) 52.222-53

Exemption from Application of the Service Contract Labor Standards to Contracts for Certain Services—Requirements (May 2014) (41 U.S.C. chapter 67).

☐

(7) 52.222-55

Minimum Wages Under Executive Order 13658 (Jan 2022).

☐

(8) 52.222-62

Paid Sick Leave Under Executive Order 13706 (JAN 2017) (E.O. 13706).

☐

(9) 52.226-6

Promoting Excess Food Donation to Nonprofit Organizations (Jun 2020) (42 U.S.C. 1792).

(d) Comptroller General Examination of Record. The Contractor shall comply with the provisions of this paragraph (d) if this contract was awarded using other than sealed bid, is in excess of the simplified acquisition threshold, as defined in FAR 2.101, on the date of award of this contract, and does not contain the clause at 52.215-2, Audit and Records—Negotiation.

(1) The Comptroller General of the United States, or an authorized representative of the Comptroller General, shall have access to and right to examine any of the Contractor's directly pertinent records involving transactions related to this contract.

(2) The Contractor shall make available at its offices at all reasonable times the records, materials, and other evidence for examination, audit, or reproduction, until 3 years after final payment under this contract or for any shorter period specified in FAR subpart 4.7, Contractor Records Retention, of the other clauses of this contract. If this contract is completely or partially terminated, the records relating to the work terminated shall be made available for 3 years after any resulting final termination settlement. Records relating to appeals under the disputes clause or to litigation or the settlement of claims arising under or relating to this contract shall be made available until such appeals, litigation, or claims are finally resolved.

(3) As used in this clause, records include books, documents, accounting procedures and practices, and other data, regardless of type and regardless of form. This does not require the Contractor to create or maintain any record that the Contractor does not maintain in the ordinary course of business or pursuant to a provision of law.

(e) (1) Notwithstanding the requirements of the clauses in paragraphs (a), (b), (c), and (d) of this clause, the Contractor is not required to flow down any FAR clause, other than those in this paragraph (e)(1), in a subcontract for commercial products or commercial services. Unless otherwise indicated below, the extent of the flow down shall be as required by the clause-

- (i) 52.203-13, Contractor Code of Business Ethics and Conduct (NOV 2021) (41 U.S.C. 3509).
 - (ii) 52.203-17, Contractor Employee Whistleblower Rights (Nov 2023) (41 U.S.C. 4712).
 - (iii) 52.203-19, Prohibition on Requiring Certain Internal Confidentiality Agreements or Statements (Jan 2017) (section 743 of Division E, Title VII, of the Consolidated and Further Continuing Appropriations Act, 2015 (Pub. L. 113-235) and its successor provisions in subsequent appropriations acts (and as extended in continuing resolutions)).
 - (iv) 52.204-23, Prohibition on Contracting for Hardware, Software, and Services Developed or Provided by Kaspersky Lab and Other Covered Entities (NOV 2021) (Section 1634 of Pub. L. 115-91).
 - (v) 52.204-25, Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment. (NOV 2021) (Section 889(a)(1)(A) of Pub. L. 115-232).
 - (vi) 52.204-27, Prohibition on a ByteDance Covered Application (Jun 2023) (Section 102 of Division R of Pub. L. 117-328).
 - (vii) 52.219-8, Utilization of Small Business Concerns (Sep 2023) (15 U.S.C. 637(d)(2) and (3)), in all subcontracts that offer further subcontracting opportunities. If the subcontract (except subcontracts to small business concerns) exceeds the applicable threshold specified in FAR 19.702(a) on the date of subcontract award, the subcontractor must include 52.219-8 in lower tier subcontracts that offer subcontracting opportunities.
 - (viii) 52.222-21, Prohibition of Segregated Facilities (APR 2015).
 - (ix) 52.222-26, Equal Opportunity (SEP 2015) (E.O. 11246).
 - (x) 52.222-35, Equal Opportunity for Veterans (JUN 2020) (38 U.S.C. 4212).
 - (xi) 52.222-36, Equal Opportunity for Workers with Disabilities (JUN 2020) (29 U.S.C. 793).
 - (xii) 52.222-37, Employment Reports on Veterans (JUN 2020) (38 U.S.C. 4212).
 - (xiii) 52.222-40, Notification of Employee Rights Under the National Labor Relations Act (DEC 2010) (E.O. 13496).
- Flow down required in accordance with paragraph (f) of FAR clause 52.222-40.
- (xiv) 52.222-41, Service Contract Labor Standards (AUG 2018) (41 U.S.C. chapter 67).
 - (xv) (A) 52.222-50, Combating Trafficking in Persons (NOV 2021) (22 U.S.C. chapter 78 and E.O. 13627).
 - (B) Alternate I (MAR 2015) of 52.222-50 (22 U.S.C. chapter 78 and E.O. 13627).
 - (xvi) 52.222-51, Exemption from Application of the Service Contract Labor Standards to Contracts for Maintenance, Calibration, or Repair of Certain Equipment-Requirements (May 2014) (41 U.S.C. chapter 67).
 - (xvii) 52.222-53, Exemption from Application of the Service Contract Labor Standards to Contracts for Certain Services-Requirements (MAY 2014) (41 U.S.C. chapter 67).
 - (xviii) 52.222-54, Employment Eligibility Verification (MAY 2022) (E.O. 12989).
 - (xix) 52.222-55, Minimum Wages Under Executive Order 13658 (JAN 2022).
 - (xx) 52.222-62, Paid Sick Leave Under Executive Order 13706 (JAN 2017) (E.O. 13706).
 - (xxi) (A) 52.224-3, Privacy Training (Jan 2017) (5 U.S.C. 552a).
 - (B) Alternate I (JAN 2017) of 52.224-3.
 - (xxii) 52.225-26, Contractors Performing Private Security Functions Outside the United States (Oct 2016) (Section 862, as amended, of the National Defense Authorization Act for Fiscal Year 2008; 10 U.S.C. Subtitle A, Part V, Subpart G Note).
 - (xxiii) 52.226-6, Promoting Excess Food Donation to Nonprofit Organizations (JUN 2020) (42 U.S.C. 1792). Flow down required in accordance with paragraph (e) of FAR clause 52.226-6.
 - (xxiv) 52.232-40, Providing Accelerated Payments to Small Business Subcontractors (Mar 2023) (31 U.S.C. 3903 and 10 U.S.C. 3801). Flow down required in accordance with paragraph (c) of 52.232-40.
 - (xxv) 52.247-64, Preference for Privately Owned U.S.-Flag Commercial Vessels (Nov 2021) (46 U.S.C. 55305 and 10 U.S.C. 2631). Flow down required in accordance with paragraph (d) of FAR clause 52.247-64.

(2) While not required, the Contractor may include in its subcontracts for commercial products and commercial services a minimal number of additional clauses necessary to satisfy its contractual obligations.

(End of clause)

Alternate I (Feb 2000). As prescribed in 12.301(b)(4)(i), delete paragraph (d) from the basic clause, redesignate paragraph (e) as paragraph (d), and revise the reference to "paragraphs (a), (b), (c), or (d) of this clause" in the redesignated paragraph (d) to read "paragraphs (a), (b), and (c) of this clause."

Alternate II (Nov 2023). As prescribed in 12.301 (b)(4)(ii), substitute the following paragraphs (d)(1) and (e)(1) for paragraphs (d)(1) and (e)(1) of the basic clause as follows:

(d)(1) The Comptroller General of the United States, an appropriate Inspector General appointed under section 3 or 8 G of the Inspector General Act of 1978 (5 U.S.C. App.), or an authorized representative of either of the foregoing officials shall have access to and right to—

- (i) Examine any of the Contractor's or any subcontractors' records that pertain to, and involve transactions relating to, this contract; and
- (ii) Interview any officer or employee regarding such transactions.

(e)(1) Notwithstanding the requirements of the clauses in paragraphs (a), (b), and (c), of this clause, the Contractor is not required to flow down any FAR clause in a subcontract for commercial products or commercial services, other than—

(i) Paragraph (d) of this clause. This paragraph flows down to all subcontracts, except the authority of the Inspector General under paragraph (d)(1)(ii) does not flow down; and

(ii) Those clauses listed in this paragraph (e)(1). Unless otherwise indicated below, the extent of the flow down shall be as required by the clause-

(A) 52.203-13, Contractor Code of Business Ethics and Conduct (NOV 2021) (41 U.S.C. 3509).

(B) 52.203-15, Whistleblower Protections Under the American Recovery and Reinvestment Act of 2009 (JUN 2010) (Section 1553 of Pub. L. 111-5).

(C) 52.203-17, Contractor Employee Whistleblower Rights (Nov 2023) (41 U.S.C. 4712).

(D) 52.204-23, Prohibition on Contracting for Hardware, Software, and Services Developed or Provided by Kaspersky Lab and Other Covered Entities (NOV 2021) (Section 1634 of Pub. L. 115-91).

(E) 52.204-25, Prohibition on Contracting for Certain Telecommunications and Video Surveillance Services or Equipment. (NOV 2021) (Section 889(a)(1)(A) of Pub. L. 115-232).

(F) 52.204-27, Prohibition on a ByteDance Covered Application (Jun 2023) (Section 102 of Division R of Pub. L. 117-328).

(G) 52.219-8, Utilization of Small Business Concerns (Sep 2022) (15 U.S.C. 637(d)(2) and (3)), in all subcontracts that offer further subcontracting opportunities. If the subcontract (except subcontracts to small business concerns) exceeds the applicable threshold specified in FAR 19.702(a) on the date of subcontract award, the subcontractor must include 52.219-8 in lower tier subcontracts that offer subcontracting opportunities.

(H) 52.222-21, Prohibition of Segregated Facilities (APR 2015).

(I) 52.222-26, Equal Opportunity (SEP 2016) (E.O. 11246).

(J) 52.222-35, Equal Opportunity for Veterans (JUN 2020) (38 U.S.C. 4212).

(K) 52.222-36, Equal Opportunity for Workers with Disabilities (JUN 2020) (29 U.S.C. 793).

(L) 52.222-40, Notification of Employee Rights Under the National Labor Relations Act (DEC 2010) (E.O. 13496).

Flow down required in accordance with paragraph (f) of FAR clause 52.222-40.

(M) 52.222-41, Service Contract Labor Standards (AUG 2018) (41 U.S.C. chapter 67).

(N) ___ (1) 52.222-50, Combating Trafficking in Persons (NOV 2021) (22 U.S.C. chapter 78 and E.O. 13627).

___ (2) Alternate I (MAR 2015) of 52.222-50 (22 U.S.C. chapter 78 and E.O. 13627).

(O) 52.222-51, Exemption from Application of the Service Contract Labor Standards to Contracts for Maintenance, Calibration, or Repair of Certain Equipment-Requirements (May 2014) (41 U.S.C. chapter 67).

(P) 52.222-53, Exemption from Application of the Service Contract Labor Standards to Contracts for Certain Services-Requirements (MAY 2014) (41 U.S.C. chapter 67).

(Q) 52.222-54, Employment Eligibility Verification (NOV 2021) (Executive Order 12989).

(R) 52.222-55, Minimum Wages Under Executive Order 13658 (JAN 2022).

(S) 52.222-62, Paid Sick Leave Under Executive Order 13706 (JAN 2017) (E.O. 13706).

(T) (1) 52.224-3, Privacy Training (JAN 2017) (5 U.S.C. 552a).

(2) Alternate I (JAN 2017) of 52.224-3.

(U) 52.225-26, Contractors Performing Private Security Functions Outside the United States (Oct 2016) (Section 862, as amended, of the National Defense Authorization Act for Fiscal Year 2008; 10 U.S.C. Subtitle A, Part V, Subpart G Note).

(V) 52.226-6, Promoting Excess Food Donation to Nonprofit Organizations. (JUN 2020) (42 U.S.C. 1792). Flow down required in accordance with paragraph (e) of FAR clause 52.226-6.

(W) 52.232-40, Providing Accelerated Payments to Small Business Subcontractors (MAR 2023) (31 U.S.C. 3903 and 10 U.S.C. 3801). Flow down required in accordance with paragraph (c) of 52.232-40.

(X) 52.247-64, Preference for Privately Owned U.S.-Flag Commercial Vessels (Nov 2021) (46 U.S.C. 55305 and 10 U.S.C. 2631). Flow down required in accordance with paragraph (d) of FAR clause 52.247-64.

FAR 52.212-5 as of FAC 2024-01 (11/14/2023) Edited 11/27/2023

Invoice and Payment Provisions (Vendor has Transitioned to IPP)

The following clause is applicable to all Purchase Orders, Task or Delivery Orders, and Blanket Purchase Agreement (BPA) Calls: **Prompt Payment** (Jan 2017) FAR 52.232-25. Highlights of this clause and NIH implementation requirements follow:

I. Invoice Requirements

- A. An invoice is the Contractor's bill or written request for payment under the contract for supplies delivered or services performed. A proper invoice is an "Original" which must include the items listed in subdivisions 1 through 12, below, in addition to the requirements of FAR 32.9. If the invoice does not comply with these requirements, the Contractor will be notified of the defect within 7 days after the date the designated billing office received the invoice (3 days for meat, meat food products, or fish, and 5 days for perishable agricultural commodities, dairy products, edible fats, or oils) with a statement of the reasons why it is not a proper invoice. (See exceptions under II., below.) Untimely notification will be considered in the computation of any interest penalty owed the Contractor.
1. Vendor/Contractor: Name, Address, Point of Contact for the invoice (Name, title, telephone number, e-mail and mailing address of point of contact).
 2. Remit-to address (Name and complete mailing address to send payment).
 3. Remittance name must match exactly with name on original order/contract. If the Remittance name differs from the Legal Business Name, then both names must appear on the invoice.
 4. Invoice date.
 5. Unique invoice #s for all invoices per vendor regardless of site.
 6. NBS document number formats must be included for awards created in the NBS: Contract Number; Purchase Order Number; Task or Delivery Order Number and Source Award Number (e.g., Indefinite Delivery Contract number; General Services Administration number); or, BPA Call Number and BPA Parent Award Number.
 7. Unique Entity Identifier (UEI) which is in the System for Award Management (SAM) and replaces the Dun & Bradstreet Data Universal Numbering System (DUNS) number.
 8. Federal Taxpayer Identification Number (TIN). In those rare cases where a Contractor does not have a UEI number or TIN, a Vendor Identification Number (VIN) must be referenced on the invoice. The VIN is the number that appears after the contractor's name on the face page of the award document.
 9. Identify that payment is to be made using a three-way match.
 10. Description of supplies/services **that match** the description on the award, by line billed.*
 11. Freight or delivery charge must be billed as shown on the award. If it is included in the item price do not bill it separately. If identified in the award as a separate line item, it must be billed separately.
 12. Quantity, Unit of Measure, Unit Price, Extended Price of supplies delivered or services performed, as applicable, and that **match** the line items specified in the award.*

Updated on March 21, 2023

NOTE: If your invoice must differ from the line items on the award, please contact the Contracting Officer before submitting the invoice. A modification to the order or contract may be needed before the invoice can be submitted and paid.

Shipping costs will be reimbursed only if authorized by the Contract/Purchase Order. If authorized, shipping costs must be itemized. Where shipping costs exceed \$100, the invoice must be supported by a bill of lading or a paid carrier's receipt.

- B. The Contractor shall submit invoices to the Department of Treasury's Invoice Processing Platform (IPP) at <https://www.ipp.gov> with a copy to the approving official, as directed below.

The Contractor shall submit a copy of the electronic invoice to the following Approving Official (Contracting Officer) and Contracting Officer Representative:

Approving Official: Contracting Officer

Name- _____ Email Address- _____

Contracting Officer Representative

Name- _____ Email Address- _____

II. Invoice Payment

- A. Except as indicated in paragraph B., below, the due date for making invoice payments by the designated payment office shall be the later of the following two events:

1. The 30th day after the designated billing office has received a proper invoice.
2. The 30th day after Government acceptance of supplies delivered or services performed.

- B. The due date for making invoice payments for meat and meat food products, perishable agricultural commodities, dairy products, and edible fats or oils, shall be in accordance with the Prompt Payment Act, as amended.

III. Interest Penalties

- A. An interest penalty shall be paid automatically, if payment is not made by the due date and the conditions listed below are met, if applicable.

1. A proper invoice was received by the designated billing office.
2. A receiving report or other Government documentation authorizing payment was processed and there was no disagreement over quantity, quality, or Contractor compliance with a term or condition.
3. In the case of a final invoice for any balance of funds due the Contractor for supplies delivered or services performed, the amount was not subject to further

settlement actions between the Government and the Contractor.

- B. Determination of interest and penalties due will be made in accordance with the provisions of the Prompt Payment Act, as amended, the Contract Disputes Act, and regulations issued by the Office of Management and Budget.

IV. PROVIDING ACCELERATED PAYMENT TO SMALL BUSINESS SUBCONTRACTORS, FAR 52.232-40 (Mar 2023).

(a)

- (1) In accordance with 31 U.S.C. 3903 <https://www.govinfo.gov/link/uscode/31/3903> and 10 U.S.C. 3801 <https://www.govinfo.gov/link/uscode/10/3801> , within 15 days after receipt of accelerated payments from the Government, the Contractor shall make accelerated payments to its small business subcontractors under this contract, to the maximum extent practicable and prior to when such payment is otherwise required under the applicable contract or subcontract, after receipt of a proper invoice and all other required documentation from the small business subcontractor.

- (2) The Contractor agrees to make such payments to its small business subcontractors without any further consideration from or fees charged to the subcontractor.

(b) The acceleration of payments under this clause does not provide any new rights under the Prompt Payment Act.

(c) Include the substance of this clause, including this paragraph (c), in all subcontracts with small business concerns, including subcontracts with small business concerns for the acquisition of commercial products or commercial services.

(End of clause).

V. HHSAR 352.232-71 Electronic Submission of Payment Requests (February 2, 2022).

(a) *Definitions.* As used in this clause—

Payment request means a bill, voucher, invoice, or request for contract financing payment with associated supporting documentation. The payment request must comply with the requirements identified in FAR 32.905(b), “Content of Invoices” and the applicable Payment clause included in this contract.

(b) Except as provided in paragraph (c) of this clause, the Contractor shall submit payment requests electronically using the Department of Treasury Invoice Processing Platform (IPP) or successor system. Information regarding IPP, including IPP Customer Support contact information, is available at www.ipp.gov or any successor site.

(c) The Contractor may submit payment requests using other than IPP only when the Contracting Officer authorizes alternate procedures in writing in accordance with HHS procedures.

(d) If alternate payment procedures are authorized, the Contractor shall include a copy of the Contracting Officer's written authorization with each payment request.

(End of clause).



Animal Use Protocol

IACUC Use Only:	Protocol No.: PK-M-07182023
Date of Receipt: 03-10-2023	Veterinarian: Personnel
Date of Approval: 03-24-2023	Chair, IACUC: Personnel

1. Project Information:

Project Title	Pharmacokinetic Studies of Non-Clinical Evaluation (NCE) Following Single or Multiple doses through oral, Intravenous, subcutaneous, intraperitoneal or other route of administration in Mice		
Type of Application	☐ Initial Submits	☒ Renewal	
Lab Address-Building, Rm#	Beijing, Pharmaron Animal Center(PAC), 5 th Floor		
Source of Funding	Pharmaron		
Period of Protocol	From 04-01-2023 to 03-31-2024		

2 Information of Principal Investigator/Study Director:

Basic Information of PI/SD	Name: Personnel	Division: PK-BA1	
	Lab phone: Personnel	Mobile phone: Personal Info	
	Email: Proprietary Info		
Experiences in animal research	>10 years of experience in preclinical in vivo pharmacokinetics studies using rodents.		

3. Personnel Working on Animal Study:

Name	Position	ext. phone #	Role in project	Working Period (Year)	Lab Animal Skill needed
Personnel			Animal Studies	13	Animal surgery; biological sample collection; drug administration
			Animal Studies	12	Animal surgery; biological sample collection; drug administration
			Animal Studies	13	Animal surgery; biological sample collection; drug administration
			Animal Studies	13	Animal surgery; biological sample collection; drug administration
			Animal Studies	8	Animal surgery; biological sample collection; drug administration

Personnel	Animal Studies	9	Animal surgery; biological sample collection; drug administration
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4. Animal Information Summaries:

Species	Strain	Sex	Grade	Quantity	Animal Source	Animal certification number	Animal Housing location	Single housing requirement*	Enrichmen
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Mouse	C57BL	♀	VAF/SPF	Depend on the research (business) need or client request	Vital River	SCXK (京) 2021-0006	PAC 5 th Floor	No	Yes
	CD-1				HuaFuKang	SCXK(京)2019-0008			
	BALB/c				Sibeifu	SCXK (京) 2019-0010			
	Balb/c nude				Anikeeper	SCXK (京) 2023-0002			
	CB-17 Scid KM NUNU FVB SV129				Jicuiyaokang	SCXK(苏) 2018-0008			

*Please specify the justification for selecting single housing.

5. Briefly explain in language understandable to a layperson the aim of the study and why the study is important to the promotion of human or animal health, the advancement of knowledge, or the good for the society. Describe what will be done with these animals:

The aim of the study is to identify the pharmacokinetic profile of the test articles in mice after oral, intravenous, subcutaneous or intraperitoneal administrations. The laboratory animals used in these studies provide the best means of assessing the pharmacokinetics of the test articles intended for human use. The information obtained from the studies will serve as important references for drug development in human. The studies do not duplicate the results of previous studies and could not be obtained by other means.

6. Explain your rationale for animal use. [The rationale should include reasons why non-animal models cannot be used.]:

Although in vitro methods have been developed to screen PK characteristics of the compounds, those methods are less predictive than systematic animal study. As an alternative approach to test potential PK characteristics in human, using animals to test the PK profile of the test articles allows investigators to experimentally gain the key information for human use, especially for those novel compounds (new drugs), which have never been used in human population.

7. Justify the appropriateness of the species selected (e.g. anatomic, physiologic, genetic, etc.) that make it desirable for this model. [The species selected should be the lowest possible on the phylogenetic scale.]:

Mouse is a commonly used species to perform preclinical pharmacokinetic study. Different kinds of mice strain may be chosen based on the corresponding drug efficiency study.

8. Justify the number of animals to be used. [The number of animals should be the minimum number required to obtain statistically valid results.]

Each PK study usually contains 2 groups and each group will have 3 or 4 animals. So each experiment will require 6-8 animals. In the last 12 months, ~50000 mice had been conducted for PK studies. For the next 12 months, we will need approximately 90000 mice.

9. Repeated or not ?

☒ No

☐ Yes If yes, Describe the necessities:

10. Anesthetics, analgesics, tranquilizers, neuromuscular blocking agents?—

☒ No

☐ Yes If yes, complete the Appendix A

11. Surgical procedures and postoperative care?

☒ No

☐ Yes If yes, complete the Appendix B

12. Dietary or fluid restriction?

☐ No

☒ Yes If yes, complete the Appendix C

13. Pharmacologic/Toxicologic Studies?

☒ No

☐ Yes If yes, complete the Appendix D

14. Production and Collection of Fluids?

☐ No

☒ Yes If yes, complete the Appendix E

15. Conscious Physical Restraint?

☒ No

☐ Yes If yes, complete the Appendix F

16. Disposition of animal at the end of study:

☒ Euthanized

☐ Transferred to another IACUC approved protocol

☐ Other

17. Euthanasia or Not?

☐ No Describe the disposition of animal at the end of study

☒ Yes please refer to Appendix G, Specify the criteria of justification:

☒ Weight loss

☒ Inappetence

☒ Weakness/inability to obtain feed or water

☒ Moribund state

☒ Infection

☒ Signs of severe organ system dysfunction and non-responsive to treatment, or
with a poor prognosis as determined by a veterinarian

18. Use of hazardous agents requires approval of the institutional Biosafety Office/Committee. Attach documentation of approval for the use of recombinant DNA or potential human pathogens

☒ No

☐ Yes

- ☐ Radioactive Agents
- ☐ Biological Agents
- ☐ Hazardous Chemicals or Drugs
- ☐ Recombinant DNA

If yes, Describe the practices and procedures required for the safe handling and disposal of animals and material associated with this study:

19. Biological material/ animal products for use in animals.

☒ No

☐ Yes Select the type from the below:

- ☐ cell lines
- ☐ antiserum
- ☐ non-pharmaceutical grade drugs (NPG)
- ☐ Others

Specify material:

For NPG, PI must provide scientific justification for using such substance and how to monitor the potential stress or toxicity to the animals.

20. Pain or not?

☒ No

☐ Yes

(1) Pain categorization: (see detail Appendix H)

(2) Pain score (see Pharmaron SOP PH-AC-206-05)

(3) Alternatives to painful procedures: No

(4) Describe pain and distress by which the animals may suffer from:

(5) Describe species, strain, numbers and frequency of use for animals

Species: Mouse strain: CD-1, C57BL, BALB/c, Balb/c nude, CB-17 Scid, KM, NUNU, FVB, SV129 etc.

Numbers: 1800 frequency: weekly

(6) Describe how to reduce pain or distress of animal:

(7) Analgesic(s) Consult Appendix (H)

(8) Experimental endpoint:

21. Detailed description of experimental design, and animal procedures. Use additional sheets if necessary. This description should allow the IACUC to understand the experimental course of an animal from its entry into the experiment to the endpoint of the study. Specifically address the following:

- (1) Experimental injections or inoculations (substances, e.g., infectious agents, adjuvant, etc.; dose, sites, volume, route, and schedules); Will inoculate the tumor into the mouse.

For oral dosing, test compound will be administered by using oral gavage (2~20 ml/kg).

For intravenous dosing, test compound will be injected through tail vein (1~10 ml/kg).

For subcutaneous dosing, test compound will be injected under the back skin (1~10 ml/kg).

For intraperitoneal dosing, test compound will be injected into the abdomen. (1~10 ml/kg).

- (2) Blood withdrawals (volume, frequency, withdrawal sites, and methodology)

Blood samples will be collected from saphenous vein, dorsal metatarsal vein, retro orbital vein or other sites.

Following oral or intravenous administration, blood samples (0.02~0.04 mL, the maximum blood volume that should be drawn is less than 15% of the total blood volume) for PK analysis will be collected at specified time points (about 8~9 time points within 24 hours) post-dosing. 0.2mL volume of saline as an complement will be injected via SC after 2 hours post administration.

Following intraperitoneal, subcutaneous or other administration, blood samples for PK analysis will be collected at the time points similar to PO above.

When collecting blood via retro orbital vein, the mice should be anesthetized by Isoflurane/O₂ mixture.

- (3) Surgical procedures (provide details of survival and non-survival surgical procedures.) **N/A**

- (4) Radiation (dosage and schedule) **N/A**

- (5) Methods of restraint (e.g., restraint chairs, collars, vests, harnesses, slings, etc.). Include how animals are restrained for routine procedures like blood withdrawal. Prolonged restraint must be justified with appropriate oversight to ensure it is minimally distressing. Describe any sedation, acclimation or training to be utilized.

For dorsal metatarsal vein collecting method, mice will be restrained by one person by holding the neck of mice with one hand; right leg of the mice will be pinched by another hand. The second person will hold the right foot and make a puncture on the right dorsal metatarsal vein and collect the blood samples. For saphenous vein collecting, animal will be temporarily restrained in a small plastic bag that has suitable diameter and airhole drilled in the tip, after that animal will be put back into the cage. Or the animal will be restrained by hand in a while when blood is collected, after blood collection animal will be put back to the cage.

- (6) Animal identification methods (e.g., ear tags, tattoos, collar, cage card, implant, etc.)

Tail mark and cage card.

- (7) Other procedures (e.g., survival studies, tail biopsies, etc.)

Occasionally, the tissue/blood ratio is needed for target tissue concentration estimated. The tissue samples including vital organs and

any other target tissues (such as brain, liver, kidney, fat, heart, spleen, lung, muscle, stomach, small intestine (duodenum, jejunum, ileum), colon, skin, pancreas, etc.) may be needed to collect based on the client's request.

Procedure: The animals will be firstly exsanguinated, and/or, the perfusion (optional) will be done as described below and then tissue samples are harvested.

Perfusion procedure: Once animals are anesthetized, 1) perfusion procedure will be performed accordingly as the options (10 mL for mice), 2) open chest cavity and expose the heart, 3) gently puncture left ventricle with needle and push the saline to the heart slowly, 4) cut a hole at right atrium and exsanguinate. Perfusion is completed once blood runs clear or liver becomes yellow. Approximately 10 mL perfusion solution (0.9% NaCl saline) will be used for a mouse. Then tissues will be harvested according to the request.

The tissue samples will be kept in the freezer for further analysis.

- (8) Resultant effects, if any, that the animals are expected to experience (e.g., pain or distress, ascites production, etc.) **N/A**
- (9) Other potential stressors and procedures to monitor and minimize distress (e.g., food or water deprivation, noxious stimuli, environmental stress) **N/A**
- (10) Veterinary care (indicate desired plan of action in case of animal illness, e.g., initiate treatment, call investigator prior to initiating treatment, euthanize)

Signed and dated records of activities relating the day-to-day running and maintenance of the study within the animal room as well as the activities relating to the observations and examinations outlined in this protocol will be recorded. All animals will be examined once daily for mortality and signs of abnormalities. More frequent observations may be undertaken if considered appropriate. Death and observed clinical signs will be individually recorded.

- (11) Experimental endpoint criteria (e.g., tumor size, percentage body weight gain or loss, inability to eat or drink, behavioral abnormalities, clinical symptomatology, or signs of toxicity) must be specified when the administration of tumor cells, biologics, infectious agents, radiation or toxic chemicals are expected to cause significant symptoms or are potentially lethal. List the criteria to be used to determine when euthanasia is to be performed. Death as an endpoint must always be scientifically justified.

After sampling the whole blood at 24 hrs, the animals will be fed and nothing will be done to the animal until CO₂ inhalation was conducted at the end of study. That will be regarded as the experimental endpoint. After CO₂ inhalation conducted, the animals should be performed cervical dislocation secondary to be sure the animal was dead. (CO₂ gas was from gas cylinder)

Experimental endpoint criteria: when animal appear suffering severe pain, discomfort or behavior change, CNS abnormalities (convulsion, seizure), due to dosing of test article, no response to the treatment and no improvement during the observation period. The animal will be euthanized after consulting with veterinary and/or communicate with

clients. See detail in the section of Appendix G “Criteria for Euthanasia of Animals Used in Research & Teaching”.



Statement

I here certify that the information provided within this application is accurate to the best of my knowledge. I also understand that should I use the project described in this application as a basis for a proposal for funding (either intramural or extramural), it is my responsibility to ensure that the description of animal use in such funding proposal is identical in principle to that contained in this application.

Personnel

Signature: _____

Date: Nov 3, 2018



This protocol has been verified and approved by:

Personnel

2023.3.24
Date

2023.3.26
Date

2023.3.24
Date

2023.3.27
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Personnel

2013.3.27
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2013.3.24
Date

IACUC Decision:

- ☒
- ☐
- ☐
- ☐

Approval (Support
Revision requested
Approval after revision
Denied

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Date:

2013.3.27



Appendix A Anesthetics Protocols

1 The procedure is

- ☐ Under sedation
- ☐ Anesthetized

2. Purpose on

- ☐ Restraint
- ☐ Drug administration
- ☐ Collection of Fluids
- ☐ Non-survival surgery
- ☐ Survival surgery
- ☐ Other

3 Describe species, strain, number and frequency of use for animals

4 Describe sedative or anesthetic term on expectancy

5 Location of anesthetic procedure

6 Premedication

Drug	Animal species	Dose	Route

7 Sedative(s) and Anesthetic(s):

Drug	Animal species	Dose	Route	Frequency

8 Neuromuscular paralytics:

Drug	Animal species	Dose	Route	Frequency

9 List personnel responsible for monitoring and observation of animals in anesthesia phase. Describe the training and experience required to perform anesthesia.

10 Criteria for judging the depth of anesthesia and for monitoring of the physical function

11 Describe postoperative evaluation for pain and distress. Please refer to Appendix H

Appendix B

Animal Surgery Protocols

1 The surgical procedure is a

- ☐ Survival surgery (Answer 2-7)
- ☐ Non-survival surgery (Answer 2-4)

If there are differences between control and experiment groups, please describe them individually.

2 Describe species, strain, number and frequency of use for animals.

3 Describe location of surgical procedure, name of surgeon(s). Describe the training and experience required to perform surgery

4 Describe the surgical procedure in detail

5 Describe postoperative care to be given and name of operator(s)

6 Will any animal undergo more than one major survival surgical procedures? If Yes, please provide an appropriate scientific justification.

7 Will animal be given analgesics or antibiotics after the operation?

☐ Yes

If yes, please describe drugs, routes, dose and frequency.

☐ No

If no, provide a scientific justification: _____



Appendix C

Dietary or fluid restriction Protocols

1 Describe species, strain, number and frequency of use for animals.

C57BL/6 or CD-1 or BALB/c or Balb/c nude or CB-17 Scid, KM, NUNU, FVB or others with body weight at 16 – 40 g will be used for each study, averaged by 150-200 studies per week.

2 The procedure is:

- ✓ Dietary restriction, please complete questions of 3-5)
- Fluid restriction, please complete questions of 6-7)

3 Describe dietary manipulations or special feeding requirements.

Animals will have access to food before experiment starting and food is removed prior to the day of dosing (fasted 12-18 hours) if fast condition need applied according to study design. Food will be supplied to animals after the 4-hour blood collection time point or according to the special request.

4 How long will animals be restricted to dietary?

12-18 hours (less than 18 hours).

5 Will neonates or rodents be fasted beyond 12 hours or other animals beyond 48 hours? If yes, provide a scientific justification:

No.

The purpose of fast is to reduce the effect from food.

6 Provide, including amount/day, monitoring of animals, criteria used to determine well-being of animals, and scientific justification

7 Will fluids be withheld for more than 24 hours or more than 5 hours for rodents? If yes, describe this aspect of the study, including the rationale and monitoring methods:

Appendix D

Pharmacologic/Toxicologic Studies

1. Describe materials to be evaluated.
2. Describe the route and duration of administration.
3. Describe the testing methods employed. (e.g., tail flick, withdrawal, LD50, etc)
4. Will the animal experience pain or distress? Describe methods to monitor the animals.
5. If pain or distress is anticipated, how will they be minimized? Describe methods, including dose and route of administration.
6. What is the endpoint of these studies?



Appendix E

Production and Collection of Fluids

1. List species: **Mice**
2. List antigen(s): **Test compounds**
3. List or describe adjuvant(s): **N/A**

Initial immunization:	
Subsequent immunizations:	

4. List or describe injection: List anatomic site, volume administered per injection site, total volume administered at one time, injection frequency and total number of administrations.

For oral dosing, test compound will be administered by using oral gavage (2~20 ml/kg).

For intravenous dosing, test compound will be injected to tail vein (1~10 ml/kg).

For subcutaneous dosing, test compound will be injected under the back skin (1~10 ml/kg).

For intraperitoneal dosing, test compound will be injected into the abdomen. (1~10 ml/kg).

5. List or describe collecting blood or other body fluids: List site, volume, frequency and method used.

Fluid Collection Table							
Fluid Collected	Frequency	Volume Collected	Method of Collection	Site of Collection	Anesthetization, Restraint, Sedation		
					Anesthetic	Restraint	Sedative
blood	8-9 times	0.02-0.04 mL	Microtube	Dorsal metatarsal vein Saphenous vein puncture or others	☐	☒	☐
					List/Describe		
					When blood is collected, animal will be restrained in a while, after that animal will be put back into the cage.		

6. Justify the use of animal ascites to produce monoclonal antibodies.
N/A

6.1 Number of animals needed for ascites production and justification:

6.2 Priming volume

6.3 Number of injections and volume administered per injection

6.4 Number and schedule for taps (maximum number of taps is 3, the last terminal):

6.5 Monitoring plan after development of ascites:

6.6 Specific euthanasia criteria to be used: Euthanasia should be based on criteria listed in Appendix J. However, specific criteria for this project should be applied for judgment.

Appendix F

Conscious Physical Restrain

1. Describe species, strain, number and frequency of use for animals.

Species	Strain	Number	frequency of use

2. Describe how the animal(s) will be restrained:

3. Indicate location where procedures will be conducted (room):

4. Describe how long the animal(s) will be restrained:

5. Describe how the animal(s) will be acclimated to the restraint method: N/A

6. Describe animal care during the conduct of experiments, including how often they will be observed:

7. If the animals show signs of distress or clinical abnormalities, what actions will be taken:

8. Will animals be restrained for more than 12 hours? If yes, provide a scientific justification:

Appendix G

Criteria for Euthanasia of Animals Used in Research & Teaching

Background

These criteria have been established by the Institutional Animal Care and Use Committee, which recognizes that euthanasia is sometimes necessary prior to the scheduled end of a study, either because of unanticipated complications, or because of the protocol itself.

Criteria

These criteria apply to all animals on experimental protocols, whether manipulated or not. Fulfillment of one criterion can constitute grounds for euthanasia. Exceptions are permitted only if approved by the Committee as part of the protocol review process (i.e. the clinical signs listed below are expected as part of the experiment and appropriate measures are taken to minimize pain or discomfort in the animals).

1. **Weight loss:**
Weight loss of 20-25% (depending on attitude, weight recorded at time of arrival, and age: growing animals may not lose weight, but may not gain normally) or if not measured, characterized by cachexia and wasting syndrome.
2. **Inappetence:**
Complete anorexia for 24 hours in small rodents, up to 5 days in large animals; partial anorexia (less than 50% of caloric requirement) for 3 days in small rodents, 7 days in large animals.
3. **Weakness/inability to obtain feed or water:**
Inability or extreme reluctance to stand, that persists for 24 hours, assuming that the animal has recovered from anesthesia.
4. **Moribund state:**
Depression coupled with body temperature below 32-34°C, assuming that the animal has recovered from anesthesia. (Note: The body surface temperature is measured by Infrared thermometer).
5. **Infection:**
Infection involving any organ system (either overt, or indicated by increased body temperature or WBC parameters), which fails to respond to antibiotic therapy within an appropriate period of time and is accompanied by systemic signs of illness.
6. **Signs of severe organ system dysfunction and non-responsive to treatment, or with a poor prognosis as determined by a veterinarian:**
 - (1) Respiratory: dyspnea, cyanosis.
 - (2) Cardiovascular: blood loss or anemia.
 - (3) Gastrointestinal: severe vomiting or diarrhea, obstruction, intussusception; peritonitis, evisceration (immediate euthanasia required).
 - (4) Urogenital: renal failure characterized by elevated BUN, creatinine or uroperitoneum.
 - (5) Nervous: CNS depression, seizures, paralysis of one or more extremities; pain unresponsive to analgesic therapy.
 - (6) Musculoskeletal: muscle damage or fracture resulting in inability to use the limb, unless anticipated as part of the study.

Appendix H

Pain and Distress Classifications & Recommendation of Analgesics for Use in Animal Research

USDA Pain and Distress Classifications and Examples

Classification B: Animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery, but not yet used for such purposes.

Examples:

- Breeding colonies of any animal species (USDA does not require listing of rats, mice, birds) that are held in legal sized caging and handled in accordance with the *Guide* and other applicable regulations. Breeding colony includes parents and offspring.
- Newly acquired animals that are held in proper caging and handled in accordance with applicable regulations.
- Animals held under proper captive conditions or wild animals that are being observed.

Classification C: Animals upon which teaching, research, experiments, or tests will be conducted involving no pain, distress, or use of pain-relieving drugs.

Examples:

- Procedures performed correctly by trained personnel such as the administration of electrolytes/fluids, administration of oral medication, blood collection from a common peripheral vein per standard veterinary practice (dog cephalic, cat jugular) or catheterization of same, standard radiography, parenteral injections of non-irritating substances.
- Euthanasia performed in accordance with the recommendations of the most recent AVMA Panel on Euthanasia, utilizing procedures that produce rapid unconsciousness and subsequent humane death.
- Manual restraint that is no longer than would be required for a simple exam; short period of chair restraint for an adapted nonhuman primate.

Classification D: Animals upon which experiments, teaching, research, surgery, or tests will be conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs will be used.

Examples:

- Surgical procedures conducted by trained personnel in accordance with standard veterinary practice such as biopsies, gonadectomy, exposure of blood vessels, chronic catheter implantation, laparotomy or laparoscopy.
- Blood collection by more invasive routes such as intracardiac or periorbital collection from species without a true orbital sinus such as rats and guinea pigs.
- Administration of drugs, chemicals, toxins, or organisms that would be expected to produce pain or distress but which will be alleviated by analgesics.

Classification E: Animals upon which teaching, experiments, research, surgery, or tests will be conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs will adversely affect the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests.

Examples:

- Procedures producing pain or distress unrelieved by analgesics such as toxicity studies, microbial virulence testing, radiation sickness, and research on stress, shock, or pain.
- Surgical and postsurgical sequela from invasion of body cavities, orthopedic procedures, dentistry or other hard or soft tissue damage that produces unrelieved pain or distress.
- Negative conditioning via electric shocks that would cause pain in humans.
- Chairing of nonhuman primates not conditioned to the procedure for the time period used.

Recommendation of Analgesics for Use in Small Mammals and Larger Animals

	Mice	Rats	Guinea Pigs	Hamsters	Dogs	Non-human Primates
Opioids						
Tramadol	5mg/kg, SC, IP	5mg/kg, SC, IP	5-10mg/kg, PO	5-10mg/kg, PO	1-4 mg/kg, PO	—
Buprenorphine	0.05-0.1 mg/kg SC	0.01-0.05 mg/kg, SC, IV 0.1-0.25 mg/kg, PO	0.05 mg/kg, SC	0.1-0.5 mg/kg SC	0.01-0.02 mg/kg, SC	0.005-0.03 mg/kg IV, SC
Morphine	2.5 mg/kg, SC	2.5 mg/kg, SC	2-5 mg/kg, SC, IM	2-5mg/kg, SC	0.25-5 mg/kg, SC, IM	1-2 mg/kg IM, SC
NSAIDs						
Ibuprofen	30 mg/kg, PO	15 mg/kg, PO	10 mg/kg, PO	—	—	7 mg/kg, PO
Carprofen	5 mg/kg, SC	5 mg/kg, SC	1-2 mg/kg, PO 4 mg/kg, SC	5 mg/kg, SC	2.2 mg/kg, PO 5 mg/kg, SC	3-4 mg/kg SC
Meloxicam	5 mg/kg, PO, SC	1 mg/kg, PO, SC	0.1-0.3mg/kg, PO, SC	—	0.2 mg/kg PO, SC	0.1-0.2 mg/kg SC, PO
Tolfedine	—	—	—	—	4 mg/kg SC, IM	—
Others						
Bupivacaine or Levobupivacaine hydrochloride	2 mg/kg, SC	2 mg/kg, SC	2 mg/kg, SC	2 mg/kg, SC	—	—

Animal Use Protocol

IACUC Use Only:	Protocol No.: PK-R-06012023
Date of Receipt: 03-10-2023	Veterinarian: Personnel
Date of Approval: 03-24-2023	Chair, IACUC: Personnel

1. Project Information:

Project Title	Pharmacokinetic study of Non-Clinical Evaluation (NCE) following a single or multiple dosing via oral, intravenous, subcutaneous, or intraperitoneal(etc.) administration in rats		
Type of Application	☐ Initial Submits	☒ Renewal	
Lab Address-Building, Rm#	Beijing, Pharmaron Animal Center(PAC), 5 th Floor		
Source of Funding	Sponsored by Pharmaron		
Period of Protocol	From 04-01-2023 to 03-31-2024		

2 Information of Principal Investigator/Study Director:

Basic Information of PI/SD	Name: Personnel	Division: PK-BA1
	Lab phone: Personnel	Mobile phone: Personal Info
	Email: Personnel	
Experiences in animal research	>10 years of experience in preclinical in vivo pharmacokinetics studies using rodents.	

3. Personnel Working on Animal Study:

Name	Position	ext. phone #	Role in project	Working Period (Year)	Lab Animal Skill needed
Personnel			Animal Studies	13	Animal surgery; biological sample collection; drug administration
			Animal Studies	12	Animal surgery; biological sample collection; drug administration
			Animal Studies	13	Animal surgery; biological sample collection; drug administration
			Animal Studies	13	Animal surgery; biological sample collection; drug administration
			Animal Studies	8	Animal surgery; biological sample collection; drug administration

Personnel	Animal Studies	9	Animal surgery; biological sample collection; drug administration
	Animal Studies	8	Animal surgery; biological sample collection; drug administration
	Animal Studies	8	Animal surgery; biological sample collection; drug administration
	Animal Studies	6	Animal surgery; biological sample collection; drug administration
	Animal Studies	7	Animal surgery; biological sample collection; drug administration
	Animal Studies	6	Animal surgery; biological sample collection; drug administration
	Animal Studies	6	Animal surgery; biological sample collection; drug administration
	Animal Studies	6	Animal surgery; biological sample collection; drug administration
	Animal Studies	5	Animal surgery; biological sample collection; drug administration
	Animal Studies	2	Animal surgery; biological sample collection; drug administration
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	Animal Studies	2	Animal surgery; biological sample collection; drug administration
	Animal Studies	1	Animal surgery; biological sample collection; drug administration

Personnel

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Animal Studies	6	Animal surgery; biological sample collection; drug administration
Animal Studies	5	Animal surgery; biological sample collection; drug administration
Animal Studies	8	Animal surgery; biological sample collection; drug administration
Animal Studies	6	Animal surgery; biological sample collection; drug administration
Animal Studies	3	Animal surgery; biological sample collection; drug administration
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Personnel

Animal Studies	1	Animal surgery; biological sample collection; drug administration
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Animal Studies	7	Animal surgery; biological sample collection; drug administration
Animal Studies	6	Animal surgery; biological sample collection; drug administration
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Animal Studies	1	Animal surgery; biological sample collection; drug administration

4. Animal Information Summary:

Species	Strain	Sex	Grade	Number	Animal Source	Animal Certification Number	Animal Housing location	Single housing requirement*	Enrichment
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Rat	SD Wistar Han Wistar F344 Wistar Kyoto		Non-SPF	Depend on the research (business) need or client request	Vital River Sibeifu	SCXK (京) 2021-0006 SCXK (京) 2021-0011 SCXK (京) 2019-0010	PAC 5 th Floor	No	Yes
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*Please specify the justification for selecting single housing.

5. Briefly explain in language understandable to a layperson the aim of the study and why the study is important to the promotion of human or animal health, the advancement of knowledge, or the good for the society. Describe what will be done with these animals:

The aim of the study is to identify the pharmacokinetic profile of the test articles in rats after oral, intravenous, subcutaneous or intraperitoneal administration. Laboratory animals are used to provide pharmacokinetic assessment of the test article, and the assessment is critical for understanding the PK properties in human. The information obtained from the studies will serve as references for clinical evaluation in further development of the test article. The studies do not duplicate the results of previous studies and could not be obtained by other means.

6. Explain your rationale for animal use. [The rationale should include reasons why non-animal models cannot be used.]:

Although in vitro methods have been developed to screen PK characteristics, the methods are usually less predictive than the in-life animal study. As an alternative to test PK characteristics in human, PK study in animal allows investigators to experimentally test novel compounds in a well-controlled environment before testing it in human.

7. Justify the appropriateness of the species selected (e.g. anatomic, physiologic, genetic, etc.) that make it desirable for this model. [The species selected should be the lowest possible on the phylogenetic scale.]:

Rat is species commonly used in pharmacokinetic study. The popular strains used in our pharmacokinetics studies are but not limited to Sprague Dawley, Wistar and Wistar Han.

8. Justify the number of animals to be used. [The number of animals should be the minimum number required to obtain statistically valid results.]

Each PK study usually has 2 groups and each group usually uses 3-4 animals. So each experiment will require 6-8 animals. In the last 12 months, 40000rats were conducted for PK studies. For next 12 months, we will need approximately 60000 rats.

9. Repeated or not?

☒ No

☐ Yes If yes, describe the necessities:

10. Anesthetics, analgesics, tranquilizers, neuromuscular blocking agents?

☐ No

☒ Yes If yes, complete the Appendix A

11. Surgical procedures and postoperative care?

☐ No

☒ Yes If yes, complete the Appendix B

12. Dietary or fluid restriction?

☐ No

☒ Yes If yes, complete the Appendix C

13. Pharmacologic/Toxicologic Studies?

☒ No

☐ Yes If yes, complete the Appendix D

14. Production and Collection of Fluids?

☐ No

☒ Yes If yes, complete the Appendix E

15. Conscious Physical Restraint?

☒ No

☐ Yes If yes, complete the Appendix F

16. Disposition of animal at the end of study:

☒ Euthanized

☐ Transferred to another IACUC approved protocol

☐ Other

17. Euthanasia or Not?

☐ No Describe the disposition of animal at the end of study:

☒ Yes Please refer to Appendix G, Specify the criteria of justification:

☒ Weight loss

☒ Inappetence

☒ Weakness/inability to obtain feed or water

☒ Moribund state

☒ Infection

☒ Signs of severe organ system dysfunction and non-responsive to treatment, or with a poor prognosis as determined by a veterinarian

Method of euthanasia of animals at end of study:

Species	Strain	Drug or Other methods	Dosage	Route
Rat	SD Wistar Han Wistar F344 Wistar Kyoto	CO ₂	A rising concentration of CO ₂	inhalation

18. Use of hazardous agents requires approval of the institutional Biosafety Office/Committee. Attach documentation of approval for the use of recombinant DNA or potential human pathogens

☒ No

☐ Yes

☐ Radioactive Agents

☐ Biological Agents

☐ Hazardous Chemicals or Drugs

☐ Recombinant DNA

If yes, describe the practices and procedures required for the safe handling and disposal of animals and material associated with this study:

19. Biological material/ animal products for use in animals.

☒ No

☐ Yes Select the type from the below:

☐ cell lines

☐ antiserum

☐ non-pharmaceutical grade drugs (NPG)

☐ Others

Specify material:

For NPG, PI must provide scientific justification for using such substance and how to monitor the potential stress or toxicity to the animals.

20. Pain or not?

☐ No

☒ Yes

(1) Pain categorization: (see detail Appendix H) D

(2) Pain score (see Pharmaron SOP PH-AC-206-05)

(3) Alternatives to painful procedures: No

(4) Describe pain and distress by which the animals may suffer from:

The rat may suffer mild pain after the surgery, which might cause discomfort. Animals will be monitored for general health symptoms until be terminated.

(5) Describe species, strain, numbers and frequency of use for animals

species: Rat strain SD, Wistar Han, Wistar Kyoto, F344 or Wistar etc.

numbers: 1200 frequency: Weekly

(6) Describe how to reduce pain or distress of animal:

Analgesic will be used when needed.

(7) Analgesic(s) (see Appendix (H))

Drug	Species	Strain	Route	Dosage	Frequency
Tramadol	Rat	SD Wistar Han Wistar Wistar Kyoto, F344	IM	2 mg/kg	once
Meloxicam	Rat	SD Wistar Han Wistar Wistar Kyoto, F344	SC	1 mg/kg	once
Lidocaine	Rat	SD Wistar Han Wistar Wistar Kyoto, F344	SC	≤10 mg/kg	Once (Only for local analgesics)
Bupivacaine or Levobupivacaine hydrochloride	Rat	SD Wistar Han Wistar Wistar Kyoto, F344	SC	≤2 mg/kg	Once (Only for local analgesics)

Note: Lidocaine, Bupivacaine or Levobupivacaine hydrochloride is only used in minor surgery for local analgesics. The other two are used in major surgery, sometimes the analgesics are not available due to the strict control of national government, be sure at least one of them is available in the stock.

(8) Experimental endpoint (see question #21(11))

21. Detailed description of experimental design, and animal procedures. Use additional sheets if necessary. This description should allow the IACUC to understand the experimental course of an animal from its entry into the experiment to the endpoint of the study. Specifically address the following:

(1) Dosing:

For oral dosing of test compound, each animal will receive ≤ 20 mL of the solution per kg body weight as an oral gavage dosing using gavage needle, or oral dosing capsule (size 9) using gavage needle.

For intravenous dosing, each animal will receive ≤ 10 mL of the solution per kg body weight as an intravenous bolus injection and/or infusion by

slow injection via tail vein and/or vasal catheter.

For subcutaneous dosing, each animal will receive ≤ 10 mL per kg body weight as a subcutaneous injection by injecting under the back skin.

For intraperitoneal dosing, each animal will receive ≤ 10 mL per kg body weight by injecting into the abdomen.

- (2) Blood withdrawals (volume, frequency, withdrawal sites, and methodology).

Blood samples will be collected from venous catheter in non-restrained non-sedated animals. Following intravenous, subcutaneous, oral or intraperitoneal administration, blood samples (0.1-0.3 mL, the maximum blood volume that should be drawn is less than 15% of the total blood volume) for PK analysis will be collected at multiple time points within 24 hours (48 hours or 72 hours will be needed sometimes according to the actual request) post-dosing, equal volume of saline as a complement will be injected via cannula after blood withdrawals.

- (3) For animal surgery, provide details of survival and non-survival surgical procedures.

Surgery will be conducted on super-clean bench. The surface will be irradiated using UV lamps for at least 30 min, followed by wiping with 75% medical ethanol before and after use. Surgical instruments are sterilized by autoclave. Used instruments will be soaked in fast glass bead sterilizer prior to using for next rat. After recording the body weight, the rats will receive anesthesia (anesthetic agent listed below, either could be used). The absence of the pedal reflex should be an indication that a surgical plane of anesthesia has been attained in rats. The surgery should finish within half an hour and initial dose of anesthetic agent usually could maintain the anesthesia. If needed, the anesthesia will be maintained by adding 1/4 of the original dose of the anesthetics.

Anesthetic Agent	Route	Dosage	Dose Volume
Zoletil 50 and Xylazine (10:1,v/v)	IM	11.4 mg/kg of Zoletil; 2.5 mg/kg of Xylazine	0.25 mL/kg
Ketamine and Xylazine (20:1,v/v)	IP	75mg/kg of Ketamine; 7.5 mg/kg of Xylazine	1.5 mL/kg

The surgeon should wear a face mask, sterile surgical gloves and other Personal Protective Equipments (PPEs).

Prior to taking the rats to the surgery area, remove hair for about 1-2 square centimeter on the neck. To prevent hypothermia, place the rat on a heating pad if needed. Carefully scrub the area with sterile cotton swab. An about 0.5 cm incision will be made at the right of the neck to explore the right external jugular veins. A catheter will be inserted in jugular

vein, pass through back neck skin, and settled by skin for sampling whole blood. The tube will be filled with 50 unit/ml heparin.

After surgery the rats should be placed back in the cage, one animal per cage. The rats should be closely monitored within 2 hours post-surgery.

For the other surgery beside jugular vein cannulation, please follow the related SOP of surgery respectively.

(4) Radiation (dosage and schedule)

N/A

- (5) Methods of restraint (e.g., restraint chairs, collars, vests, harnesses, slings, etc.). Include how animals are restrained for routine procedures like blood withdrawals. Prolonged restraint must be justified with appropriate oversight to ensure it is minimally distressing. Describe any sedation, acclimation or training to be utilized.

After the administration of anesthesia, animal will be temporarily restrained with abdomen upwards on the surgery board. The surgery should finish in half an hour and initial dose of the anesthetics will maintain the anesthesia for the whole surgery. If needed, the anesthesia will be maintained by adding 1/4 of the original dose of the anesthetics.

- (6) Animal identification methods e.g., ear tags, tattoos, collar, cage card, implant, etc.)

Both tail mark and cage card are used.

- (7) Other procedures (e.g., survival studies, tail biopsies, etc.)

Occasionally, the tissue/blood ratio is needed for target tissue concentration estimated. The tissue samples including vital organs and any other target tissues (such as brain, liver, kidney, fat, heart, spleen, lung, muscle, stomach, small intestine (duodenum, jejunum, ileum), colon, skin, pancreas, etc.) may be needed to collect based on the client's request.

Procedure: The animals will be firstly exsanguinated, and/or, the perfusion (optional) will be done as described below and then tissue samples are harvested.

Perfusion procedure: Once animals are anesthetized, 1) perfusion procedure will be performed accordingly as the options (20 mL for rats), 2) open chest cavity and expose the heart, 3) gently puncture left ventricle with needle and push the saline to the heart slowly, 4) cut a hole at right atrium and exsanguinate. Perfusion is completed once blood runs clear or liver becomes yellow. Approximately 20 mL perfusion solution (0.9% NaCl saline) will be used for a rat. Then tissues will be harvested according to the request.

The tissue samples will be kept in the freezer for further analysis.

- (8) Resultant effects, if any, that the animals are expected to experience (e.g., pain or distress, ascites production, etc.)

N/A

- (9) Other potential stress and procedures to monitor and minimize distress (e.g., food or water deprivation, noxious stimuli, environmental stress)

Animals will have access to food before the day of dosing. Otherwise, the animals will be fasted 12-18 hours (less than 18 hours) before dosing and food will be supplied to animals after the 4-hour blood collection time point if needed according to the request.

- (10) Veterinary care (indicate desired plan of action in case of animal illness, e.g., initiate treatment, call investigator prior to initiating treatment, euthanize)

Signed and dated records of activities relating the day-to-day running and maintenance of the study within the animal room as well as the activities relating to the observations and examinations outlined in this protocol will be recorded. All animals will be examined once daily for mortality and signs of abnormalities. More frequent observations may be undertaken if considered appropriate. Death and observed clinical signs will be individually recorded.

- (11) Experimental endpoint criteria (e.g., tumor size, percentage body weight gain or loss, inability to eat or drink, behavioral abnormalities, clinical symptomatology, or signs of toxicity) Experimental endpoint criteria must be specified when the administration of tumor cells, biologics, infectious agents, radiation or toxic chemicals are expected to cause significant symptoms or are potentially lethal. List the criteria to be used to determine when euthanasia is to be performed. Death as an endpoint must always be scientifically justified.

After sampling the whole blood at final time point, the animal will be conducted with CO₂ inhalation. That will be regarded as the experimental endpoint. After CO₂ inhalation conducted, the animals should be performed cervical dislocation secondary to be sure the animal was dead. (CO₂ gas was from gas cylinder)

Statement

I here certify that the information provided within this application is accurate to the best of my knowledge. I also understand that should I use the project described in this application as a basis for a proposal for funding (either intramural or extramural), it is my responsibility to ensure that the description of animal use in such funding proposal is identical in principle to that contained in this application.

Personnel

Signature: _____

Date: 10/25/18



This protocol has been verified and approved by:

Personnel

2023.3.24
Date

2023.3.26
Date

2023.3.24
Date

2023.3.27
Date

2023.3.24
Date

2023.3.29
Date

2023.3.27
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2023.3.29
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2023.3.24
Date

2023.3.27
Date

2023.3.27
Date



Personnel

2023 03 27
Date

2023. 3. 24
Date

IACUC Decision:

- ☒ **Approval (Support** **; Objective** **)**
☐ **Revision requested**
☐ **Approval after revision**
☐ **Denied**

Date:

2023. 3. 27



Appendix A Anesthetics Protocols

1. The procedure is
☐ Under sedation
☒ Anesthetized

2. Purpose on
☒ Restraint
☐ Drug administration
☐ Collection of Fluids
☐ Non-survival surgery
☒ Survival surgery
☐ Other

3. Describe species, strain, number and frequency of use for animals

Wistar Han or SD or F344 or Wistar Kyoto or Wistar or other rats with body weight at 180 ~350 g will be used for each study, averaged by 150-200 studies per week.

4. Describe sedative or anesthetic term on expectancy

Anesthetic term will be lasted for about an hour and a half and initial dose of the anesthetics will maintain the anesthesia for the whole surgery. If needed, the anesthesia will be maintained by adding 1/4 of the original dose of the anesthetics

5. Location of anesthetic procedure

Surgery room at Pharmaron Animal Facility

6. Premedication: N/A

Drug	Animal species	Dose	Route

7. Sedative(s) and Anesthetic(s): either one is ok

Drug	Animal Species	Dose (mg/kg)	Route	Frequency
Zoletil 50® Plus Xylazine	Rat	11.4 2.5	IM	Before surgery (initial dose) and maintain anesthesia by adding 1/4 of original dose if needed.
Ketamine plus Xylazine	Rat	75 7.5	IP	Before surgery (initial dose) and maintain anesthesia by adding 1/4 of original dose if needed.

8. Neuromuscular paralytics: **N/A**

Drug	Animal species	Dose	Route	Frequency

9. List personnel responsible for monitoring and observation of animals in anesthesia phase. Describe the training and experience required to perform anesthesia.

Personnel

Personnel

will monitor and observe the animals in anesthesia phase.

All of them have the experience to perform anesthesia for more than 4 years.

10. Criteria for judging the depth of anesthesia and for monitoring of the physical function

The absence of the pedal reflex should be an indication that a surgical plane of anesthesia has been attained in rats. The surgery should be finished in half an hour and initial dose of the anesthetics will maintain the anesthesia for the whole surgery. If needed, the anesthesia will be maintained by adding 1/4 of the original dose of the anesthetics.

11. Describe postoperative evaluation for pain and distress. Please refer to Appendix H

Experimental surgeries will be conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic will be used.



Appendix B

Animal Surgery Protocols

1. The surgical procedure is a
☒ Survival surgery (Answer 2-7)

☐ Non-survival surgery (Answer 2-4)

If there are differences between control and experiment groups, please describe them individually.

2. Describe species, strain, number and frequency of use for animals.

Wistar Han or SD or F344 or Wistar Kyoto or Wistar or other rats with body weight at 180~350 g will be used for each study, averaged by 150-200 studies per week.

3. Describe location of surgical procedure, name of surgeon(s). Describe the training and experience required to perform surgery

For surgery, jugular vein, femoral vein, portal vein, carotid artery, bile duct intubation will be conducted in the surgery room at Pharmaron animal facility. People who are permitted to conduct the surgery must have been trained and has to pass the corresponding tests.

4. Describe the surgical procedure in detail

Surgery will be conducted on super clean bench. The surface should be irradiated using UV lamps for at least 30 min, followed by wiping with 75% medical ethanol before and after use.

Surgical instruments and at minimum of 4 sets sterile instruments should be sterilized by autoclave. Used instruments will be soaked in fast glass bead sterilizer and used for next rat.

After recording the body weight, the rat will receive anesthetics accordingly. The absence of the pedal reflex should be an indication that a surgical plane of anesthesia has been attained in rats. The surgery should be finished in about half an hour and initial dose of the anesthetics will maintain the anesthesia for the whole surgery. If needed, the anesthesia will be maintained by adding 1/4 of the original dose of the anesthetics. The surgeon should wear a face mask, sterile surgical gloves and other PPEs. Surgeons should change their gloves for each rat.

Prior to taking the rats to the surgery area, remove hair for about 1-2 centimeter on the neck. To prevent hypothermia, place the rat on a heating pad. Carefully scrub the area with sterile cotton swab. An about 1 cm incision at the right of midline is made at the neck for uncovering the right external jugular veins. A catheter will be inserted in jugular vein, pass through back neck skin, and settled by skin for sampling whole blood. The tube will be infused of 50 unit/ml heparin.

After surgery the rat should be placed back in the cage, one animal per cage. Rats, especially the surgical site, should be monitored throughout recovery from the anesthesia.

For the other surgery type, similar procedure and related SOP should be followed.

5. Describe postoperative care to be given and name of operator(s)

☐ Major surgery: Any surgical intervention that penetrates and exposes a body cavity; any procedure that has the potential for inducing permanent anatomic (physical) or physiologic impairment and/or any procedure associated with orthopedics or extensive tissue dissection or transection.

☐ A minor surgical procedure is one that neither penetrates or exposes a body cavity, nor induces permanent impairment of physical or physiologic function. Examples are laparoscopy, superficial vascular cut down, and percutaneous biopsy.

Postoperative care: Detail observation period, body temperature, clinical sign and post operation treatment

After surgery the rat should be placed back in the cage individually that is lined with corn cob litter. Rats should be monitored throughout recovery (usually 2 hours) from the anesthesia. The surgical site should be monitored through cage observation twice during working hours by experienced scientists. Postoperative care is performed follow PK SOP "SOP-DMPK-In-life-023 (Postoperative care in Rodents)".

6. Will any animal undergo more than one major survival surgical procedures? If Yes, please provide an appropriate scientific justification.

N/A

7. Will animal be given analgesics or antibiotics after the operation?

☒ Yes If yes, please describe drugs, routes, dose and frequency.

Lidocaine will be given at dose of 10mg/kg, SC for analgesia or Meloxicam will be given at dose of 1mg/kg, SC for analgesia or Tramadol will be given at dose of 2mg/kg, IM for analgesia or

Bupivacaine or Levobupivacaine hydrochlorid will be given at dose of 2mg/kg, SC for analgesia

☐ No If no, provide a scientific justification: _____

Appendix C

Dietary or fluid restriction Protocols

1. Describe species, strain, number and frequency of use for animals.

Wistar Han or SD or F344 or Wistar Kyoto or Wistar or other rats with body weight at 180 – 350 g will be used for each study, averaged by 150-200 studies per week.

2. The procedure is:

☒ Dietary restriction, please complete questions of 3-5

☐ Fluid restriction, please complete questions of 6

3. Describe dietary manipulations or special feeding requirements.

Animals will have access to food before experiment starting and food is removed prior to the day of dosing (fasted 12-18 hours). Food will be supplied to animals after the 4-hour blood collection time point or according to the special request from sponsor.

4. How long will animals be restricted to dietary?

12-18 hours (less than 18 hours).

5. Will rodents be fasted beyond 18 hours? If yes, provide a scientific justification:

No

The purpose of fast is to reduce the effect from food.

6. Will fluids be withheld for more than 24 hours or more than 5 hours for rodents? If yes, describe this aspect of the study, including the rationale and monitoring methods:

No

Appendix D Pharmacologic/Toxicologic Studies

1. Describe materials to be evaluated.
2. Describe the route and duration of administration.
3. Describe the testing methods employed. (e.g., tail flick, withdrawal, LD50, etc)
4. Will the animal experience pain or distress? Describe methods to monitor the animals.
5. If pain or distress is anticipated, how will they be minimized? Describe methods, including dose and route of administration.
6. What is the endpoint of these studies?



Appendix E

Production and Collection of Fluids

1. List species:

Rat

2. List antigen(s):

Test compounds

3. List or describe adjuvant(s): **N/A**

Initial immunization:	
Subsequent immunizations:	

4. List or describe injection: List anatomic site, volume administered per injection site, total volume administered at one time, injection frequency and total number of administrations.

Single injection to the tail vein at 5 mL/kg (max 10mL/kg) for intravenous dosing, single injection to the abdomen at 5 mL/kg (max 10mL/kg) for intraperitoneal dosing, single injection under the back skin at 5 mL/kg (max 10mL/kg) for subcutaneous dosing, single injection to the stomach at 10 mL/kg (max 20mL/kg) for oral dosing, etc.

5. List or describe collecting blood or other body fluids: List site, volume, frequency and method used.

Fluid Collection Table							
Fluid Collected	Frequency	Volume Collected	Method of Collection	Site of Collection	Anesthetization, Restraint, Sedation		
					Anesthetic	Restraint	Sedative
blood	9-10 times	0.1-0.3 ml	catheter	Jugular veins			
				Portal vein	☐	☒	☐
				Carotid			
				artery			

6. Justify the use of animal ascites to produce monoclonal antibodies.

N/A

- 6.1 Number of animals needed for ascites production and justification:

- 6.2 Priming volume

- 6.3 Number of injections and volume administered per injection

- 6.4 Number and schedule for taps (maximum number of taps is 3, the last terminal):

- 6.5 Monitoring plan after development of ascites:

- 6.6 Specific euthanasia criteria to be used: Euthanasia should be based on criteria listed in Appendix J. However, specific criteria for this project should be applied for

judgment.



Appendix F

Conscious Physical Restrain

1. Describe species, strain, number and frequency of use for animals.
2. Describe how the animal(s) will be restrained:
3. Indicate location where procedures will be conducted (room):
4. Describe how long the animal(s) will be restrained:
5. Describe how the animal(s) will be acclimated to the restraint method:
6. Describe animal care during the conduct of experiments, including how often they will be observed:
7. If the animals show signs of distress or clinical abnormalities, what actions will be taken:
8. Will animals be restrained for more than 12 hours? If yes, provide a scientific justification:



Appendix G

Criteria for Euthanasia of Animals Used in Research & Teaching

Background

These criteria have been established by the Institutional Animal Care and Use Committee, which recognizes that euthanasia is sometimes necessary prior to the scheduled end of a study, either because of unanticipated complications, or because of the protocol itself.

Criteria

These criteria apply to all animals on experimental protocols, whether manipulated or not. Fulfillment of one criterion can constitute grounds for euthanasia. Exceptions are permitted only if approved by the Committee as part of the protocol review process (i.e. the clinical signs listed below are expected as part of the experiment and appropriate measures are taken to minimize pain or discomfort in the animals).

1. **Weight loss:**
Weight loss of 20~25% (depending on attitude, weight recorded at time of arrival, and age: growing animals may not lose weight, but may not gain normally) or if not measured, characterized by cachexia and wasting syndrome.
2. **Inappetence:**
Complete anorexia for 24 hours in small rodents, up to 5 days in large animals; partial anorexia (less than 50% of caloric requirement) for 3 days in small rodents, 7 days in large animals.
3. **Weakness/inability to obtain feed or water:**
Inability or extreme reluctance to stand, that persists for 24 hours, assuming that the animal has recovered from anesthesia.
4. **Moribund state:**
Depression coupled with body temperature below 32-34°C, assuming that the animal has recovered from anesthesia. (Note: The body surface temperature is measured by Infrared thermometer).
5. **Infection:**
Infection involving any organ system (either overt, or indicated by increased body temperature or WBC parameters), which fails to respond to antibiotic therapy within an appropriate period of time and is accompanied by systemic signs of illness
6. **Signs of severe organ system dysfunction and non-responsive to treatment, or with a poor prognosis as determined by a veterinarian:**
 - (1) Respiratory: dyspnea, cyanosis.
 - (2) Cardiovascular: blood loss or anemia.
 - (3) Gastrointestinal: severe vomiting or diarrhea, obstruction, intussusception; peritonitis, evisceration (immediate euthanasia required).
 - (4) Urogenital: renal failure characterized by elevated BUN, creatinine or uroperitoneum.
 - (5) Nervous: CNS depression, seizures, paralysis of one or more extremities; pain unresponsive to analgesic therapy.
 - (6) Musculoskeletal: muscle damage or fracture resulting in inability to use the limb, unless anticipated as part of the study.

Appendix H

Pain and Distress Classifications & Recommendation of Analgesics for Use in Animal Research

USDA Pain and Distress Classifications and Examples

Classification B: Animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery, but not yet used for such purposes.

Examples:

- Breeding colonies of any animal species (USDA does not require listing of rats, mice, birds) that are held in legal sized caging and handled in accordance with the *Guide* and other applicable regulations. Breeding colony includes parents and offspring.
- Newly acquired animals that are held in proper caging and handled in accordance with applicable regulations.
- Animals held under proper captive conditions or wild animals that are being observed.

Classification C: Animals upon which teaching, research, experiments, or tests will be conducted involving no pain, distress, or use of pain-relieving drugs.

Examples:

- Procedures performed correctly by trained personnel such as the administration of electrolytes/fluids, administration of oral medication, blood collection from a common peripheral vein per standard veterinary practice (dog cephalic, cat jugular) or catheterization of same, standard radiography, parenteral injections of non-irritating substances.
- Euthanasia performed in accordance with the recommendations of the most recent AVMA Panel on Euthanasia, utilizing procedures that produce rapid unconsciousness and subsequent humane death.
- Manual restraint that is no longer than would be required for a simple exam; short period of chair restraint for an adapted nonhuman primate.

Classification D: Animals upon which experiments, teaching, research, surgery, or tests will be conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs will be used.

Examples:

- Surgical procedures conducted by trained personnel in accordance with standard veterinary practice such as biopsies, gonadectomy, exposure of blood vessels, chronic catheter implantation, laparotomy or laparoscopy.
- Blood collection by more invasive routes such as intracardiac or periorbital collection from species without a true orbital sinus such as rats and guinea pigs.
- Administration of drugs, chemicals, toxins, or organisms that would be expected to produce pain or distress but which will be alleviated by analgesics.

Classification E: Animals upon which teaching, experiments, research, surgery, or tests will be conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs will adversely affect the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests.

Examples:

- Procedures producing pain or distress unrelieved by analgesics such as toxicity studies, microbial virulence testing, radiation sickness, and research on stress, shock, or pain.
- Surgical and postsurgical sequela from invasion of body cavities, orthopedic procedures, dentistry or other hard or soft tissue damage that produces unrelieved pain or distress.
- Negative conditioning via electric shocks that would cause pain in humans.
- Chaining of nonhuman primates not conditioned to the procedure for the time period used.

Recommendation of Analgesics for Use in Small Mammals and Larger Animals

	Mice	Rats	Guinea Pigs	Hamsters	Dogs	Non-human Primates
Opioids						
Tramadol	5mg/kg, SC, IP	5mg/kg, SC, IP	5-10mg/kg, PO	5-10mg/kg, PO	1-4 mg/kg, PO	—
Buprenorphine	0.05-0.1 mg/kg SC	0.01-0.05 mg/kg, SC, IV 0.1-0.25 mg/kg, PO	0.05 mg/kg, SC	0.1-0.5 mg/kg SC	0.01-0.02 mg/kg, SC	0.005-0.03 mg/kg IV, SC
Morphine	2.5 mg/kg, SC	2.5 mg/kg, SC	2-5 mg/kg, SC, IM	2-5mg/kg, SC	0.25-5 mg/kg, SC, IM	1-2 mg/kg IM, SC
NSAIDs						
Ibuprofen	30 mg/kg, PO	15 mg/kg, PO	10 mg/kg, PO	—	—	7 mg/kg, PO
Carprofen	5 mg/kg, SC	5 mg/kg, SC	1-2 mg/kg, PO 4 mg/kg, SC	5 mg/kg, SC	2.2 mg/kg, PO 5 mg/kg, SC	3-4 mg/kg SC
Meloxicam	5 mg/kg, PO, SC	1 mg/kg, PO, SC	0.1-0.3mg/kg, PO, SC	—	0.2 mg/kg PO, SC	0.1-0.2 mg/kg SC, PO
Tolfedine	—	—	—	—	4 mg/kg SC, IM	—
Others						
Bupivacaine or Levobupivacaine hydrochloride	2 mg/kg, SC	2 mg/kg, SC	2 mg/kg, SC	2 mg/kg, SC	—	—