DEPARTMENT OF THE ARMY
U.S. ARMY CONTRACTING COMMAND – NEW JERSEY
PICATINNY ARSENAL, NEW JERSEY 07806-5000

REPLY TO
ATTENTION OF

14 September 2020

Army Contracting Command – New Jersey
ACC-NJ, Building 9
Picatinny Arsenal, NJ 07806

SUBJECT: Technical Direction Letter for Medical CRBN Defense Consortium (MCDC), Request for Prototype Proposals (RPP) 17-03, Sub-Objective 17-07 Ceiling Increase Modification for "The GeneXpertÂ® Omni: A Man-Portable Diagnostic Testing Device for the DoD Government"

REF: Request for Updated Proposal Submitted in Response to RPP-17-03 under OTA W15QKN-16-9-1002 for Sub-Objective 17-07 Modification, dated 29 July 2020

Advanced Technology International (ATI)
ATTN: (b) (6), Sr. Contracts Manager
315 Sigma Drive
Summerville, SC 29486

Dear (b) (6),

The Army Contracting Command – New Jersey (ACC-NJ), in supporting the Joint Project Manager – Medical Countermeasure Systems (JPM-MCS), issued a Request for Proposal Update under MCDC RPP-17-03, Sub-Objective 17-07 on 29 July 2020 to ATI, for distribution to Cepheid. This request would allow Cepheid to proceed with revisions to current project tasks, and specifically incorporate the development of a hybrid SARS-CoV-2/Flu/RSV Assay in lieu of the Pan Coronavirus Assay, and to remove all unfunded options. The Government received the proposal update on 04 September 2020, and evaluated the costs and documentation accordingly. Based on the acceptable update of Cepheid's proposal, the Government is increasing the Project Agreement ceiling value by $5,500,000.00, from $81,064,949.00 to $86,564,949.00. The Government is also increasing the MCDC CMF Administrative Cost Ceiling by $(b) (4) from $(b) (4) to $(b) (4) Please see the below table for additional details.

	MCDC-17-03-07-009 Current Ceiling	MCDC-17-03-07-009 Proposed Increase ((b) % admin rate)	MCDC-17-03-07-009 Revised Ceiling
Member Ceiling	$81,064,949.00	$5,500,000.00	$86,564,949.00
MCDC Admin Cost	$(b) (4)	$(b) (4)	$(b) (4)
MCDC Admin Fee	$(b) (4)	$0	$(b) (4)
Total	$(b) (4)	$(b) (4)	$(b) (4)

Work will be performed in accordance with the SOW, entitled, "Encl 3_MCDC-17-03-07-009_FluVid Mod_SOW_Rev2" (See Attachment 1). Cepheid should utilize the not-to-exceed

existing obligation amount of $52,477,474.64 to continue work on the project. COVID funds are tracked separately, and proper assignment shall be coordinated with the Agreements Officer's Representative (AOR).This Project Agreement is anticipated to be incrementally funded. The Government reserves the right to award future milestones/fund additional months of project tasks. If the Government decides to do so, the MCDC member will be notified via ATI. The Government's liability will never exceed the current amount of funding obligated under the Project Agreement. The Project Agreement Holder shall notify ATI when they are approaching 75% of current funding obligated in incurred costs by written notice.

The prime contractor is considered a small business, nontraditional defense contractor, or nonprofit research institution and determined to be providing a significant contribution. The affirmation of business status certifications submitted as part of the proposal are hereby incorporated into the agreement. The contractor shall notify the MCDC CMF of any deviation from the final proposed affirmation of business status certifications that would affect the contributions of the small business, nontraditional defense contractor, or nonprofit research institution as proposed.

In accordance with 10.U.S.C. 2371b(f), and upon a determination that the prototype project for this transaction has been successfully completed, this competitively awarded prototype OTA may result in the award of a follow-on production contract or transaction without the use of competitive procedures.

In addition, ATI is advised of the implementation guidance for Section § 889(a)(1)(B) of the John S. McCain National Defense Authorization Act (NDAA) for Fiscal Year 2019 (Pub. L. 115–232), which prohibits executive agencies from entering into, extending, or renewing a contract with an entity that uses any equipment, system, or service that uses covered telecommunications equipment or services as a substantial or essential component of any system, or as critical technology as part of any system. While the interim rule and Defense Pricing and Contracting (DPC) implementation memorandum are directed to FAR-based contracts, the § 889(a)(1)(B) prohibition went into effect August 13, 2020, and applies to Other Transactions (OTs) for Prototype Projects under § 2371b of title 10, United States Code (U.S.C.). Any OT for Prototype Project agreement on or after August 13, 2020 must contain an article for the Prohibition on the Use of Certain Telecommunications and Video Surveillance Services or Equipment that requires the offeror to represent if it uses any equipment, system, or service that uses covered telecommunications equipment or services.

ATI must receive § 889(a)(1)(B) Certification from the MCDC member prior to executing any new project agreements or modification to an existing project agreement. A copy of the certification should be provided to the undersigned.

Points of Contact:

Agreements Specialist:
Ms. (b) (6)
E-mail (b) (6)
Phone: (b) (6)

Agreements Officer:
Mr. (b) (6)
E-mail (b) (6)
Phone: (b) (6)

Regards,

X (b) (6)

(b) (6)
Agreements Officer
Signed by: (b) (6)

Attachments:
Attachment 1: Encl 3_MCDC-17-03-07-009_FluVid Mod_SOW_Rev2

Attachment A
Statement of Work

For
Man-Portable Diagnostics System (MPDS) – Expanded Scope

RPP: 17-03
Project Identifier: MCDC-17-03-07-009
Consortium Member: Cepheid
Title: The GeneXpertÂ® Omni: A Man-Portable Diagnostic Testing Device for the Government

1.0 Introduction, Background, Scope, and Objectives

1.1 Introduction

In accordance with Request for Project Proposal (RPP) MCDC-RPP-17-03, the Joint Product Management Office for Diagnostics (JPMO-DX) seeks to develop a portable *In Vitro Diagnostic (IVD)* device for use in far-forward (non-laboratory) environments where the forces may not have access to traditional healthcare. The desired capability shall diagnose infections caused by (b) (4) biological warfare and infectious diseases of operational concern as well as provide a capability to differentiate between bacterial and viral infections.

The scope of this Statement of Work includes all activities required to develop a Man-Portable Diagnostic System (MPDS) and up to four prototype assay cartridges1 compatible with a modified Commercial-off-the-Shelf (COTS) diagnostic analyzer (the GeneXpert® Omni), software and firmware updates specific to ***Government*** requirements, and all regulatory and test activities required to achieve FDA clearance.

The final prototype instrument shall be a single, FDA-cleared device that is lightweight, simple to use and maintain, and provide rapid results. The system shall provide highly sensitive results using Polymerase Chain Reaction (PCR) or isothermal DNA amplification, immunoassay, or serological testing methods. The device shall enable a syndromic approach to diagnostics, whereby the targets may be grouped by clinical presentation, sample type, or range of prevalent and non-prevalent diseases, and if possible, incorporate host response biomarkers or multidrug resistance.

This prototype technology is being developed to meet a validated ***Government*** requirement and the statement of work is specific to that requirement. However, the ***Government***-configured instrument technology may be used and improved upon by Cepheid for incorporation into Cepheid's commercial offerings. ***Government***-specific software controls, security controls, user settings, and ***Government*** C360-related capabilities will be protected from unauthorized disclosure. However, they may be leveraged and improved upon generally by Cepheid in its commercial offerings. All other engineering and software enhancements made to the Omni system and Cart A+ consumables may be applied to Cepheid commercial offerings and are not under disclosure control.

In addition, the bacterial vs. viral cartridge, hemorrhagic fever cartridge, and Tropical fever cartridge developed under this OTA will have application for both military and civil uses to assist in the diagnosis of endemic diseases and to monitor and control disease outbreaks globally. As Cepheid is permitted to develop this technology for both civil and military applications, these three products will not be controlled under 22 CFR 121.1. The bacterial agent cartridge is being developed primarily for ***Government*** use and is intended for use by the ***Government*** and authorized ***Government*** users. The bacterial agent panel may be subject to control under 22 CFR 121.1).

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1 In this SOW, a "prototype device" is a paired diagnostic instrument and the consumable assays that function on it. Because each assay cartridge/instrument pairing is considered a "device" by the United States Food and Drug Administration, the statement of work allows for the development of up to four assay cartridge development efforts to meet threshold and objective diseases described in the RPP. Each assay cartridge/instrument pairing constitutes a separate prototype capability.

1.2 Background Information: GeneXpert Omni Solution

GeneXpert Omni System:

The GeneXpert® Omni system, currently under development, is being proposed as the solution to address the U.S. Forces' needs for access to testing in a variety of operational settings. Omni is a product line extension to the current family of GeneXpert systems (GX-I, GX-II, GX-4, GX-16, Infinity 48 and 80). Omni will further expand molecular diagnostic testing in decentralized locations around the world that demand portability, connectivity and ease of use. These locations range from remote, extremely resource-limited (austere) settings to specialty clinics. Cepheid's proven Xpert® cartridge technology will remain a cornerstone of Omni. Cepheid's cartridge technology automates and integrates sample preparation, nucleic acid amplification, and detection of the target sequence in simple or complex samples using real-time PCR.

At the heart of the Omni, is a solid state digital electronic architecture that provides durability, portability, and connectivity, while lowering power consumption. Omni has consolidated and miniaturized components compared to the current GeneXpert systems to improve portability, reliability and serviceability. The Omni instrument contains an on-board battery that allows for 4 hours of autonomous operation and the instrument can be recharged with a standard USB-C power cord connected to a wall socket, automotive USB or lighter system, or a 12-5V DC converter from a standard automotive 12V battery. A portable USB-C external battery pack can supply an additional 8-10 hours of battery life, above and beyond the on-board battery.

The Omni instrument, which manages all operations to process a Cepheid test cartridge, including PCR, data collection and analysis, is paired with an Android-based mobile device, which hosts the user interface. Commands driven off the Android mobile device include starting a test, viewing/ managing test results and performing administrative functions and maintenance. The Omni instrument and the Android mobile device combine to form the Omni system. All assay test results are stored in the instrument's flash memory, which has a storage capacity of up to 10,000 results, using full AES 256- bit encryption. Assay results are persistent on the instrument and in the Cepheid C360 system, a platform that enables data analytics and broad administrative function. Features of Cepheid C360 are described in the subsequent paragraphs.

The Android mobile device communicates with the Omni instrument via WiFi and/or Bluetooth technology. TCP/IP over BlueTooth. An internet connection is not required to process a test cartridge or view and act on results. However, internet access is required through either Cepheid provided global SIM card or WiFi to access C360 Admin and C360 Analytics.

Every Omni instrument comes equipped with Cepheid C360. Cepheid C360 is a secure, hosted platform that securely collects and aggregates data real-time information from any GeneXpert® System- whether operating in a centralized or decentralized testing environment. Cepheid C360 Administration (Cepheid C360 Admin) is a web portal that provides the ability to remotely manage end-users with the proper authentication, access control, and user preferences, as well as receive GeneXpert system and test software updates. Omni Administrative user accounts will be provided by Cepheid at the time of purchase for initial set-up and provisioning will require internet access.

Cepheid C360 uses a combination of full data encryption, intense physical security of the Cepheid C360 servers outside the U.S. full access control including two-factor authentication, and deep service/database segregation to ensure all HIPAA, ISO, and other medical data security requirements are met globally. The system data is fully encrypted both at rest and in transit with AES 256-bit encryption technology using hardware based key infrastructure with unique keys for each separate institution. Customers only have keyed access to their particular records.

As cyber security is of critical concern to the ***Government***, Cepheid has planned a development project in this proposal to create a non-radio communication and a dedicated ***Government*** Cepheid C360 environment to address this priority. Details of the development project are discussed in the scope of work below.

The table below outlines some key dimensions of the Omni Instrument.

Note: Final mobile device will be an Android phone. All sample processing, detection and analysis occur on the Omni. Commands to start and view test results are driven from mobile phone.

Approximate Dimensions	Height: 9.1" (23.1cm) Width: 3.0" (7.6cm) Depth: 4.2" (10.6cm)
Approximate Weight Shipping Weight	Weight: 2.2lbs (1.0kg including on board battery) < 20lbs
Power	USB-C standard connector, 5/12/20v formats
Data Storage	Approximately 10,000 test results (4-8GB)
Acquisition Cost	(b) (4)
User Interface	Simple, intuitive user interface, driven by a dedicated mobile device controlling at least a single Omni and up to 4 Omni(s).

Concurrent with this Omni system development, Cepheid started working on our next generation cartridge, Cart A+, which will enable greater flexibility in sample preparation and detection to perform complex multiplexing assays. Details of the Cart A+ technology are outlined in the Technical Approach and Plan, Section (b) of this proposal. Together, the Omni system and Cart A+ will allow the U.S forces to be able to perform tests on a decentralized basis for the bio threat agents of concern. In the scope of work, Cepheid proposes to group assay development based on syndrome and sample size requirements.

When completed, the proposed solution will have the capabilities to meet the JPMO-DX's objectives and sub-objective as defined in the table of the Technical proposal, Section (a). Details of the scope of work and progression of work are outlined below.

1.3 Scope & Objective

The scope of this prototyping effort is to modify the existing COTS capability of the GeneXpert® Omni system currently under development by Cepheid to address ***Government*** ruggedization and security considerations, and to develop up to four prototype assay cartridges leveraging a next generation plastic cartridge. The Omni system hardware is in the final stages of design lock and will soon move into formal hardware verification testing followed by validation, and Cepheid has already begun developmental work on the next generation plastic cartridge, Cart A+, which will enable greater flexibility in sample preparation needed to perform complex multiplexing assays.

The first two assay cartridges (required) will address a validated United States SOCOM requirement for a portable diagnostic capability for diseases of operational interest (BWA and infectious diseases grouped by syndromic presentation); development of the other two panels are dependent upon feasibility studies and the approval of a Joint CDD anticipated in 4QFY18. The objective is delivery of FDA-cleared prototype cartridges that run on GeneXpert and GeneXpert Omni systems and a prototype ***Government***-configured instrument.

Cepheid shall enhance the current commercial GeneXpert Omni system development effort to specifically address the Government's concerns around cyber security and enable the Omni to perform more complex multiplexing assays.

The scope of the development projects that Cepheid proposes on the Omni system and cartridge technology is as follows:

1) (b) (4)
2) (b) (4)

3) (b) (4) [redacted]
4) (b) (4) [redacted]
5) (b) (4) [redacted]

Cepheid proposes development of up to four assay cartridges for the ***Government*** in a phased approach. In Phase I, Cepheid will develop two multiplex assays for pathogen detection that are grouped based on syndrome and sample size as well as conduct assay development and alpha study activities for a prototype assay that differentiates bacterial from viral infections. A progress-based development decision will initiate Phase II development of up to two additional cartridges. The assay consumables are discussed below.

1.) "Tropical Fever" Panel cartridge (WBS 5.0): sample size 100 µL of whole blood (finger stick or venous draw). The design of this cartridge would include all targets listed below. The final decision to report out the *Leptospira* species target will depend on the sensitivity of detection from a 0.1 ml finger stick sample. If the sensitivity is insufficient *Leptospira* will not be reported. A follow-on statement of work will be developed to request the funding needed to modify the assay to improve sensitivity by increasing the sample volume of venipuncture whole blood
   - *Plasmodium* species (includes *P. falciparum*, *P. vivax*, *P. malariae*, *P. knowlesi* and *P. ovale*).
   - *P. falciparum*
   - Chikungunya virus
   - Zika virus
   - Dengue virus (Serotypes DENV-1 to DENV-4 would all be detected but reported together as Dengue)
   - *Leptospira* species (Leptospirosis)
   - *Salmonella* Typhi and Paratyphi (Part of Tropical Fever test but Cepheid funded)

2.) "Hemorrhagic Fever" Panel cartridge (WBS 6.0): sample size 100 µL of whole blood (finger stick or venous draw). This cartridge would identify and report the following targets:

   - Ebola virus – pan species detection without specific reporting for Zaire, Sudan, Taï Forest, or Bundibugyo
   - Crimean-Congo Hemorrhagic fever virus
   - Marburg virus
   - Lassa fever virus

3.) Bacterial vs. Viral Host Response Biomarker validation work (WBS 8.0): The Cepheid team will conduct assay development and initial evaluation activities leading up to an alpha study that assesses the assays ability to differentiate between bacterial and viral infections.

   Under the terms of the negotiated SOW, the team will work through the Concept and Feasibility phases of Cepheid's product development process, ending with external alpha studies utilizing samples and sites provided by JSTO. Cepheid will be performing biomarker evaluation for this effort.

   If the alpha study meets the success criteria, the Cepheid team will develop a follow-on statement of work to justify the funding needed to develop the assay further, including performing the extended verification studies and validation studies (clinical trials) needed to support an FDA submission and subsequent clearance. Further development of the Bacterial vs. Virus Assay is part of Phase 2 of the project.

4.) "Bacterial Agents" Panel cartridge (WBS 7.0): sample size 1mL of whole blood. This assay will identify and report the following targets below, using a prototype base assay developed by the Alland Lab at Rutgers. The Cepheid team will also develop targeted16S rRNA gene assays, providing a confirmatory target per agent on the panel for increased confidence that a positive test is a "true" result rather than a false positive. The 16S rRNA gene is present in multiple copies per cell, improving assay sensitivity, and is less likely to tolerate genetic modifications, leading to reduced susceptibility to natural or manmade sequence changes.

   - Bacillus anthracis (anthrax)
   - Yersinia pestis (plague)
   - Francisella tularensis (tularemia)

5.) ***<u>Phase 3 "Coronavirus" cartridge (WBS 9.0) Emergency Use Authorization (EUA):</u> The Cepheid team will undertake product development and optimization activities to develop a diagnostic assay that detects SARS-CoV-2. This scope of work is highlighted in Section 4.7.1.1.***

6.) ***"Xpert SARS CoV-2/Flu/RSV" (WBS 10.0) Emergency Use Authorization (EUA): The Cepheid team will undertake product activities to optimize a diagnostic assay that detects SARS-CoV-2, Flu A, Flu B and RSV RNA from individuals suspected of respiratory tract infection by their healthcare provider. This scope of work is highlighted in Section 4.8***

Cepheid shall conduct the clinical studies/trials for all assays that will be developed under this project in order to generate the data required for FDA submission (WBS 5.4, 6.4, and 7.4).2 Cepheid shall be the sponsor of the FDA submission and to take these assays through *de novo* classification and 510(K) clearance (WBS 5.5, 6.5, and 7.5). The Government shall be a sponsor-designated co-contact for the products. Cepheid will gain government concurrence on pre-submission packages and strategy before approaching the FDA. During the pre-submission process, Cepheid will discuss and explore CLIA Waiver applications with the FDA.

2.0 References

List of Applicable References for Assay Development:

1. (b) (4) [redacted]
2. (b) (4) [redacted]
3. (b) (4) [redacted]
4. (b) (4) [redacted]
5. (b) (4) [redacted]
6. (b) (4) [redacted]
7. (b) (4) [redacted].
8. (b) (4) [redacted]
9. (b) (4) [redacted]
10. (b) (4) [redacted]
11. (b) (4) [redacted]

2 FDA studies for the bacterial vs. viral cartridge will be addressed, at the Government's request, if a revised SOW is requested following successful alpha studies.

12. (b) (4) [redacted]
13. (b) (4) [redacted]
14. (b) (4) [redacted]

3.0 Project Objectives

When completed, the proposed solution shall have the capabilities to meet the JPMO-DX's objectives and sub-objective as defined in the table below. Objective (desired) Performance Attributes are within scope, but final achievements may vary depending on development. Details of the scope of work, progression of work are outlined after the table and our technical approach and plan is in Section (b) of this proposal.

Threshold Performance Attributes:	**Objective Performance Attributes (Desired):**
•FDA Cleared In Vitro Diagnostic Device	
Diagnostics for eleven (11) warfare diseases: •Ebola, Zika, Malaria, Chikungunya, Crimean-Congo Hemorrhagic Fever, Dengue, Lassa, Anthrax, Plague, Tularemia, and Marburg	Additional disease diagnostics: •Q-Fever, Brucellosis, Melioidosis, Glanders, Typhus, ***Leptospirosis***, Smallpox, Venezuelan Equine Encephalitis
System Weight and Volume: •In tactical carry configuration (packed in soft case inside other portable container/backpack), the system shall weigh not more than 10 lbs. or exceed 400 cubic inches in volume. •In Transit/Shipping Configuration (with hard sided reusable shipping case): 20 lbs.	System Weight and Volume: •Instrument/controller plus eight single-use assays (mission set) shall weigh not more than 4 lbs. or exceed 300 cubic inches in volume.
Sample preparation: •The device shall not require manual sample preparation steps once sample is collected from the patient (excluding steps to get sample into liquid form, if needed) or operator timed steps	Sample preparation: •Less than 1 minute hands on time
Clinical Sample Types: •Whole blood (venous), Capillary blood (finger-stick)	Additional Clinical Sample Types: •urine, sputum
Complexity: •CLIA Moderately Complex	Complexity: •CLIA Waived
System set up time: •≤10 minutes after transport	System set up time: • <1 minutes after transport
Time to result: •Single Clinical Sample Throughput maximum 75 minutes, sample preparation through result	Time to result: •10 minutes
Multiplexing: •Simultaneous identification of 5 or more analytical targets (not counting necessary controls) per analytical run	Multiplexing: •Simultaneous analysis of multiple diseases of interest, five or more analytical readouts per analytical run. (Up to 100)
Power/battery: •Electric powered components will be UL listed •Reusable battery operable system and battery replacement without tools. •Perform a minimum of 2 successful end to end analyses (runs) per battery charge.	Power/battery: •System capable of being externally DC powered (12-32VDC). •System capable of being externally powered 110-240VAC, 50-60Hz

	•Device capable of performing six (6) or more successful runs per charge
Environmental Operating Conditions : •Temperature: +10° to +40°C •Pressure: 75.3kPa •Altitude: sea level to 2438m (8000 ft) •Relative Humidity: 15-90%	Environmental Operating Conditions : •Temperature: +4°C to +54°C •Pressure: 57.2kPa •Altitude: sea level to 4600m (15000 ft) •Relative Humidity: 5-100%
Transport Considerations: •Altitude: Capable of normal operation after transport or storage from sea level to 4,600m (15,000 ft.) (unpressurized air cargo) •Transit shock: Withstand drop of 1m (3ft) in shipping case	Transport Considerations: •Altitude: Capable of normal operation after transport or storage from sea level 12,200m (40,000 ft.) (unpressurized air cargo) •Transit shock: Withstand drop of 1.8m (5ft) in shipping case
Assay, consumable stability*: •Standard Storage: ≥12 months at +18°C to +30°C, ≤ +40% relative humidity •Excursion stability: ≥2 months at 40°C.	Assay, consumable stability: •+ Standard Storage: ≥36 months at +18°C to +30°C, ≤ +40% relative humidity Excursion stability: ≥6 months at 40°C and unaffected for 72 hours at +54°C

**Kit stability studies will be tested at 2ºC, 30ºC, 35ºC, 40ºC, and 55ºC to determine final storage conditions and shelf life.*

Specific WBS objectives are summarized in the subsequent subsections.

3.1 WBS1 Objectives

- Develop Software and Firmware on Omni system to accommodate non-radio connectivity mode for ***Government*** users
- Develop C360 Cloud Software for ***Government*** applications
- Implement dedicated custom Cepheid C360 Cloud Server infrastructure for hosting Government data and pushing requisite software updates:
    - Server shall be physically located in the Continental United States (CONUS)
    - Cloud shall be administered by a ***Government*** 8570.01-M compliant U.S. Citizen
- Implement a CLIA-waived system
- Implement simple email scenario;
- Password based on user role
- Disable C360 Analytics
- Support Phase activities and planning ***Government*** Omni

3.2 WBS 2 Objectives

- Update I-CORE hardware design to support electro-optical integration of commercially-sustainable raw component supply chain
- Update I-CORE hardware design to increase system durability and reliability
- Update I-CORE hardware design to increase system manufacturability
- Development of 10-Color Omni System detection to support multiplexing assays
- Define 10-color calibration and manufacturing process
- Release 10-color Omni systems to assay development teams for integration into ***Government*** effort

3.3 WBS 3 Objectives

- Hardware development acceleration for ***Government*** purposes
- Update hardware design to support a commercially-sustainable raw component supply chain for the ultrasonic horn, fluidic drive systems motor components, and the instrument exterior housing
- Update hardware design to increase system durability and reliability
- Update hardware design to increase system manufacturability
- Accelerate development of tools and processes used to increase system manufacturability

- Early instrument build (pilot manufacturing) and system verification testing
- Contractor developmental testing
- Design lock and manufacturing data transfer to instrument manufacturer

3.4 WBS 4 Objectives

- Cart A+ Development Acceleration
- Cart A+ consumable manufacturing qualification and validation
- Manufacturing Scale-Up for ***Government*** prototype production demands (developmental, clinical, and operational testing)

3.5 Assay Development Objectives (WBS 5.0, 6.0, 7.0, 8.0, *and 9.0)*

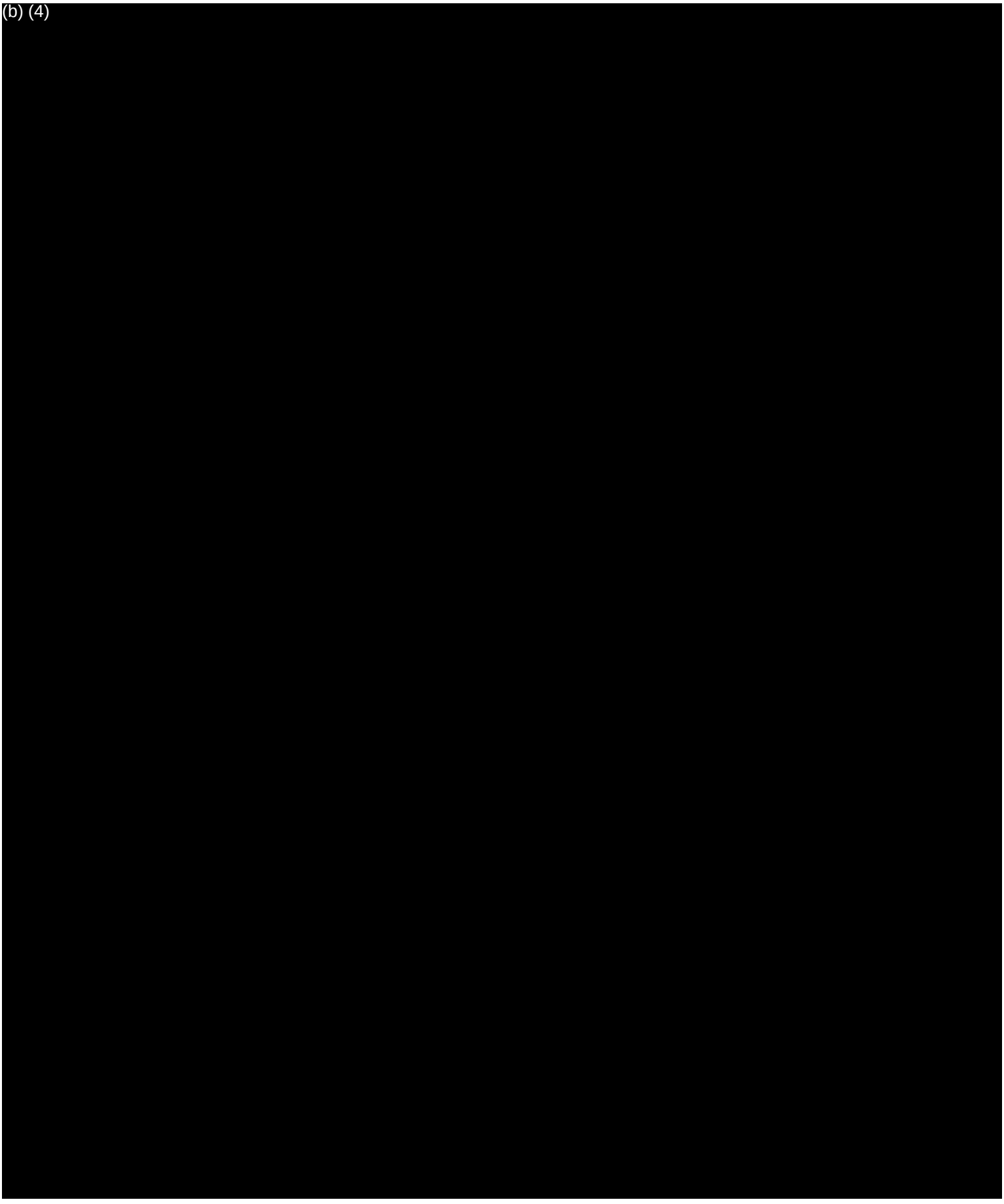
WBS 5.0 – ***9.0*** are assay development activities. Figure 1 summarizes prototype development objectives.

Figure 1: Government Assay Development Objectives

Effort	**Objectives**
Tropical Fever Cartridge Development and Clearance (WBS 5.0)	FDA granting the *de novo* request of Tropical Fever Cartridge (100 µL of whole blood) (finger stick or venous draw) that identifies and reports the following targets: • *Plasmodium* species (includes *P. falciparum*, *P. vivax*, *P. malariae*, *P. knowlesi* and *P. ovale*). • *P. falciparum* • Chikungunya virus • Zika virus • Dengue virus (Serotypes DENV-1 to DENV-4 would all be detected but reported together as Dengue) • *Leptospira* species (Leptospirosis) • *Salmonella* Typhi/ParaTyphi (Cepheid funded)
Hemorrhagic Fever Cartridge Development and Clearance (WBS 6.0)	FDA clearance of Hemorrhagic Fever Cartridge (100 µL of whole blood) (finger stick or venous draw) that identifies and reports the following targets: • Ebola virus – pan species detection without specific reporting for Zaire, Sudan, Taï Forest, or Bundibugyo • Crimean-Congo Hemorrhagic fever virus • Marburg virus • Lassa fever virus
Bacterial Agents Cartridge Development and Clearance (WBS 7.0)	FDA clearance of Bacterial Agents Panel (sample size up to 1 ml of whole blood; finger stick sample desired) that identifies and reports the following targets: • Bacillus anthracis (anthrax) • Yersinia pestis (plague) • Francisella tularensis (tularemia)
Bacterial Vs. Viral Host Validation Work (WBS 8.0) **Development is a Phase 2 activity.**	**Assay development and initial evaluation activities leading up to an alpha study.** The goal is to assesses the assay's ability to differentiate between bacterial and viral infections
Manufacturing Scale-Up for *Government* Production Demands	• **To be determined**

4.0 Requirements

(b) (4)



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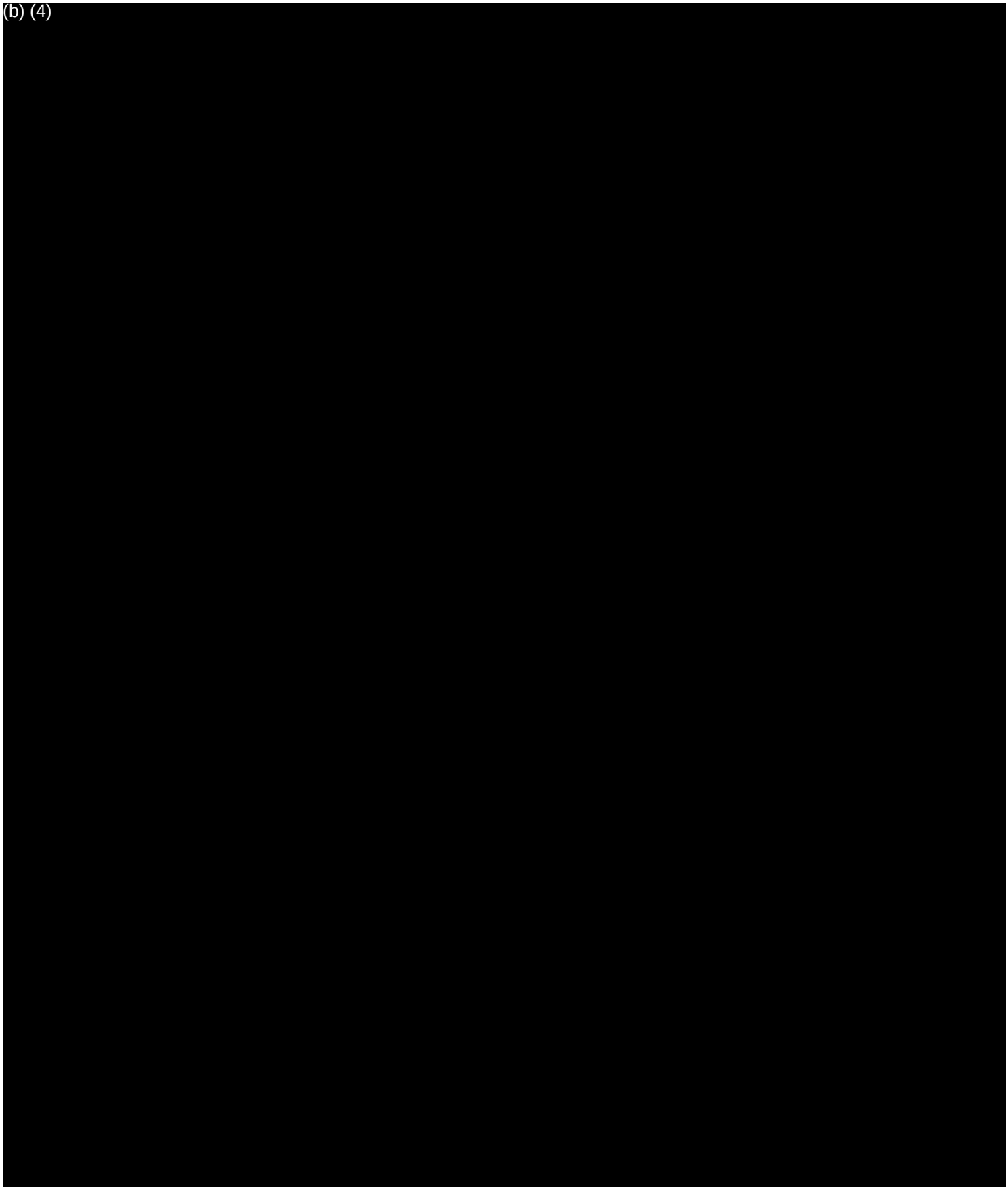

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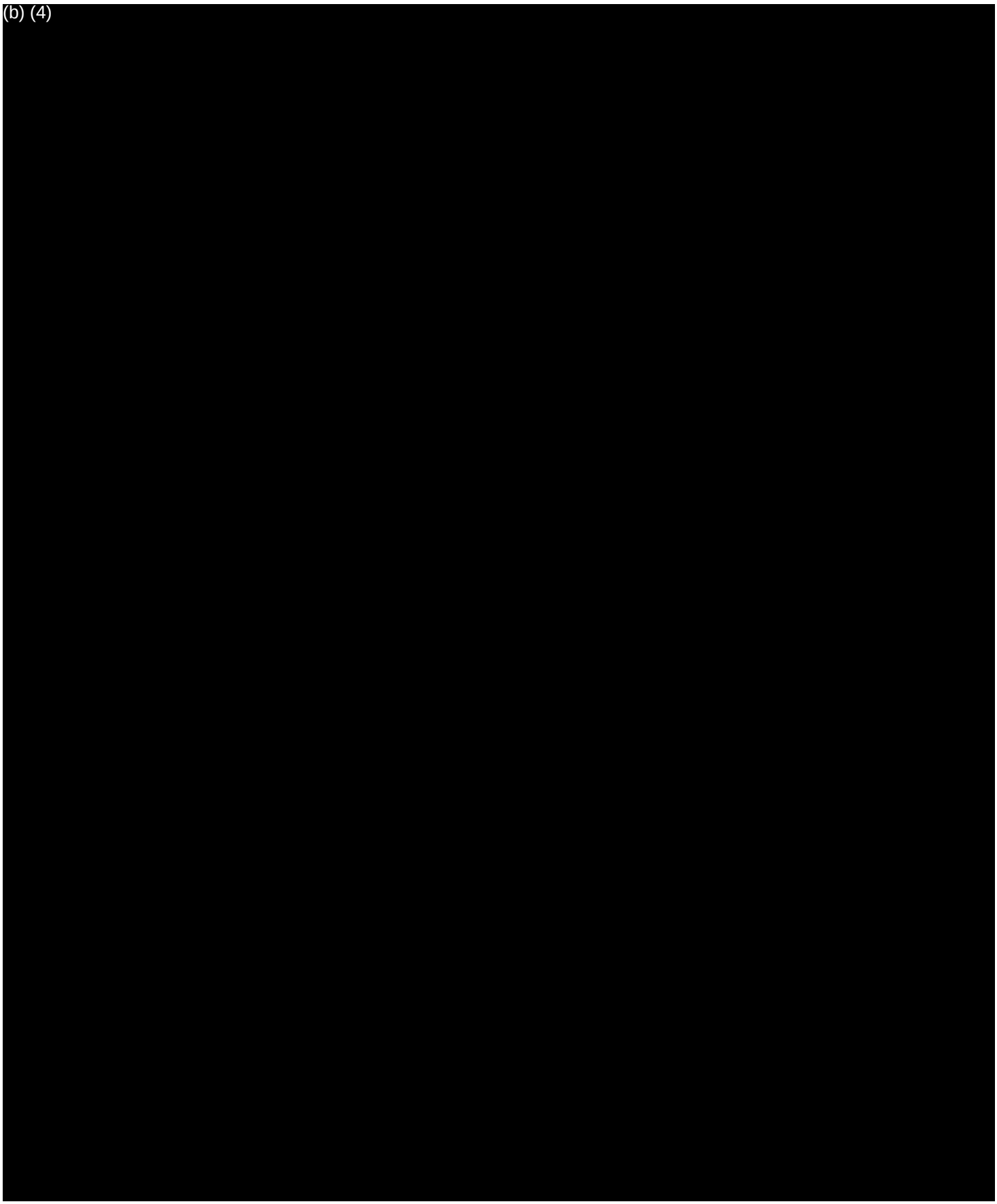

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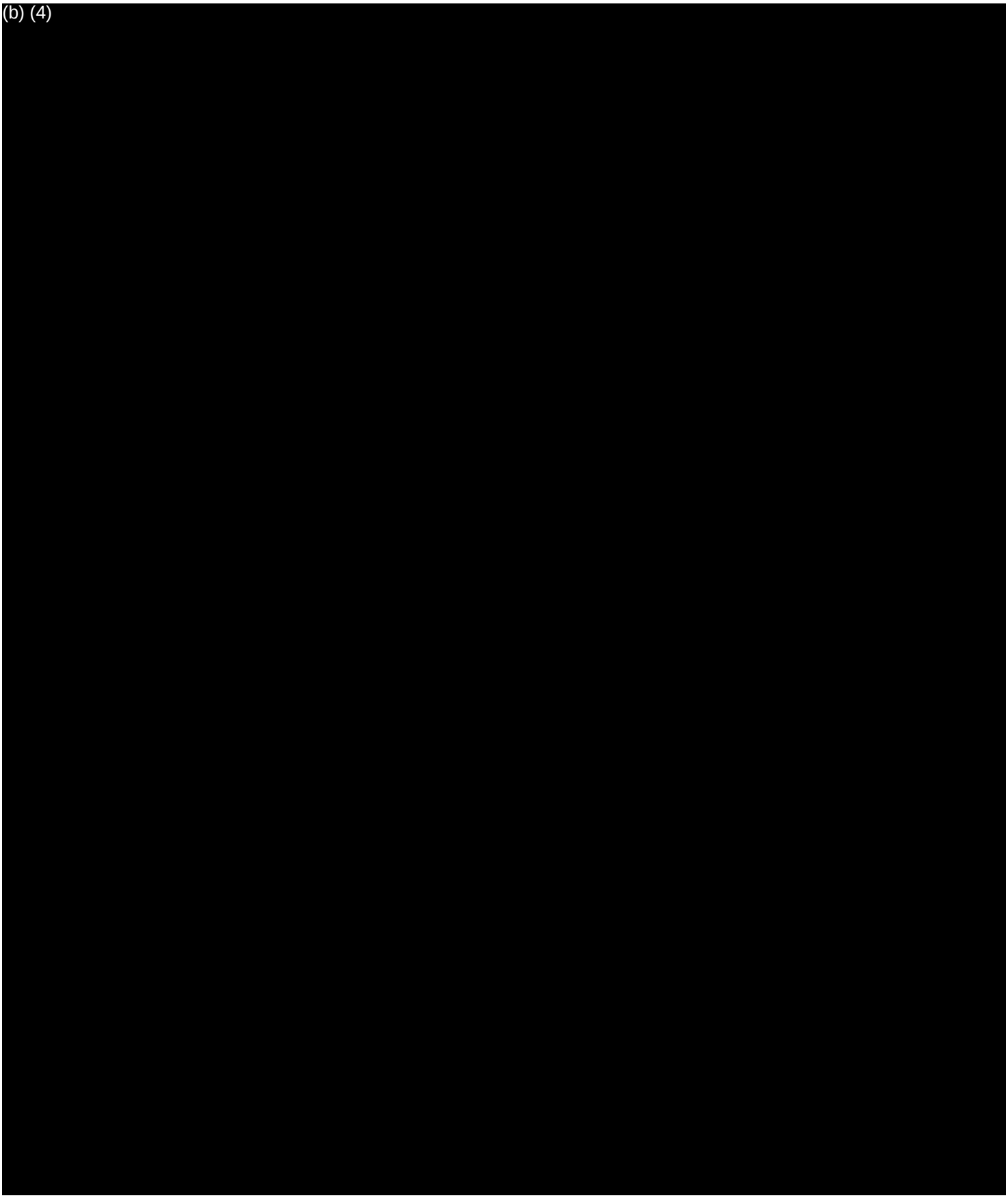


(b) (4)

[redacted]

Data Deliverables

The following table provides a summary matrix for data deliverables.

Title of Data Deliverable	**Frequency**
Integrated Master Schedule	Initial plus updates
Integrated Master Plan	Initial plus Updates
Work Breakdown Structure	Initial plus updates
Monthly and Final Reports	Monthly plus final
Monthly Financial Status and Expenditure Forecast Report	Monthly
Test Plans, Test Status, Test Reports	As needed
Regulatory Deliverables	As needed
Meetings and Reviews	As needed

Production Capability Data	One time
Logistics Data	As needed
Patents – Reporting of Subject Inventions	Annual and at completion of project
Quarterly Status Reports	Quarterly
Annual Status Reports	Annually

Project Reporting Requirements

Cepheid shall report on the progress of the activity checklist through a monthly PowerPoint progress report. For months in which quarterly or annual reporting requirements are due, these are submitted in lieu of the monthly report.

At a minimum, the monthly progress report shall include:

- Overall Monthly Progress and Key Events in Upcoming Month
- Technical Progress (Overall and by Major WBS Element)
- Regulatory Planning or Execution Activities
  Management and Administrative Updates
- GFI/GFM and Associated Coordination (including any reviews, information, or materials needed from Government over the next 60 days)
- Overview schedule including upcoming decision dates within next quarter
- Risk Update – New Risks or Risks Mitigated/Closed
- A slide for each major WBS element (e.g. WBS 1, 2, 3, etc.) addressing progress through the activity phases

A monthly financial report shall be provided to accompany the monthly progress report. The financial report shall include:

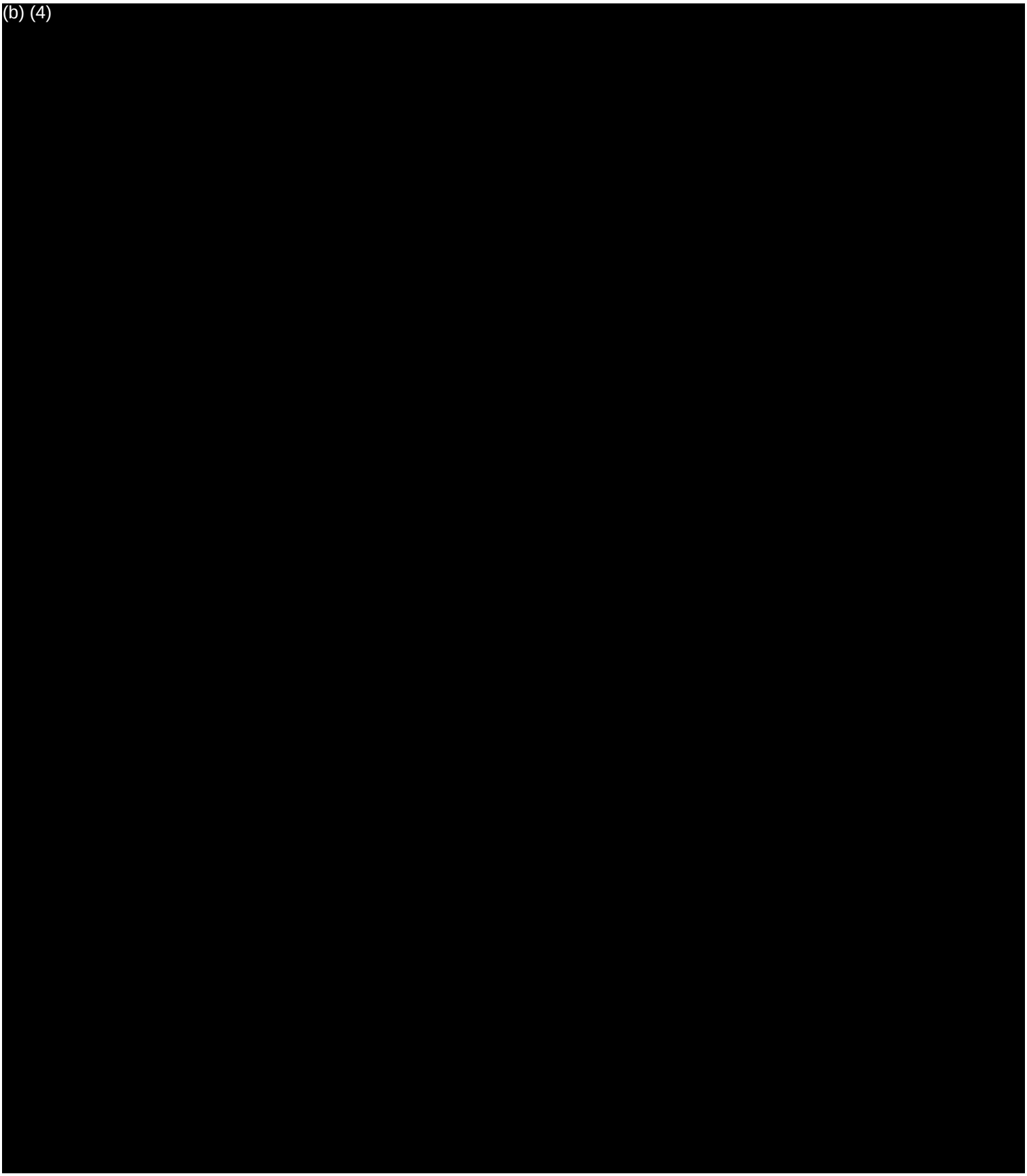
- A separate worksheet for each major WBS element (WBS 1-6 and Bacterial vs. Viral task)
- The current phase for each major WBS element.
- The estimated spend plan for each phase resource and core team member allocation (provided after concept phase planning)
- Estimated date and estimated amount for large material and/or subcontractor expenses that represent a significant deviation from straight line expenditure.
- Labor hours billed by Core Team Member

Sections 4.1-4.8 describe the technical approach for the major development tasks (WBS 1.0-WBS 8.0) under this prototype agreement. Each section describes the effort involved and deliverables required for the Omni system and consumable prototype development effort.

4.1 WBS1: Omni System Software/Firmware Development for Non-Radio Connectivity Mode, Custom C360 Cloud Software, and Dedicated Custom C360 Cloud Server Infrastructure for Hosting the *Government* Requisite Data, a CLIA-waived system.

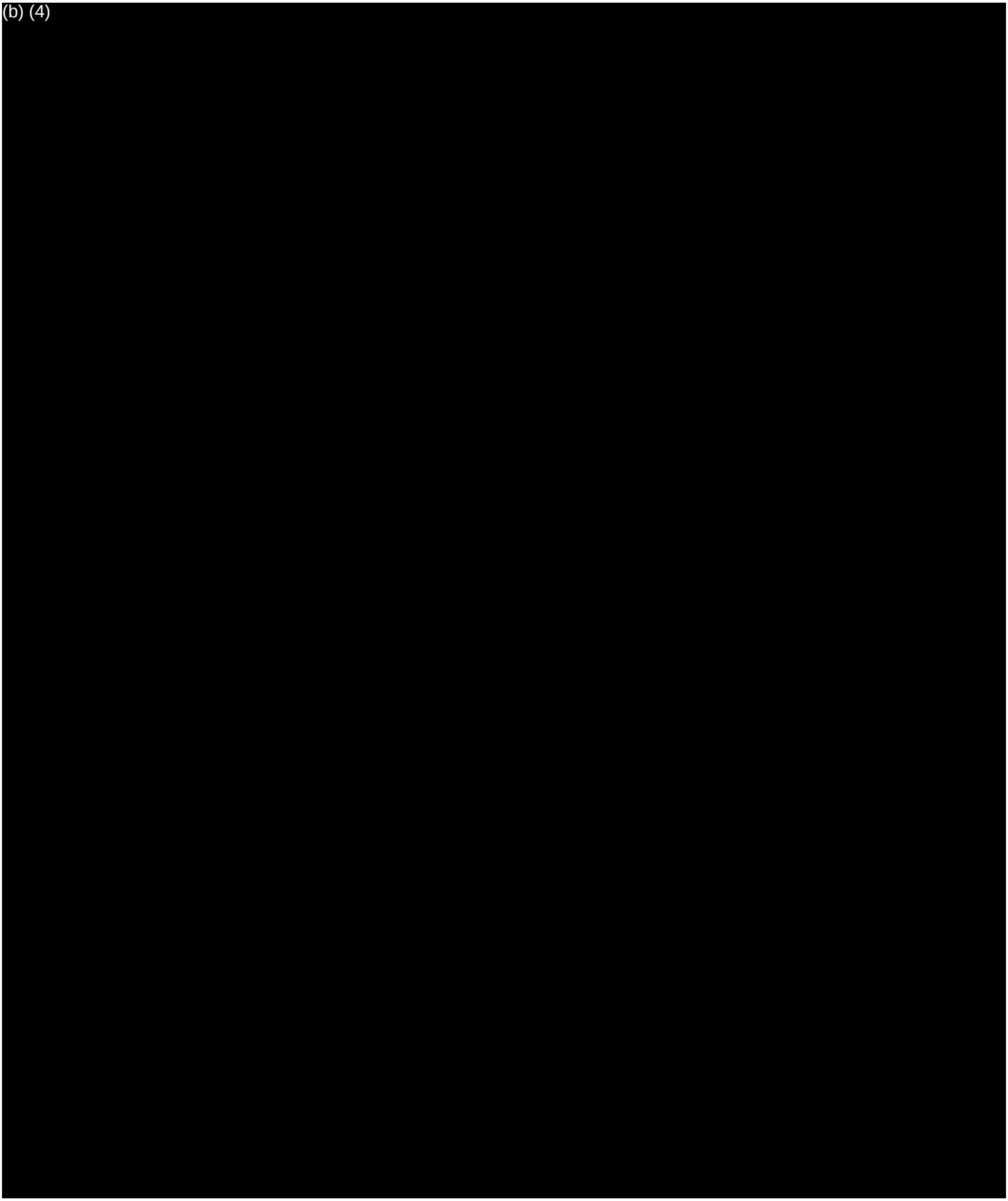
(b) (4)

(b) (4)



(b) (4)

(b) (4)



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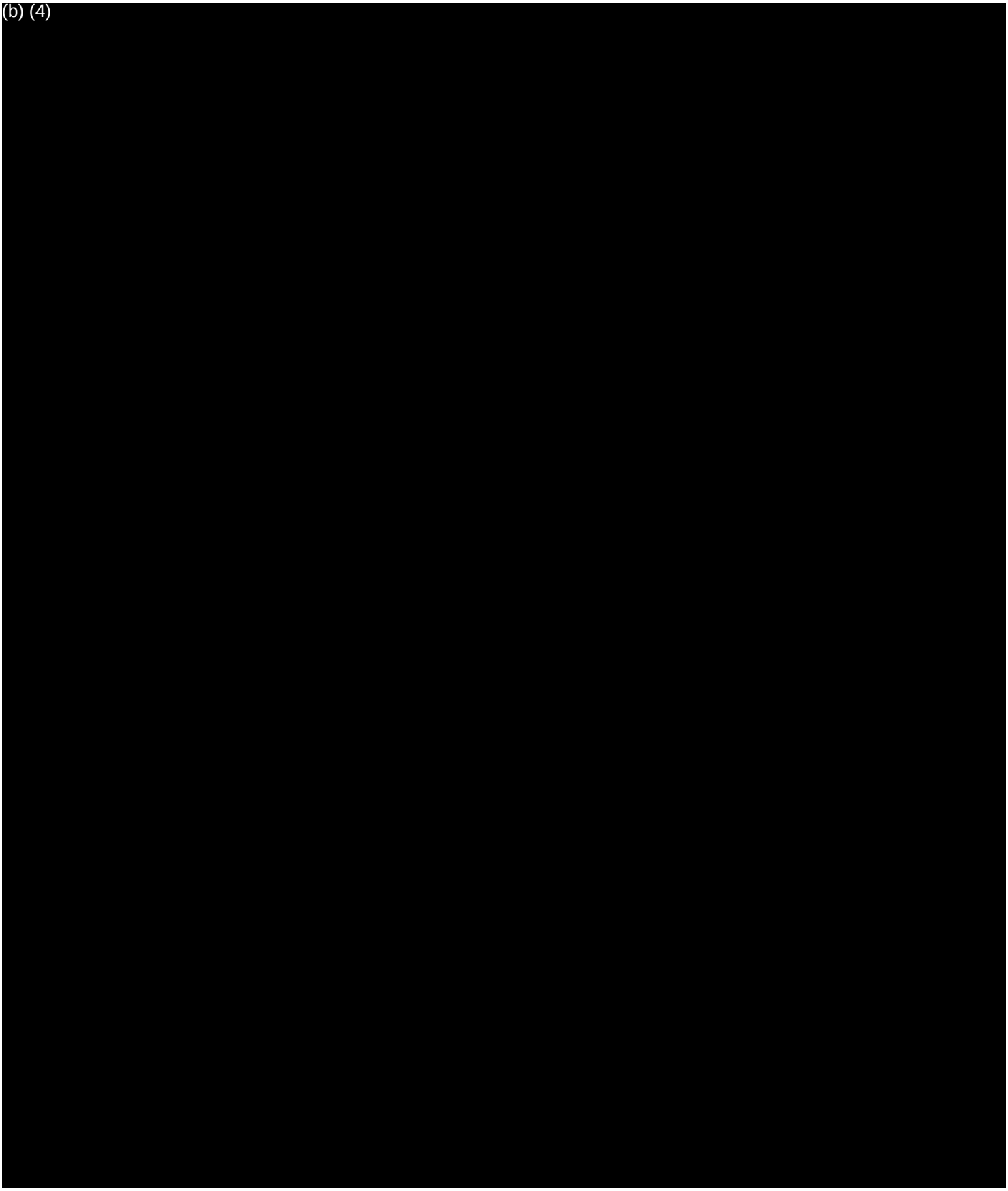

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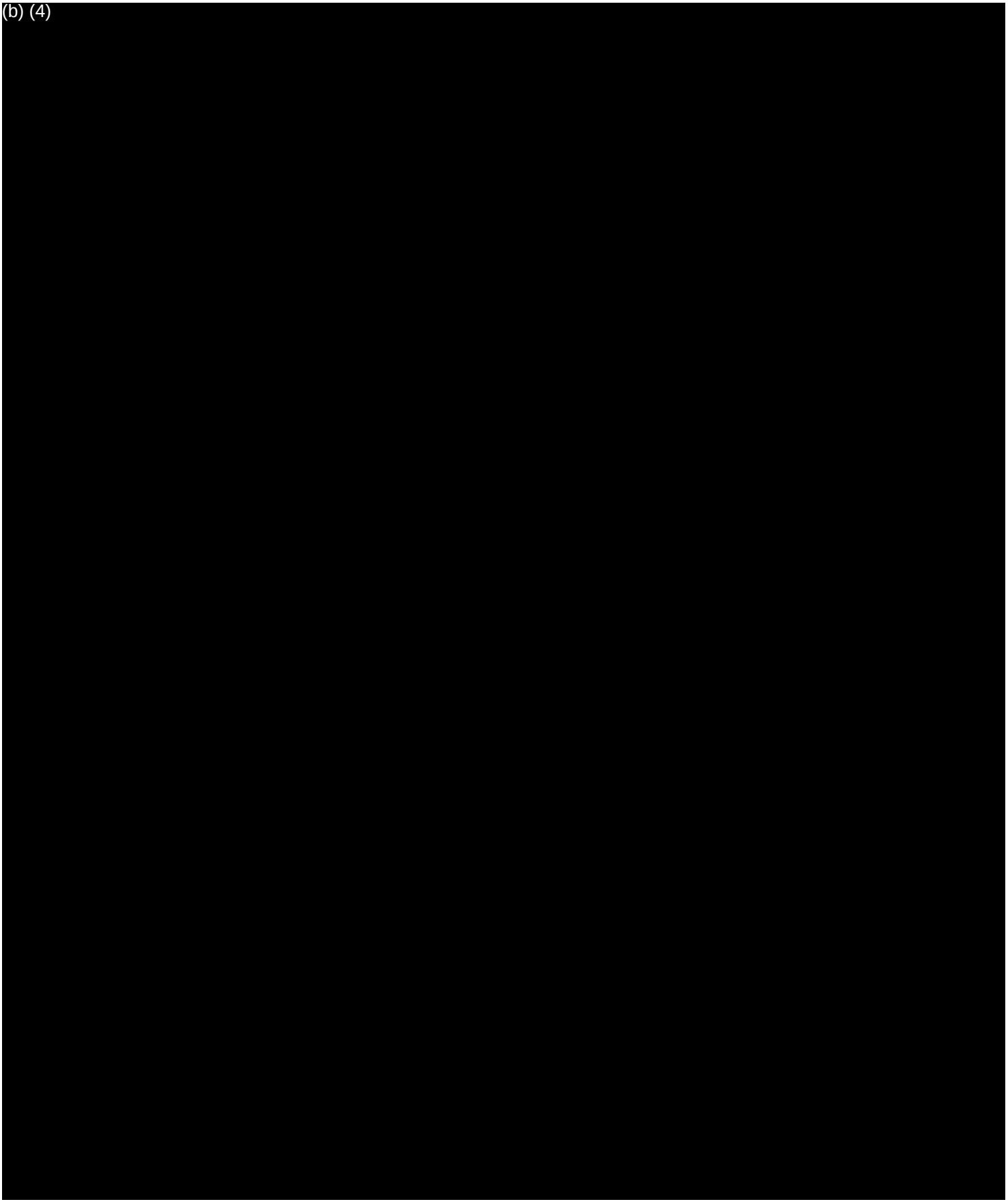

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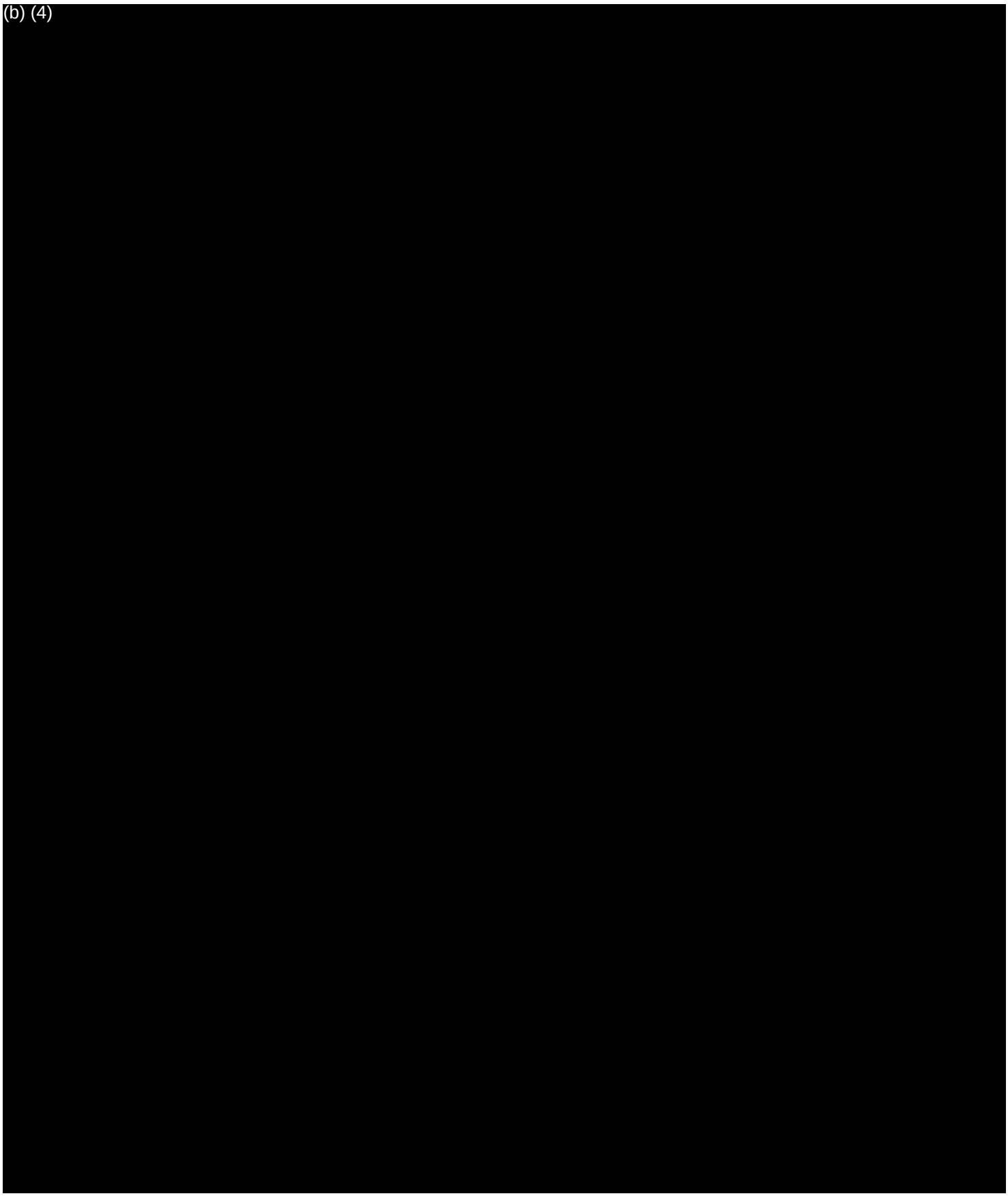
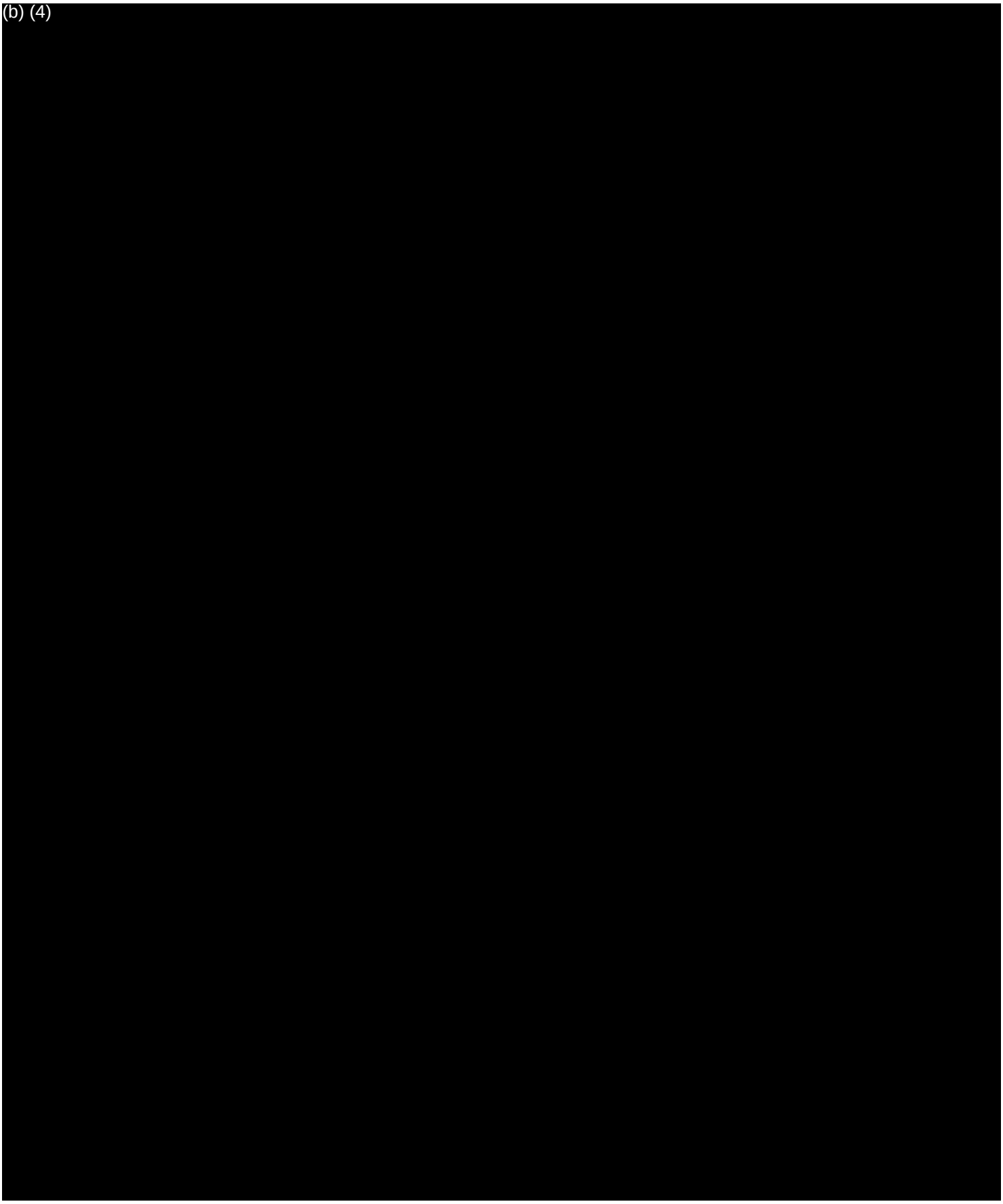
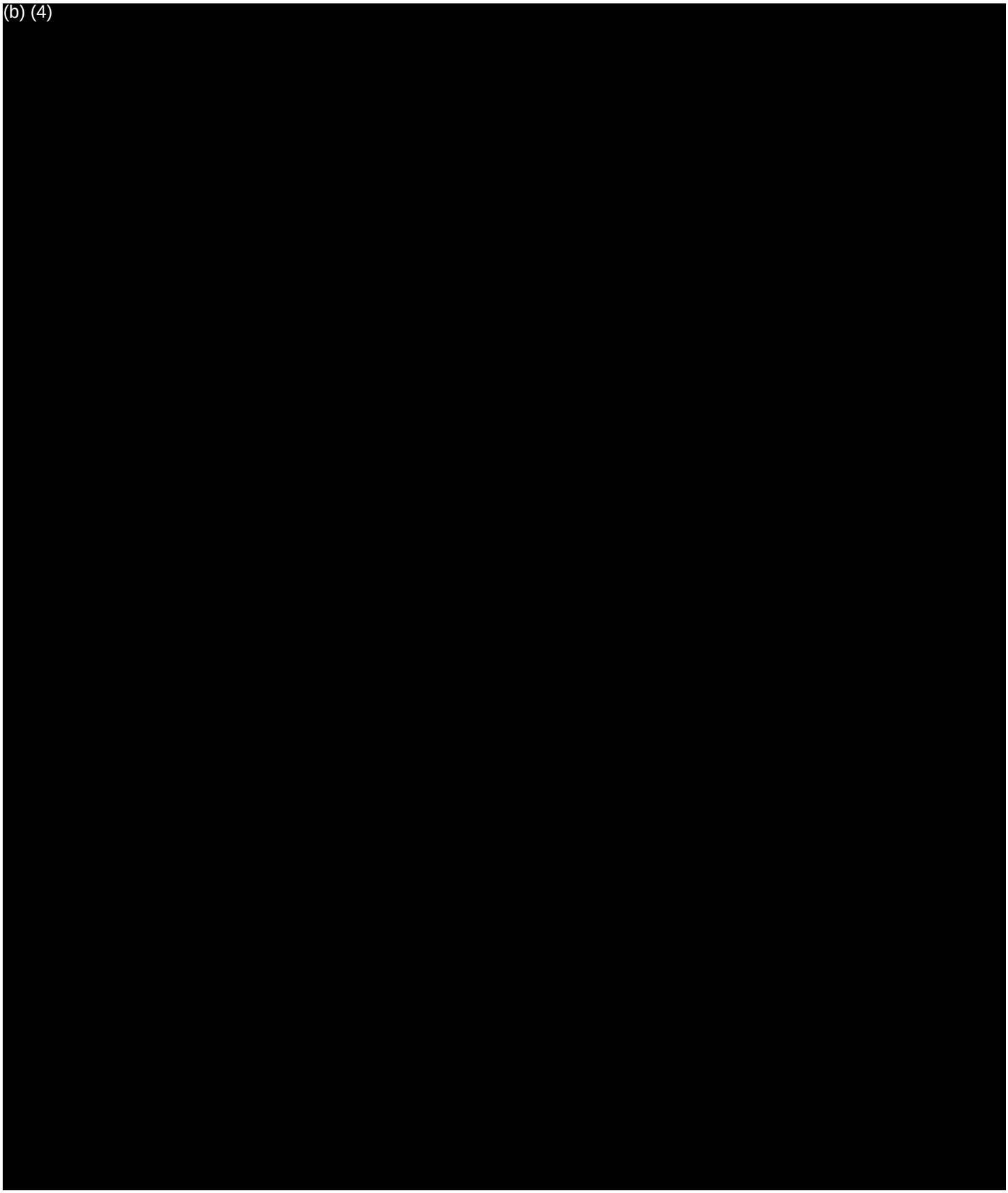


(b) (4)



(b) (4)



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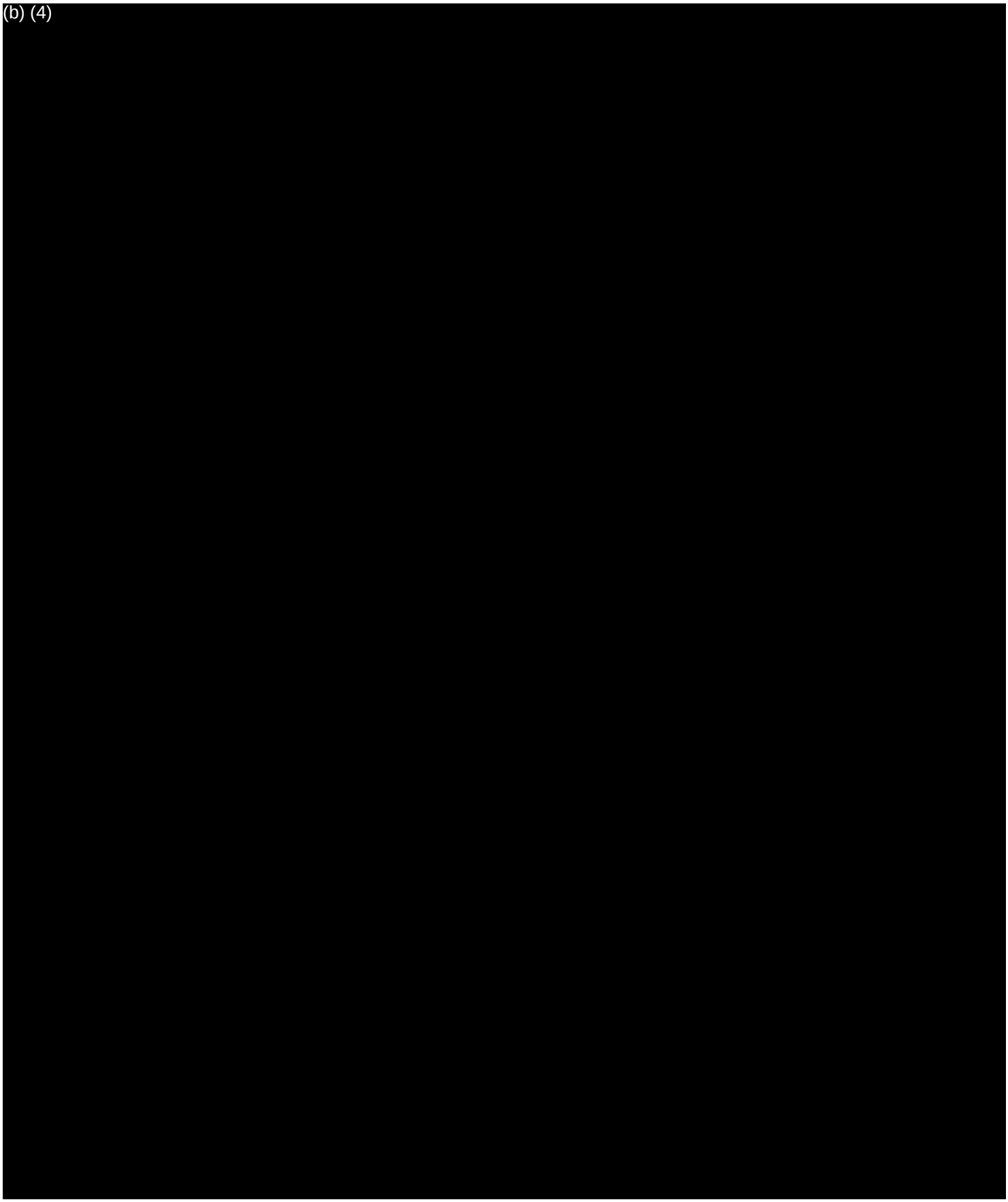

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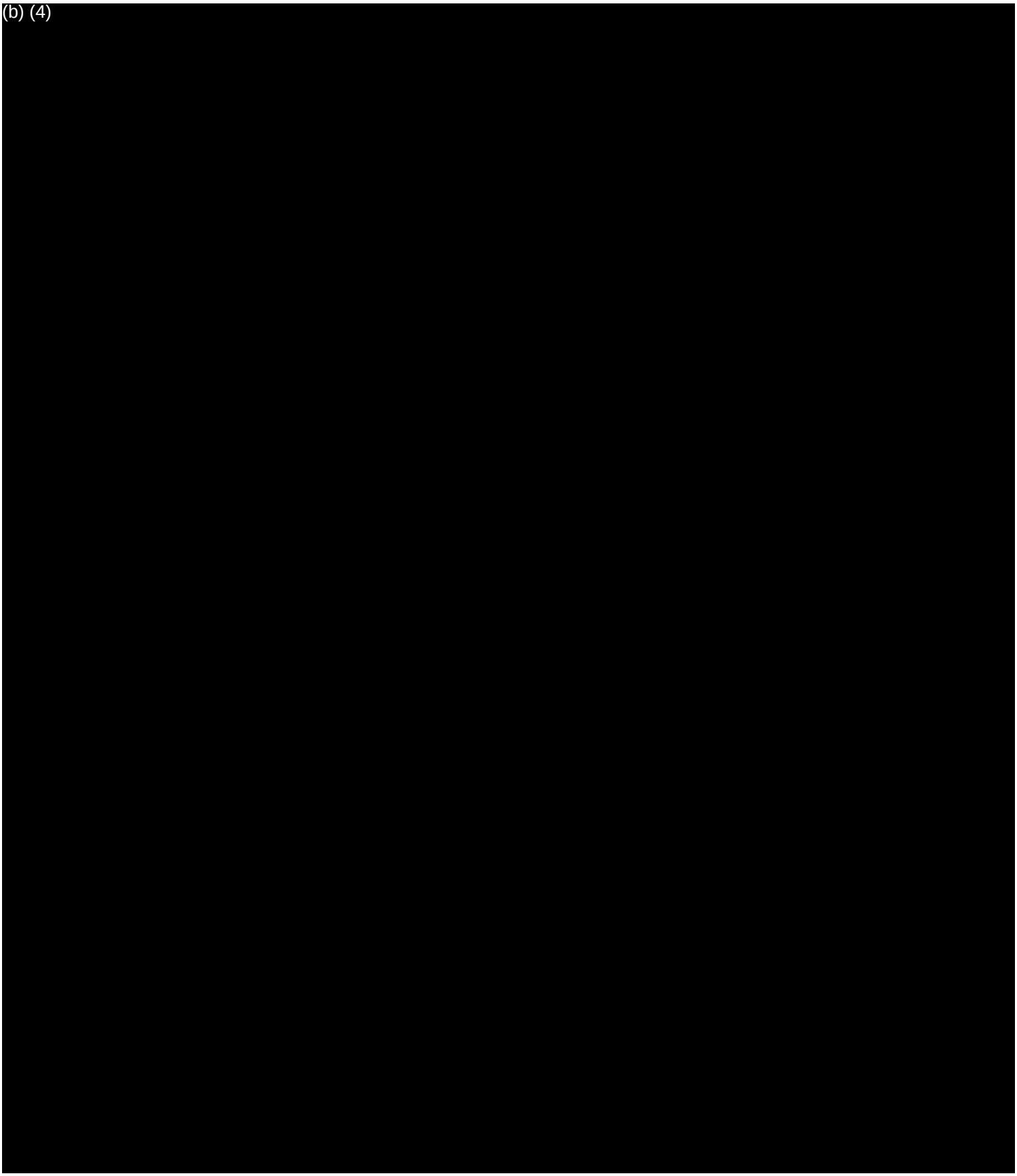


(b) (4)

[redacted]

4.5 WBS 5.0, 6.0, 7.0, 8.0, and *9.0*: Development and Delivery of "Tropical Fever," "Hemorrhagic Fever," "Bacterial Agents," "Bacterial vs. Viral Host Response," *and "Coronavirus"* Cartridges

4.5.1 Assay Development Concept Phase

The Concept Phase involves the following activities:

1. Product definition – specifications are captured in the Design Input Requirements (DIR) document (example from Xpert Ebola is included below for reference). DIR requirements are translated from a Market Essentials Characteristic (MEC) document that outlines the customer requirements.
2. Project Definition – project scope is described in a Project Plan. It will incorporate elements contained in the SOW below.
3. Project Risk Management Plan– a living project document reviewed rigorously by the core team throughout the project to foresee risks, estimate impact, and define mitigations.
4. Project Regulatory Plan - establishes specific project deliverables and responsibilities to successfully meet FDA requirements.

4.5.1.1 Assay Development Concept Phase Specifics for the Xpert Bacterial Agents (WBS 7.0)

(b) (4)

4.5.2 Assay Development Technical Feasibility Phase

The Feasibility Phase involves the following activities:

1. Assay optimization

a. Sample preparation – since cartridge-based sample preparation methods from 0.1 ml and 1.0 ml of blood have been developed by Cepheid (0.1 ml; Xpert HIV Qual and Ebola CE-marked products) and collaborators (1.0 ml for sensitive detection of *Francisella tularensis*[8] with feasibility for processing up to 2.0 ml demonstrated), *de novo* development is not required. Fluidics and reagent chemistries will be reviewed and either confirmed to be optimum, or revised as needed.

b. Oligonucleotide Design

i. Bioinformatics. Although Cepheid will leverage existing designs if available, additional bioinformatics work will be needed for in silico identification of sequences that meet assay specificity (inclusivity for design targets and exclusivity for non-target organisms) requirements. A bioinformatics consultant will be used as a sub-contractor to augment internal efforts. (b) (4)

ii. Thermal profile. All individual PCR reactions and oligonucleotide sequences will be designed to operate optimally at the same annealing (b) (4) and denaturation (b) (4) temperatures and times. Cepheid has proprietary special bases that can raise the melting temperature of a given oligonucleotide from (b) to (b) which provides the ability to "dial-in" common annealing temperatures independently of base composition.

c. PCR assay optimization

i. Reagent composition. The concentrations of critical reagents; primers, probes, Mg, KCl, dNTPs, buffers, and enzyme selection and level will be optimized for optimum performance using a multi-parameter design of experiments (DOE) approach.

ii. Dye and quencher selection. With the exception of FAM, Cepheid utilizes proprietary dyes and quenchers that will be selected based on spectral and assay compatibility.

iii. Multiplexing. Combining up to seven individual targets in a single cartridge will require a minimum of 21 oligonucleotides, with more likely needed to provide sufficient strain coverage. Computer software will be used to create designs that avoid deleterious intra- and inter-molecular interactions that can reduce amplification efficiency, but not all interactions are predictable. It is anticipated that this will need to be resolved empirically through iterative oligonucleotide re-design and testing.

d. Software s*pecific to Xpert Bacterial Agents (WBS 7.0)*

i. Software development. (b) (4)

2. Cross-talk correction factors are assigned for each dye in all Cepheid assays to compensate for signal bleeding into adjacent optical channels.
3. Transfer to dried format. Once demonstrated to be optimum in liquid amplification reactions, the PCR reagents will be dried into lyophilized beads using standard Cepheid lyophilization buffers and lyophilization conditions that enable proper dried bead morphology, rapid dissolution, and long term stability. (b) (4) A consultant (b) (4) is needed to perform freeze-dry microscopy and differential scanning calorimetry in order to define the critical temperatures of each bead, that are dependent on the assay-specific salts and other components of the reaction mix.

The drying parameters that are optimal vary, and are dependent on the critical temperature of that specific bead.

4. Establishment of thermal and optical parameters for ***Government*** assays to transfer to the Omni system. ***Government*** assays will be configured to run on the fully automated GeneXpert/Infinity and Omni systems. Both systems utilize the same sample preparation and PCR reagents contained in the exact same disposable cartridge. However, differences in the hardware between the systems will require modification to the thermal profile and optical settings for the assay to run on the Omni. Two assay definition files (ADF) carried on the barcode will therefore be needed for the assay, one for the GeneXpert/Infinity and one for the Omni. The intended use will be the same for both platforms and performance characteristics described in the package insert will be statistically equivalent. Work performed on the current Gene Xpert or Infinity system is within scope to the extent that supports efforts to develop, optimize, and validate assays for ***Government*** capability on the Omni system. Additional work required for the purposes of commercializing ***Government*** assays on non-Omni platforms is outside of the scope of this effort.
5. Robustness testing to define limits of failure. A multi-parameter design of experiments (DOE) approach will be used to define edge of failure for each critical component.
6. Alpha testing on clinical samples will be a combination of clinical specimens sourced externally as well as samples spiked into negative clinical matrix.
7. Preliminary performance testing. A series of analytical studies including; limit of detection (LoD), linearity, inclusivity, and exclusivity will be conducted to demonstrate that the assay meets the performance specifications described in the DIR.
8. Design Lock. The primary outputs of the Feasibility Phase are assays that have final designs, subject to confirmation by more extensive verification and validation studies conducted in subsequent phases.
   a. Oligonucleotide design. The sequences, dyes, and quenchers of the individual oligonucleotide used in the assay are finalized.
   b. The ADF, an assay developer configurable software that defines all the commands and settings needed to manufacture and run the assay. (b) (4) [redacted]

4.5.3 Assay Design and Development

Work performed during this phase will require the manufacturing of at least (b) (4) [redacted] The results, or design outputs, must meet the design input requirements described in the DIR.

1. Assay verification studies - analytical studies to support non-clinical performance claims in the package insert.
   a. Limit of Detection (LoD)
   b. Linearity
   c. Precision
   d. Reproducibility
   e. Inclusivity
   f. Exclusivity
   g. In cartridge hold-time
   h. Amplicon contamination
   i. Interfering substances
   j. Failure mode testing
2. Sample stability studies. The allowable storage time and temperatures for whole blood following blood draw will be defined (b) (4) [redacted]
3. Kit stability studies. Stability will be tested (b) (4) [redacted]
4. Development of oligonucleotide synthesis and purification methods. This will be completed in-house at Cepheid's oligonucleotide manufacturing facility (b) (4) [redacted] Methods will be established and validated at a scale needed to support demand at launch.
5. Establishment of QC procedures and acceptance criteria used during manufacturing. This will be a two-step process that includes control limit studies (CLS) where R&D defines the test methods, test material, and acceptance criteria used for kit release during manufacturing followed by test method validation (TMV) performed by manufacturing. Three independent lots are used for each set of studies.
6. External beta study conducted to obtain preliminary performance data in the hands of the end user on the final product configuration
7. Controls. External quality controls (QC) will be developed to monitor shifts, trends, operator errors, and systematic variation. For novel molecular assays, Cepheid works with multiple external vendors to develop and manufacture non-infectious external QC controls. Cepheid will pursue multiple options to develop controls that are stable at ambient temperature and anticipates

evaluating technologies from (b) (4) before selecting the best option.

Note. Verification studies, QC release procedures, and beta testing will be run on both GeneXpert to achieve efficiencies in schedule and Omni systems. Sample and kit stability studies need only to be run on one system.

4.5.4 Assay Validation

Validation Phase activities are as follows:

1. Assay validation. Clinical trials conducted to validate assay performance and support U.S. FDA submission.
2. Manufacturing process validation. Three independent process validation (PV) lots are built to demonstrate the reproducibility of the manufacturing process including validating QC release procedures and acceptance criteria.
3. Regulatory submissions.

4.5.5 Regulatory Strategy and Planning

Cepheid will sponsor the FDA submissions related to the development of the proposed assays and Omni System including firmware and software. The Government will be a sponsor-designated co-contact for all Government-funded assay development efforts and will provide concurrence on the pre-submission package prior to approaching the FDA. Cepheid's end goal would be to file for FDA marketing authorization for the (b) (4) ***and Pan-Coronavirus*** assays depending on the successful completion of clinical trials.

The Regulatory Core Team Member will develop a Regulatory Plan outlining the process for obtaining FDA clearance/ *de novo* classification. The pre-submission process will be used to define the regulatory path and analytical/ clinical study design for all assays. Requirements for obtaining a CLIA Waiver will also be obtained during the pre-submission process. Following a *de novo* classification, a CLIA Waiver by Application will be submitted. For any panels that are eligible for 510(k) pathway, a dual 510(k) and CLIA Waiver will be submitted as appropriate. Some assays, e.g. (b) (4), and Pan-Coronavirus, may not qualify as CLIA waived. In this situation, CLIA Waiver related studies, e.g. flex study and reproducibility study with untrained users, will be performed and data will be submitted. However, a formal CLIA Waiver designation will not be requested from the FDA.

The Omni System will be cleared together with the first assay on Omni submitted to FDA. For later assays on the Omni System, firmware and software changes will be included in the corresponding assay submission prior to implementation. Previous submissions that included new instrument system or updated firmware/ software sections have not extended review times.

4.5.5.1 Regulatory Specifics for the Xpert Tropical Fever (WBS 5.0)

The Tropical Fever test submission will follow a *de novo* pathway. The pathway allows novel assays (without predicates) to be classified as class II, that would otherwise require class III Premarket Approval applications. The new device classification established through this process may be used by follow-on 510(k) submissions for devices in the same product family. The regulatory pathway has been confirmed by FDA through pre-submission. The regulatory landscape will be closely monitored in order to identify possible (future) predicates for the Xpert Tropical Fever test.

It is not possible to request *de novo* and CLIA Waiver in the same submission. Therefore, a "CLIA Waiver by Application" will be submitted after FDA grants the Xpert Tropical Fever's *de novo* request. The CLIA Waiver requirements for the assay have been confirmed with FDA through pre-submission.

4.5.5.2 Regulatory Specifics for the Xpert Hemorrhagic Fever (WBS 6.0)

The Hemorrhagic Fever test will be submitted through a 510(k) pathway. Cepheid has identified a predicate device for the assay. The predicate and regulatory path have been confirmed with FDA through pre-submission.

The Hemorrhagic Fever test may not qualify as a CLIA waived assay (BSL4 pathogen targets). Therefore, a formal CLIA Waiver designation will not be requested from FDA. Nevertheless, the flex study and reproducibility study with untrained users will be performed, and data will be made available to the ***Government*** and as necessary submitted to FDA.

4.5.5.3 Regulatory Specifics for the Xpert Bacterial Agents (WBS 7.0)

The Bacterial Agents test submission will likely follow a 510(k) pathway. There are currently on-market product(s) that can serve as predicate(s) for the assay. The predicate device, regulatory path, and analytical/ clinical study design will be confirmed with FDA through pre-submission.

The Bacterial Agents test may not qualify as a CLIA waived assay (BSL3 pathogen targets). Therefore, a formal CLIA Waiver designation will not be requested from FDA. Nevertheless, the flex study and reproducibility study with untrained users will be performed, and data will be made available to the ***Government*** and as necessary submitted to FDA.

4.5.6 Clinical Trial Planning

The following clinical trial planning process applies to all assay cartridge development and subsequent FDA marketing authorization activities.

- Protocols & Associated Documents
    - Study Protocol: contains the background, description of investigational device, proposed intended use, study objectives, study design, eligibility criteria, sample size calculation, statistical analysis, overview of expectations for monitoring, test procedures, data management, external controls, overview of regulatory responsibilities of the investigator and sponsor;
    - Methods and Procedures: outlines the methods and procedures used at the clinical trial site and ranges from specimen preparation and testing to data file management, (i.e. upload of data to sFTP site); electronic case report form entry
    - Forms, including but not limited to:
        - Case Report Forms
        - Material Traceability
        - Protocol Deviation
        - Adverse Event Reporting (not for the subject but if anything happened with the operator during the testing phase)
- Institutional Review Board Review
    - Ethics review and approval or exemption of the clinical protocol
    - Informed consent, if required (not required if using leftover clinical specimens or contrived specimens)
- Additional institutional or government protocol review and approval, as necessary (e.g. ***Government*** Human Research Protections Office [HRPO]).
- Data Management Plan: includes but is not limited to the plan for how the sponsor will handle the data, source verification, queries, data integrity and audit.
- Clinical Monitoring Plan: The monitoring plan includes the parameters for site qualification, training, initiation, interim and remote monitoring as well as the close visit for the study and data for the sites.
- Medical Safety Monitoring & Reporting – not applicable: no reporting of investigational device results will be provided to subjects or healthcare providers and the specimens will be de-identified Standard of Care (SOC) or contrived specimens

4.5.6.1 Tropical Fever

Assumptions:

[redacted]

4.5.6.2 Hemorrhagic Fever

Assumptions:

[redacted]

4.5.6.3 Bacterial vs. Viral

Assumptions:

[redacted]

4.5.6.4 Bacterial Agents

Assumptions:

[redacted]

Below are 4 templates of a Clinical Trial Investigational Plans Cepheid has drafted to provide an example of how we would plan for the clinical trials of the assays we have proposed to develop under the scope of this project:

Xpert® Tropical Fever Test Study Synopsis

Study Title	Clinical Evaluation of the Xpert Tropical Fever Test
Background	Fever is a common cause of morbidity, mortality, and health center visits in LMICs, but diagnostic tests to establish causes other than malaria, especially viral agents are often lacking. Rapid diagnosis is critical to optimizing therapy since the potential causes are treated with very different antimicrobial regimens.[1-3]
Proposed Intended Use	The Xpert Tropical Fever Test utilizes real time polymerase chain reaction (PCR) for the detection of DNA from *P. species* (*P. malariae*, *P. vivax*, *P. ovale*), and *P. falciparum* and reverse transcriptase PCR (RT-PCR) for the detection of Chikungunya, Zika and Dengue viruses, DNA from Leptospiral species and Salmonella Typhi/paratyphi. This test is intended for the qualitative detection of nucleic acids of these agents in capillary or venous whole blood collected in EDTA from individuals with fever and signs and symptoms of infection.
Device Description	The GeneXpert® Omni Instrument System automates and integrates sample preparation, nucleic acid amplification, and detection of the target sequence in simple or complex samples using real time PCR for DNA or reverse transcriptase PCR (RT-PCR) for RNA, which uses fluorescence to detect the nucleic acids of interest. The system consists of an instrument, personal computer or mobile device, and preloaded software for running tests and viewing the results. The system requires single-use disposable GeneXpert cartridges that hold the reagents and host the amplification and detection processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. The Xpert Tropical Fever Test includes reagents for the detection of the *Plasmodium species* (*P. malariae, P. vivax, and P. ovale*), *Plasmodium falciparum*, Chikungunya virus, Zika virus, Dengue virus, Leptospira and salmonella typhi/paratyphi in whole blood specimens collected in EDTA. The sample processing control (SPC) is used to ensure adequate processing of the target and to monitor the presence of inhibitor(s) in the RT and PCR reactions. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.
Investigational Device	Xpert Tropical Fever Test
Objective	To evaluate the clinical performance of the Xpert Tropical Fever Test in clinical specimens and/or contrived specimens. The sensitivity and specificity of the Xpert Fever Panel will be estimated relative to the validated reference method for each of the individual targets or the collective targets for *Plasmodium species*.
Study Design	The purpose of this study is to conduct a performance evaluation of the Xpert Tropical Fever Test in moderately complex and CLIA waived clinical testing facilities. This multi-site investigational study will include prospectively collected and archived leftover whole blood (WB) specimens collected in EDTA, if available, as well as contrived specimens. Only those specimens meeting the inclusion criteria will be included in the study. The specimens will be tested by both the Xpert Tropical Fever Test and the validated

<table>
<tr><td></td><td>reference method. To eliminate bias, the specimens will be blinded to the operators. The study will be conducted using the Omni System.</td></tr>
<tr><td>Study Population / Specimen Description</td><td>(b) (4) [redacted]</td></tr>
<tr><td>Inclusion / Exclusion</td><td>WB specimens from subjects who have the signs and symptoms of fever or contrived specimens.</td></tr>
<tr><td>Sample Size</td><td>(b) (4) [redacted]</td></tr>
<tr><td>Statistical Analysis</td><td>The performance of the Xpert Tropical Fever Test will be determined according to the following definitions:
<table>
<tr><td colspan="2"></td><td colspan="3">Comparator Method</td></tr>
<tr><td colspan="2"></td><td>POS</td><td>NEG</td><td>Total</td></tr>
<tr><td rowspan="3">Xpert Assay</td><td>POS</td><td>a</td><td>b</td><td>a+b</td></tr>
<tr><td>NEG</td><td>c</td><td>d</td><td>c+d</td></tr>
<tr><td>Total</td><td>a+c</td><td>b+d</td><td>a+b+c+d</td></tr>
</table>
Definitions:
PPA (positive percent agreement) = a/(a + c)
NPA(negative percent agreement) = d/(b +d)</td></tr>
<tr><td>Study Duration</td><td>See master schedule</td></tr>
<tr><td>Testing Sites</td><td>BSL1/2 clinical study sites for prospective specimens
BSL3/BSL4 laboratories for banked and contrived samples</td></tr>
<tr><td>References</td><td>[redacted]</td></tr>
</table>

Xpert® Hemorrhagic Fever Test Study Synopsis

Study Title	Clinical Evaluation of the Xpert Hemorrhagic Fever Test
Background	Fever accompanied by hemorrhaging can be caused by one of several highly contagious viral infections. These are all associated with high morbidity and mortality. Diagnostic tests to establish the cause are often lacking. Rapid determination of the cause of fever for therapy (experimental antiviral agents) and to initiate precautions to prevent spread of disease is critical[1-4].
Proposed Intended Use	The Xpert Hemorrhagic Fever Test is a real-time reverse transcription polymerase chain reaction (RT-PCR) test intended for the qualitative detection of RNA from the Ebola viruses, Crimean-Congo hemorrhagic fever virus, Marburg virus and Lassa virus in EDTA venous whole blood from individuals

	with signs and symptoms of hemorrhagic fever.infection.
Device Description	The GeneXpert® Omni Instrument System automates and integrates sample preparation, nucleic acid amplification, and detection of the target sequence in simple or complex samples using RT-PCR which uses fluorescence to detect the RNA of interest. The systems consist of an instrument, personal computer or mobile device, and preloaded software for running tests and viewing the results. The systems require the use of single-use disposable GeneXpert cartridges that hold the RT-PCR reagents and host the RT-PCR processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. The Xpert Hemorrhagic Fever Test includes reagents for the detection of the Ebolavirus, Crimean-Congo hemorrhagic fever virus, Marburg virus and Lassa virus RNA in whole blood specimens. The sample processing control (SPC) is used for adequate processing of the target and to monitor the presence of inhibitor(s) in the RT and PCR reactions. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.
Investigational Device	Xpert Hemorrhagic Fever Test
Objective	To evaluate the clinical performance of the Xpert Hemorrhagic Fever Test in clinical specimens and/or contrived specimens. The sensitivity and specificity of the Xpert Hemorrhagic Fever Test will be estimated relative to the validated reference method for each of the individual targets.
Study Design	The purpose of this study is to conduct a performance evaluation of the Xpert Hemorrhagic Fever Test in a moderately complex clinical testing facility. This multi-site investigational study will include leftover or prospectively whole blood (WB) specimens collected in EDTA, if available,) and contrived specimens with viral isolates from different subjects who were infected with the various viruses detected by this Xpert assay. Only those specimens meeting the inclusion criteria were will be included in the study. The specimens will be tested by both Hemorrhagic Fever Test and the validated reference method. To eliminate bias, the specimens will blinded to the operators. The study will be conducted using the Omni System.
Study Population / Specimen Description	(b) (4) [redacted] .
Inclusion / Exclusion	Contrived specimens or WB specimens from subjects who have fever and the signs and symptoms of Hemorrhagic Fever, if available.
Sample Size	(b) (4) [redacted]
Statistical Analysis	The performance of the Xpert Hemorrhagic Fever Panel Assay will be determined according to the following definitions: Definitions: PPA = TP/(TP + FN) NPA = TN/(TN + FP) (TP: True Positive; FN: False Negative; TN: True Negative
Study Duration	See master schedule
Testing Sites	BSL1: Clinical study/collection sites for prospective specimens and contrived specimens with inactivated organisms BSL4 laboratories for contrived specimens with live organisms
References	([redacted]

	[redacted]

Clinical Study Synopsis
Xpert® Bacterial Agents Panel

Study Title	Clinical Evaluation of the Xpert Bacterial Agents Panel
Background	Multiple bacterial pathogens can cause similar syndromes including sepsis, pneumonia, and skin lesions. Optimal antimicrobial therapy differs for each of these pathogens. Thus, rapid and accurate identification of the causative agent of disease is critical for therapeutic selection to improve outcomes and, in the case of plague, reduce spread of infection.[1-3]
Proposed Intended Use	The Xpert Bacterial Agents Panel utilizes real time polymerase chain reaction (PCR) for the detection of DNA from *Bacillus anthracis*, *Yersinia pestis*, *Fancisella tularensis.* This test is intended for the qualitative detection of nucleic acids in venous whole blood collected in EDTA from individuals with signs and symptoms of infection.
Device Description	The GeneXpert® Omni Instrument Systems automates and integrates sample preparation, nucleic acid amplification, and detection of the target sequence in simple or complex samples using polymerase chain reaction (PCR) for DNA or reverse transcriptase PCR (RT-PCR) for RNA and uses fluorescence to detect the nucleic acids of interest. The system consists of an instrument, personal computer and preloaded software for running tests and viewing the results. The system requires single-use disposable GeneXpert cartridges that hold the reagents and host the amplification and detection processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. The Xpert Bacterial Agents Panel includes reagents for the detection of the *Bacillus anthracis*, *Yersinia pestis*, *Fancisella tularensis* in EDTA whole blood specimens. The sample processing control (SPC) is used to ensure adequate processing of the target and to monitor the presence of inhibitor(s) in the RT and PCR reactions. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.
Investigational Device	Xpert Bacterial Agents Panel
Objective	To evaluate the performance of the Xpert Bacterial Agents Panel. The positive and negative agreement of the Xpert Bacterial Agents Panel will be determined according to the expected outcome of the contrived and fresh prospective specimens for each target organism.
Study Design	The purpose of this study is to conduct a performance evaluation of the Xpert Bacterial Agents Panel in clinical specimens and/or contrived specimens. The multi-center investigational study will include fresh prospectively collected and leftover whole blood (WB) specimens, if available, for *Brucella* sp. and sp. as well as contrived specimens. Specimens for all other agents will only be contrived. The specimens will be tested by both the Xpert Bacterial Agents Panel assay and a validated reference method. To eliminate bias, the samples will be blinded to the operators. The testing will be conducted using the Omni system.
Study Population / Specimen Description	(b) (4) [redacted]
Inclusion / Exclusion	WB specimens from subjects who have the signs and symptoms of infection or contrived specimens.
Sample Size	(b) (4) [redacted]
Statistical Analysis	The performance of the Xpert Bacterial Agents Panel will be determined according to the following

<table>
<tr><td></td><td>definitions:

<table><tr><td colspan="2"></td><td>Expected Outcome</td><td></td><td></td></tr><tr><td colspan="2"></td><td>POS</td><td>NEG</td><td>Total</td></tr><tr><td rowspan="3">Xpert BA Panel</td><td>POS</td><td>a</td><td>b</td><td>a+b</td></tr><tr><td>NEG</td><td>c</td><td>d</td><td>c+d</td></tr><tr><td>Total</td><td>a+c</td><td>b+d</td><td>a+b+c+d</td></tr></table>
Definitions:
True positive (TP) = a, True negative (TN) = d, False positive (FP) = b, False negative (FN) = c
Positive Percent Agreement (PPA) = TP/(TP+FN)
Negative Percent Agreement (NPA) = TN/(TN+FP)</td></tr>
<tr><td>Clinical Study Duration</td><td>See the master schedule</td></tr>
<tr><td>Testing Sites</td><td>BSL3/BSL4 laboratories as appropriate</td></tr>
<tr><td>References</td><td>[[redacted]
] [redacted]
4. [redacted]</td></tr>
</table>

4.5.7 Regulatory Execution

The Regulatory Core Team Member will execute upon the following regulatory strategy:

- Cepheid will use the pre-submission to define a regulatory pathway for all assays. Cepheid shall gain concurrence from the Government on the pre-submission package prior to approaching the FDA.
- Cepheid will get FDA's concurrence on assay analytical and clinical study design through pre-submission.
- The CLIA Waiver requirements and the corresponding study design will also be obtained through pre-submission to FDA.
- Cepheid has a proven track record for securing FDA's authorizations of 510(k) and *de novo* requests, for obtaining CLIA waiver designations, and for handling submissions with new instrument system and software.
- For assay-specific regulatory aspects, see Section 4.5.5.

4.5.8 Clinical Trial Execution

- **Site Management, Communications, Activities**
  - A Clinical Study Lead will be assigned to manage each study or group of studies. A qualified Clinical Research Associate will be assigned to each site.
  - Site qualification, training, initiation, monitoring and closeout visits will be conducted per the Clinical Study Monitoring Plan
- **Recruitment, screening, enrollment**
  - As part of the clinical study protocol, eligibility requirements will be detailed so that the appropriate specimens will be included in the study. De-identified clinical specimens or contrived specimens may be obtained through ***Government.*** Note: the study Protocol and Methods Procedures will contain specific procedures for how to handle specimens or for contrived specimens, how to prepare the specimens.
- **Execution of safety subject monitoring -** not applicable: no reporting of investigational device results will be provided to subjects or healthcare providers
- **Quality and data management**

- The sites and data will be audited in accordance with the Cepheid Clinical Affairs SOPs and the Data management and Monitoring plans.

4.5.9 Clinical Trial Data Management and Biostatistics

- Data Management – a data management plan will be developed and executed to ensure data quality and integrity
- Biostatistics – A statistical analysis plan will be developed and followed

4.5.10 Clinical Trial Clinical Report

- A clinical trial report will be written and will include but is not limited to, a brief description of the product, proposed intended use, an overview of the study design, specimen accountability, and if any, data exclusions and reason(s), protocol deviations, as well as the study results with tables and figures and conclusions.

4.5.11 Launch Phase

The following deliverables are associated with the Launch Phase:

- U.S. Regulatory Submission
- Regulatory Approval
- Complete Stability Studies and Report

4.6 SOW WBS 8.0 – Developmental Work on Bacterial vs. Viral Host Response Biomarker Cartridge

(b) (4)

[redacted]

[redacted]

4.7 *SOW WBS 9.0 - Novel Coronavirus Assay (EUA)*

The Cepheid team will undertake product development activities to develop a diagnostic assay that detects SARS-CoV-2 RNA from individuals meeting CDC SARS-CoV-2 clinical criteria. The team has evaluated known primer/probe sequences from CDC and other public sources and selected sequences to develop a unique Cepheid Xpert assay specific design & signature for optimal detection

capability. To support EUA and expedite product-to-market timeline, Cepheid shall leverage sample preparation and cartridge fluidics from Cepheid's Xpress Flu/RSV product that is already on the market. As part of the optimization work, the team will further assess the PCR performance (including sensitivity and specificity) of the primers/probes and evaluate performance with synthetic test materials. Cepheid will work with collaborators with access to the live or inactivated virus for analytical and clinical testing. Cepheid will pursue the developmental activities, including:

- ***Assay optimizations to Ensure Performance based on MEC Requirements***
- ***Algorithm development***
- ***Analytical testing***
- ***Clinical Testing***
- ***Accelerated Stability Testing***
- ***Manufacturability***

Manufacturability will be assessed post product launch for manufacturing sustainability, including spec setting, process validation, and longer-term stability testing.

4.7.1 Assay Development Concept Phase for Xpert SARS-CoV-2

Due to public health urgency and much compressed development timeline, Xpert SARS-CoV-2 EUA will conduct Pre-Technical Feasibility activities similar to what has already been defined in section 4.5.1.

4.7.1.1 Assay Development Technical Feasibility for Xpert SARS-CoV-2

Assay shall utilize the existing 510(k) U.S. FDA cleared Xpert Xpress Flu/RSV assay configuration to fast-track technical feasibility deliverables listed in section 4.5.2-1) Assay Optimization and 4) Establishment of thermal and optical parameters, while conducting evaluations of remaining deliverables to ensure product quality. The EUA assay shall be developed exclusively for the use of all Cepheid GeneXpert instruments, except GeneXpert Omni.

4.7.1.2 Assay Design and Development for the Xpert SARS-CoV-2

A subset of design and development testing in section 4.5.3. for the Xpert SARS-CoV-2 EUA assay performance and stability evaluations, shall be performed based on U.S. FDA requirements for EUA clearance.

4.7.1.3 Regulatory Specifics for Xpert SARS-CoV-2

Cepheid will sponsor Xpert SARS-CoV-2 EUA authorization. Cepheid has submitted a Pre-EUA and received FDA's feedback on analytical and clinical study designs. Cepheid will continue working with FDA through an interactive review process until obtaining the EUA authorization. The Government will be a sponsor-designated co-contact. Due to the time sensitive nature, prior agreement of FDA communications by the Government is not always possible. Nevertheless, the Government will be copied on all correspondences with the FDA. Cepheid's end goal would be to obtain the EUA authorization depending on the successful completion of relevant studies.

4.7.1.4 Clinical Trial Planning for Xpert SARS-CoV-2

Assumptions:

- ***Contrived samples prepared in individual negative nasopharyngeal swab specimens collected from US patients with signs and symptoms of respiratory infection will be used***
- ***FDA guidelines on coronavirus assay development will be closely monitored and Cepheid will gain the Agency's concurrence on assay design, verification and clinical studies through the pre-submission process***

Below is a template of the Clinical Trial Investigational Plan Cepheid has drafted to provide an example of how Cepheid would plan for the clinical trials of the assay proposed for development under the scope of this project:

Clinical Study Synopsis
Xpert® SARS-CoV-2 Test

Study Title	***Clinical Evaluation of the Xpert SARS-CoV-2 Test***

Background	***An outbreak of pneumonia of unknown etiology in Wuhan City, Hubei Province, China was initially reported to the World Health Organization (WHO) on December 31, 2019. Chinese authorities identified a novel coronavirus (SARS-CoV-2), which has resulted in thousands of confirmed human infections in multiple provinces throughout China and exported cases in several Southeast Asian countries and more recently the United States and other countries. Cases of severe illness and deaths have been reported. As of February 24, 2020, over 2500 deaths have occurred with nearly 80,000 total number of cases 1. Cepheid Inc. has decided to respond to the situation by developing an Emergency Use Authorization assay which can detect SARS-CoV-2 nucleic acid material directly from nasopharyngeal swab specimens. The Xpert SARS-CoV-2 test is a molecular in vitro diagnostic test that aids in the detection and diagnosis of SARS-CoV-2 and is based on widely used nucleic acid amplification technology. The Xpert SARS-CoV-2 assay contains primers and probes and internal controls used in real-time reverse-transcriptase polymerase chain reaction for the in vitro qualitative detection of SARS-CoV-2 RNA in nasopharyngeal swab specimens.***
Proposed Intended Use Statement	***The Xpert SARS-CoV-2 test is a real-time RT-PCR test intended for the qualitative detection of nucleic acid from the SARS-CoV-2 in nasopharyngeal swab specimens from individuals meeting CDC SARS-CoV-2 clinical criteria in conjunction with CDC SARS-CoV-2 epidemiological criteria. Testing is limited to qualified laboratories designated by CDC and, in the United States, certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories.*** ***Results are for the identification of SARS-CoV-2 RNA. The SARS-CoV-2 RNA is generally detectable in nasopharyngeal swab specimens during the acute phase of infection. Positive results are indicative of active infection. Laboratories within the United States and its territories are required to report all positive results to the appropriate public health authorities.*** ***Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.*** ***The Xpert SARS-CoV-2 test is intended for use by trained laboratory personnel who are proficient in performing real-time RT-PCR assays. The Xpert SARS-CoV-2 is only for use under the Food and Drug Administration's Emergency Use Authorization.***
Device Description	***The Xpert SARS-CoV-2 test is an automated in vitro diagnostic test for qualitative detection of nucleic acid from SARS-CoV-2. The Xpert SARS-CoV-2 test is performed on GeneXpert Instrument Systems.*** ***The GeneXpert Instrument Systems automate and integrate sample preparation, nucleic acid extraction and amplification, and detection of the target sequences in simple or complex samples using real-time PCR assays. The systems consist of an instrument, computer, and preloaded software for running tests and viewing the results. The systems require the use of single-use disposable cartridges that hold the RT-PCR reagents and host the RT-PCR process. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, see the GeneXpert Dx System Operator Manual or the GeneXpert Infinity System Operator Manual.*** ***The Xpert SARS-CoV-2 test includes reagents for the detection of RNA from SARS-CoV-2 in nasopharyngeal swab specimens. A Sample Processing Control (SPC) and a Probe Check Control (PCC) are also included in the cartridge utilized by the GeneXpert System instrument. The SPC is present to control for adequate processing of the sample and to monitor for the presence of potential inhibitor(s) in the RT-PCR reaction. The SPC also ensures that the RT-PCR reaction conditions (temperature and time) are appropriate for the amplification reaction and that the RT-PCR reagents are functional. The PCC verifies reagent rehydration, PCR tube filling, and confirms that all reaction components are present in the cartridge including monitoring for probe integrity and dye stability.*** ***The nasopharyngeal swab specimen is collected and placed into a viral transport tube containing 3 mL transport medium. The specimen is briefly mixed by vigorously shaking the collection tube 3 or 4 times. Using the supplied transfer pipette, the sample is transferred to the sample chamber of the Xpert SARS-CoV-2 cartridge. The GeneXpert cartridge is loaded onto the GeneXpert Instrument System platform, which performs hands-off, automated sample processing, and real-time RT-PCR for detection of viral RNA.***

Investigational Device	***Xpert SARS-CoV-2 Test***
Study Objectives	***To evaluate the performance of the Xpert SARS-CoV2 test.*** ***The clinical evaluation data shall be used by Cepheid to support a US-FDA EUA review of Cepheid's Xpert SARS-CoV-2 test.***
Study Design	***A fully contrived sample testing study with one clinical testing site to evaluate the performance of the Xpert SARS-CoV-2 test.***
Study Samples	***Contrived samples in negative nasopharyngeal swab specimen matrix collected from US patients with signs and symptoms of respiratory infection.***
Sample Size	***The numbers of positive and negative contrived samples are requested by FDA for SARS-CoV-2 EUA.*** • ***50 contrived positive samples in individual negative clinical matrix (nasopharyngeal swab specimens) collected from US patients with signs and symptoms of respiratory infection. The spiking procedure will follow FDA's recommendation in Table 5 of the SARS-CoV-2 EUA Interactive Review Template – Molecular-based, January 19, 2020, and communications between Cepheid and FDA.*** • ***50 individual negative nasopharyngeal swab specimens collected from US patients with signs and symptoms of respiratory infection.***
Testing Approach	***The contrived samples will be evaluated in accordance with the proposed diagnostic algorithm, including retesting when appropriate. In instances where retesting could not be performed, the initial results will be analyzed for performance and equivocal/indeterminate results will be counted against the final performance.***
Testing Site	***One clinical testing site with BSL3 laboratory for spiking and testing contrived samples with live virus.***
Comparator Method for percent agreement performance calculations	***Positive: Compare to expected/known "positive" result.*** ***Negative: Compare to expected/known "negative" result.***
Statistical Analysis Plan	***The positive percent agreement (PPA) will be calculated for the expected/known positive specimens and the negative percent agreement (NPA) will be calculated for the expected/known negative specimens.*** ***PPA = TP / (TP + FN)*** ***NPA = TN / (TN + FP)*** ***(TP: True Positive; FN: False Negative; TN: True Negative)*** ***The 95% confidence interval (CI) for the positive and negative percent agreement will be also calculated.***
Acceptance Criteria	• ***95% PPA for contrived positive samples at 1x-2x limit of detection (LOD) spiking levels*** • ***100% PPA for contrived positive samples at other spiking levels*** • ***100% NPA for negative samples***
Discordant Analysis	***Investigation of discrepant results:*** ***If the panel test results do not meet the acceptance criteria shown below, we will investigate the assay files, contrived sample preparation and testing procedures, etc.*** ***Additional testing with other validated PCR test such as CDC 2019-nCoV Real-Time RT-PCR test under EUA or targeted sequencing for investigation of discrepant results will not be performed.***
Study Duration	***The study is expected to last approximately 2 weeks***

Reference	***1. WHO Coronavirus disease 2019 (COVID-19) Situation Report – 35. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200224-sitrep-35-covid-19.pdf?sfvrsn=1ac4218d_2. Accessed on 28 February, 2020***

4.8 *SOW WBS 10.0 – Xpert® SARS-CoV-2/Flu/RSVAssay (EUA)*

The Cepheid team will undertake product activities to optimize a diagnostic assay that detects SARS-CoV-2, Flu A, Flu B and RSV RNA from individuals suspected of respiratory tract infection by their healthcare provider. The team has utilized the current on market Xpress Flu/RSV primer/probe sequences and selected sequences for SARS-CoV-2 to develop a unique Cepheid Xpert SARS-CoV-2/Flu/RSV assay specific design & signature for optimal detection capability. To support EUA and expedite product-to-market timeline, Cepheid shall leverage sample preparation and cartridge fluidics from Cepheid's Xpress Flu/RSV product that is already on the market. As part of the optimization work, the team will further assess the PCR performance (including sensitivity and specificity) of the primers/probes and evaluate performance with synthetic and inactivated test materials. Cepheid will work with collaborators with access to banked clinical specimens for SARS-CoV-2, Flu and RSV for analytical and clinical testing. Cepheid will pursue the activities, including:

- ***Assay optimizations to Ensure Performance based on MEC Requirements***
- ***Algorithm optimization***
- ***Analytical testing***
- ***Clinical Testing***
- ***Accelerated Stability Testing***
- ***Manufacturability***

Manufacturability will be assessed post product launch for manufacturing sustainability, including spec setting, process validation, and longer-term stability testing.

4.8.1.1 Assay Development Concept/Technical Feasibility Phase for Xpert SARS-CoV-2/Flu/RSV

Due to public health urgency and much compressed development timeline, the product development process combines the concept and technical feasibility phases.

Xpert SARS-CoV-2/Flu/RSV EUA conducts Conccept and Technical Feasibility activities described below. Assay shall utilize the existing 510(k) U.S. FDA cleared Xpert Xpress Flu/RSV assay configuration to fast-track technical feasibility deliverables) Assay Optimization and 4) Establishment of thermal and optical parameters, while conducting evaluations of remaining deliverables to ensure product quality. The EUA assay has been developed exclusively for the use of all Cepheid GeneXpert instruments, except GeneXpert Omni.

1. Product definition – specifications are captured in the Design Input Requirements (DIR) document. DIR requirements are translated from a Market Essentials Characteristic (MEC) document that outlines the customer requirements.
2. Project Definition – project scope is described in a Project Plan.
3. Project Risk Management Plan– a living project document reviewed rigorously by the core team throughout the project to foresee risks, estimate impact, and define mitigations.
4. Project Regulatory Plan - establishes specific project deliverables and responsibilities to successfully meet FDA requirements.

1. Assay optimization

a. Sample preparation – leverage cartridge-based sample preparation methods from Xpress Flu/RSV. Fluidics and reagent chemistries will be reviewed and either confirmed to be optimum, or revised as needed.

b. Oligonucleotide Design

i. Bioinformatics. Although Cepheid will leverage existing designs if available, additional bioinformatics work will be needed for in silico optimization of sequences that meet assay specificity (inclusivity for design targets and exclusivity for non-target organisms) requirements. A bioinformatics consultant will be used as a sub-contractor to augment internal efforts. (b) (4) [redacted]

ii. Thermal profile. All individual PCR reactions and oligonucleotide sequences will be optimized to operate

at the same annealing and denaturation temperatures and times. (b) (4) [redacted]

c. PCR assay optimization

i. Reagent composition. The concentrations of critical reagents; primers, probes, Mg, KCl, dNTPs, buffers, and enzyme selection and level will be optimized for optimum performance using a multi-parameter design of experiments (DOE) approach.

ii. Dye and quencher selection. With the exception of FAM, Cepheid utilizes proprietary dyes and quenchers that will be selected based on spectral and assay compatibility.

iii. Multiplexing. Computer software will be used to create designs that avoid deleterious intra- and inter-molecular interactions that can reduce amplification efficiency, but not all interactions are predictable. It is anticipated that this will need to be resolved empirically through iterative oligonucleotide re-design and testing.

2. Cross-talk correction factors are assigned for each dye in all Cepheid assays to compensate for signal bleeding into adjacent optical channels.

3. Transfer to dried format. Once demonstrated to be optimum in liquid amplification reactions, the PCR reagents will be dried into lyophilized beads using standard Cepheid lyophilization buffers and lyophilization conditions that enable proper dried bead morphology, rapid dissolution, and long term stability.

7. Preliminary performance testing. A series of analytical studies including a mini limit of detection (LoD) will be conducted to demonstrate that the assay meets the performance specifications.

8. Design Lock. The primary outputs of the Feasibility Phase are assays that have final designs, subject to confirmation by more extensive verification and validation studies conducted in subsequent phases.

a. Oligonucleotide design. The sequences, dyes, and quenchers of the individual oligonucleotide used in the assay are finalized.

b. The ADF, an assay developer configurable software that defines all the commands and settings needed to manufacture and run the assay. (b) (4) [redacted]

4.8.1.2 Assay Design and Development for the Xpert SARS-CoV-2/Flu/RSV

A subset of design and development testing in section 4.5.3. for the Xpert SARS-CoV-2/Flu/RSV EUA assay performance and stability evaluations shall be performed based on U.S. FDA requirements for EUA clearance.

4.8.1.3 Regulatory Specifics for Xpert SARS-CoV-2/Flu/RSV

Cepheid will sponsor Xpert SARS-CoV-2/Flu/RSV EUA authorization. Cepheid has submitted a Pre-EUA and received FDA's feedback on analytical and clinical study designs. Cepheid will continue working with FDA through an interactive review process until obtaining the EUA authorization. The Government will be a sponsor-designated co-contact. Due to the time sensitive nature, prior agreement of FDA communications by the Government is not always possible. Cepheid's end goal would be to obtain the EUA authorization depending on the successful completion of relevant studies.

4.8.1.4 Clinical Trial Planning for Xpert SARS-CoV-2/Flu/RSV

Assumptions:

- ***Contrived samples are no longer acceptable and banked clinical specimens from US patients with signs and symptoms of respiratory infection are needed for testing.***
- ***FDA guidelines on coronavirus assay development will be closely monitored and Cepheid will gain the Agency's concurrence on assay design, verification and clinical studies through the pre-submission process***

Below is a template of the Clinical Trial Investigational Plan Cepheid has drafted to provide an example of how Cepheid would plan for the clinical trials of the assay proposed for development under the scope of this project:

Clinical Study Synopsis

Xpert SARS-CoV-2/Flu/RSV	***Clinical Evaluation of the Xpert SARS-CoV-2/Flu/RSV EUA Test***

EUA Test*Study Title*	
Background	***In December of 2019, an outbreak of respiratory illness [coronavirus infectious disease 2019 (COVID-19)] caused by a novel coronavirus (SARS-CoV-2) was first detected in Wuhan City, Hubei Province, China.[1] Initially believed to be contained to individuals who visited a live animal market, the expectation was that the spread was limited to animal-to-person transmission. In January of 2020, a growing number of individuals who did not have exposure to an animal market became infected with the virus, indicating that person-to-person spread was a viable form of transmission. The rapid growth of confirmed cases of COVID-19 inside and outside of China influenced the WHO to declare a public health emergency of international concern on January 20th, 2020.[1] This declaration of a public health emergency was based on individuals in their home country outside of China who had not visited Wuhan City becoming infected, demonstrating that person-to-person spread was occurring outside of China.[2] On March 11th, the global spread caused the WHO to declare a pandemic. By June 3rd, 2020, there have been over 6.3 MM global cases and over 383,000 deaths in 188 countries/regions.[3]*** ***As the SARS-CoV-2 pandemic unfolds, the world's expectations and needs for respiratory virus testing are changing. Coverage of the pandemic has led to to the public's understanding and fear of the virus, not seen before with other respiratory viruses. With awareness around SARS-CoV-2, both patient and clinician expectations will include SARS-CoV-2 testing as the standard of care for upper respiratory tract infection (URTI) testing, where once Flu and Flu/RSV were sufficient in most cases. The logical shift is to expand Flu/RSV testing to include SARS-CoV-2 in an accurate, rapid offering that can be used across multiple use settings. Xpert SARS-CoV-2/Flu/RSV will have a significant impact, as it allows for testing to be performed where the patient presents.***
Proposed Intended Use Statement	***The Xpert SARS-CoV-2/Flu/RSV test is a rapid, real-time RT-PCR test intended for the qualitative detection and differentiation of SARS-CoV-2, influenza A, influenza B, and respiratory syncytial virus (RSV) viral RNA in either nasopharyngeal swab, nasal swab or nasal wash/ aspirate specimens collected from individuals suspected of respiratory tract infection by their healthcare provider.*** ***Testing of nasopharyngeal swab and nasal swab specimens using the Xpert SARS-CoV-2/Flu/RSV test run on the GeneXpert Dx and GeneXpert Infinity systems is limited to laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high and moderate complexity tests.*** ***Testing of nasopharyngeal or nasal swab specimens using the Xpert SARS-CoV-2/Flu/RSV test run on the GeneXpert Xpress System (Tablet and Hub Configurations) is authorized to be distributed and used in patient care settings outside of the clinical laboratory environment.*** ***SARS-CoV-2, influenza A, influenza B and RSV RNA identified by this test are generally detectable in upper respiratory specimens during the acute phase of infection. Positive results are indicative of the presence of the identified virus, but do not rule out bacterial infection or co-infection with other viruses.*** ***For SARS-CoV-2 positive specimens, clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. The agent detected may not be the definite cause of disease. Laboratories within the United States and its territories are required to report all positive SARS-CoV-2 results to the appropriate public health authorities.*** ***Negative results do not preclude respiratory tract infection and should not be used as the sole basis for treatment or other patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.*** ***Testing with the Xpert SARS-CoV-2/Flu/RSV test is intended for use by trained operators who are proficient in performing tests using either GeneXpert Dx, GeneXpert Infinity and/or GeneXpert Xpress systems. The Xpert Xpress SARS-CoV-2/Flu/RSV test is only for use under the Food and Drug Administration's Emergency Use Authorization***

Device Description	***The Xpert SARS-CoV-2/Flu/RSV test is an automated in vitro diagnostic test for qualitative detection of nucleic acid from SARS-CoV-2, Flu A, Flu B and RSV. The Xpert SARS-CoV-2/Flu/RSV test is performed on GeneXpert Instrument Systems.*** ***The GeneXpert Instrument Systems automate and integrate sample preparation, nucleic acid extraction and amplification, and detection of the target sequences in simple or complex samples using real-time PCR assays. The systems consist of an instrument, computer, and preloaded software for running tests and viewing the results. The systems require the use of single-use disposable cartridges that hold the RT-PCR reagents and host the RT-PCR process. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, see the GeneXpert Dx System Operator Manual or the GeneXpert Infinity System Operator Manual.*** ***The Xpert SARS-CoV-2/Flu/RSV test includes reagents for the detection of RNA from SARS-CoV-2 , Flu A, Flu B and RSV in nasopharyngeal or nasal swab specimens. A Sample Processing Control (SPC) and a Probe Check Control (PCC) are also included in the cartridge utilized by the GeneXpert System instrument. The SPC is present to control for adequate processing of the sample and to monitor for the presence of potential inhibitor(s) in the RT-PCR reaction. The SPC also ensures that the RT-PCR reaction conditions (temperature and time) are appropriate for the amplification reaction and that the RT-PCR reagents are functional. The PCC verifies reagent rehydration, PCR tube filling, and confirms that all reaction components are present in the cartridge including monitoring for probe integrity and dye stability.*** ***The nasopharyngeal/nasal swab specimen is collected and placed into a viral transport tube containing 3 mL transport medium. The specimen is briefly mixed by vigorously shaking the collection tube 3 or 4 times. Using the supplied transfer pipette, the sample is transferred to the sample chamber of the Xpert SARS-CoV-2/Flu/RSV cartridge. The GeneXpert cartridge is loaded onto the GeneXpert Instrument System platform, which performs hands-off, automated sample processing, and real-time RT-PCR for detection of viral RNA.***
Investigational Device	***Xpert SARS-CoV-2/Flu/RSV EUA Test***
Study Objectives	***To evaluate the performance of the Xpert SARS-CoV-2/Flu/RSV test.*** ***The clinical evaluation data shall be used by Cepheid to support a US-FDA EUA review of Cepheid's Xpert SARS-CoV-2/Flu/RSV test.***
Study Design	***Clinical specimen testing study with one clinical testing site to evaluate the performance of the Xpert SARS-CoV-2/Flu/RSV test.***
Study Samples	***Banked clinical specimens from US patients with signs and symptoms of respiratory infection are needed for testing.***
Sample Size	***The numbers of positive and negative samples proposed to FDA for Xpert SARS-CoV-2/Flu/RSV test EUA.*** • ***45 individual NP swab Flu A positive samples in VTM collected from US patients with signs and symptoms of respiratory infection.*** • ***45 individual NP swab Flu B positive samples in VTM collected from US patients with signs and symptoms of respiratory infection.*** • ***45 individual NP swab RSV positive samples in VTM collected from US patients with signs and symptoms of respiratory infection.*** • ***45 individual NP swab SARS-CoV-2 positive samples in VTM collected from US patients with signs and symptoms of respiratory infection.*** • ***45 individual NP swab Flu A, Flu B, and RSV negative samples in VTM collected from US patients with signs and symptoms of respiratory infection.*** • ***45 individual NP swab SARS-CoV-2 negative samples in VTM collected from US patients with signs and symptoms of respiratory infection.***
Testing Approach	***The clinical specimen testing will be evaluated in accordance with the proposed diagnostic algorithm, including retesting when appropriate. In instances where retesting could not be performed, the initial results will be analyzed for performance and equivocal/indeterminate results will be counted against the final performance.***

<table>
<tr><td>Testing Site</td><td>One clinical testing site.</td></tr>
<tr><td>Comparator Method for percent agreement performance calculations</td><td>Positive: Compare to Xpress Flu/RSV or Xpert SARS-CoV-2 “positive” result.

Negative: Compare to Xpress Flu/RSV or Xpert SARS-CoV-2 “negative” result.</td></tr>
<tr><td>Statistical Analysis Plan</td><td>The positive percent agreement (PPA) will be calculated for the expected/known positive specimens and the negative percent agreement (NPA) will be calculated for the expected/known negative specimens.
PPA = TP / (TP + FN)
NPA = TN / (TN + FP)
(TP: True Positive; FN: False Negative; TN: True Negative)
The 95% confidence interval (CI) for the positive and negative percent agreement will be also calculated.</td></tr>
<tr><td>Acceptance Criteria</td><td><table><tr><th>Target</th><th>PPA</th><th>NPA</th></tr><tr><td>FluA, FluB, RSV</td><td>≥95%</td><td>≥97%</td></tr><tr><td>SARS-CoV-2</td><td>≥95%</td><td>≥95%</td></tr></table></td></tr>
<tr><td>Discordant Analysis</td><td>Investigation of discrepant results:

If the test results do not meet the acceptance criteria shown above, we will investigate the assay files, contrived sample preparation and testing procedures, etc.

Additional testing with other validated PCR test such as CDC 2019-nCoV Real-Time RT-PCR test under EUA or targeted sequencing for investigation of discrepant results will not be performed.</td></tr>
<tr><td>Study Duration</td><td>The study is expected to last approximately 2 weeks</td></tr>
<tr><td>Reference</td><td>1. https://www.cdc.gov/coronavirus/2019-ncov/summary html
2. https://www.cdc.gov/media/releases/2020/p0130-coronavirus-spread.html
3. https://coronavirus.jhu.edu/map html
Accessed 03 June, 2020</td></tr>
</table>

If the Phase I EUA filing is successful, the Government may request a follow-on statement of work to extend the EUA to the GeneXpert Omni as part of Phase II. The Government may also request a follow-on statement of work to obtain a 510(k) clearance as part of Phase II, which could include a cost share arrangement with Cepheid funding clearance on the GeneXpert and the Government funding clearance on the GeneXpert Omni.

4.7 Commercially Available Assays

To support on-going test and evaluation activities on the Omni system, Cepheid will make cartridges available to the U.S. Government, on an as-needed basis. The minimum and maximum order quantities are as follows:

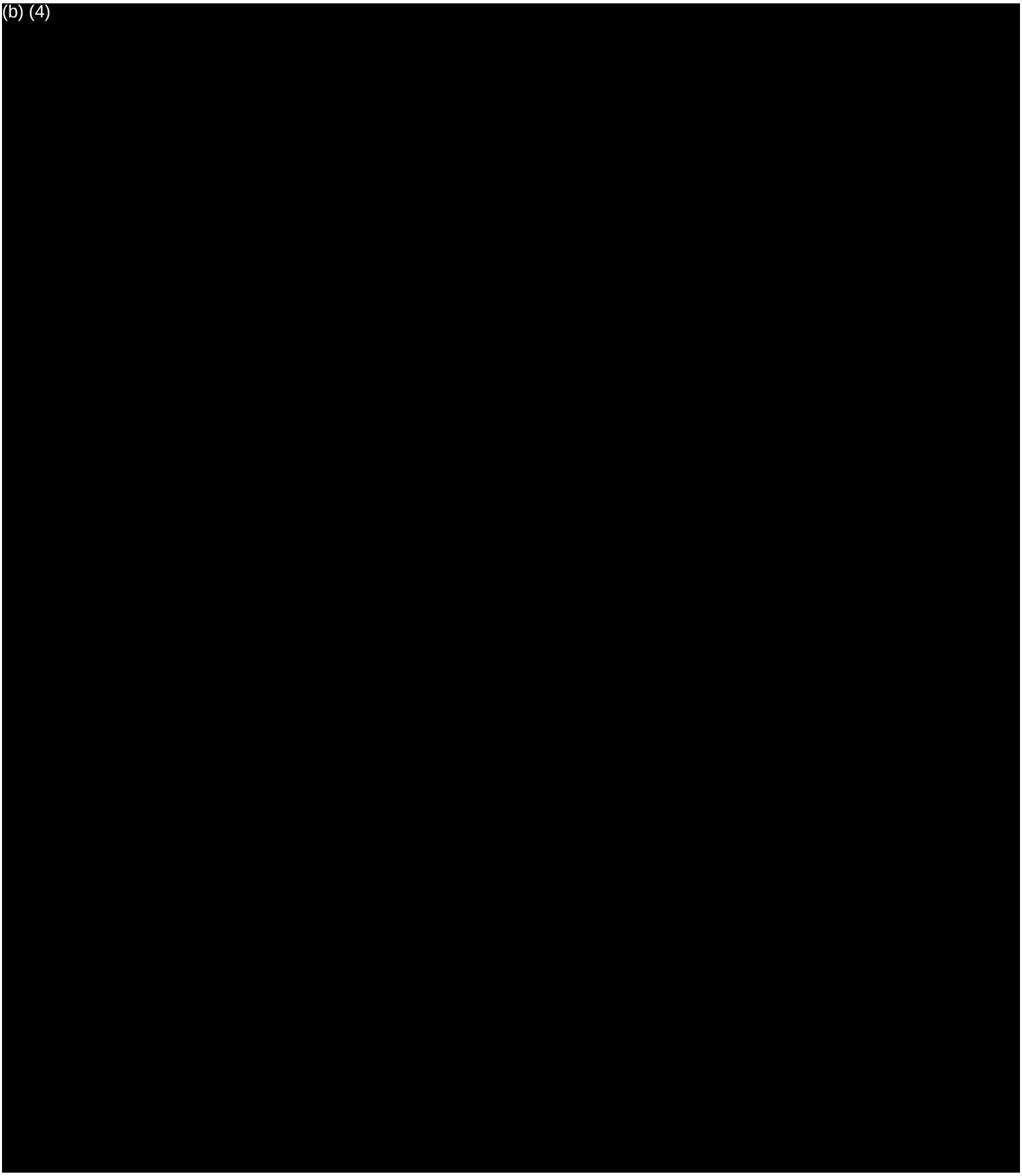
Minimum quantity: 480 cartridges

Maximum quantity: N/A

(b) (4) [redacted]

5. Deliverables

(b) (4)



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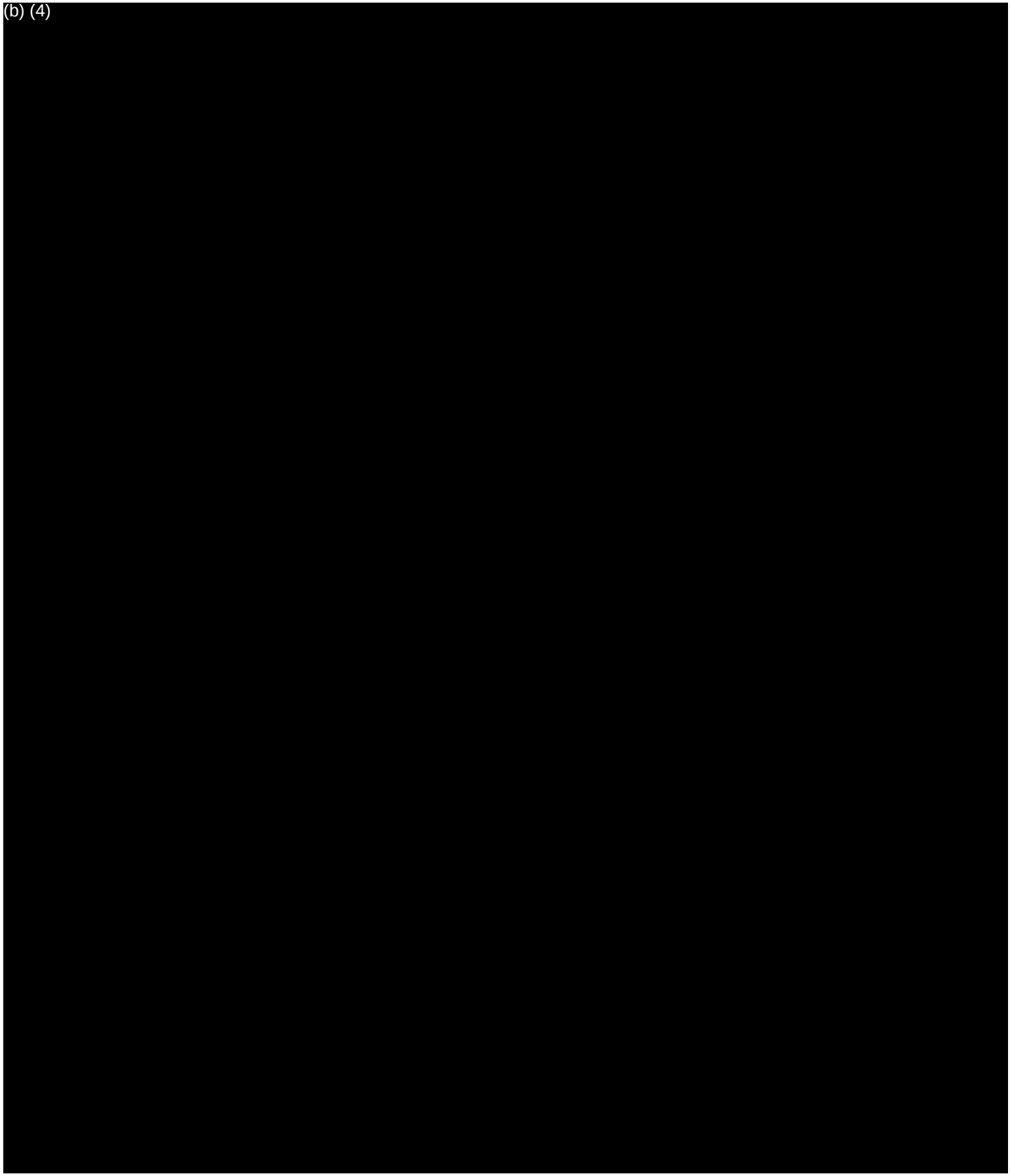

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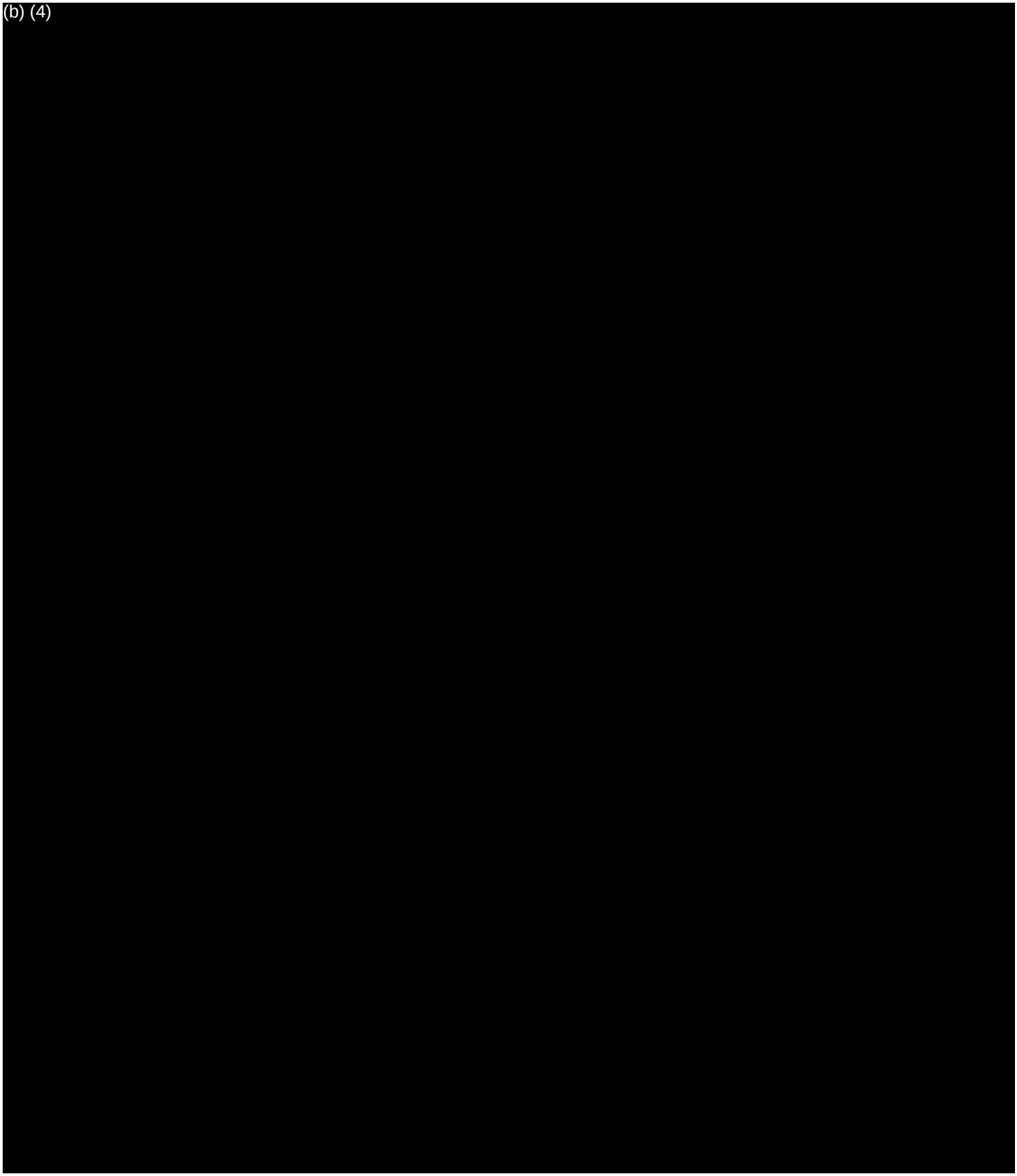
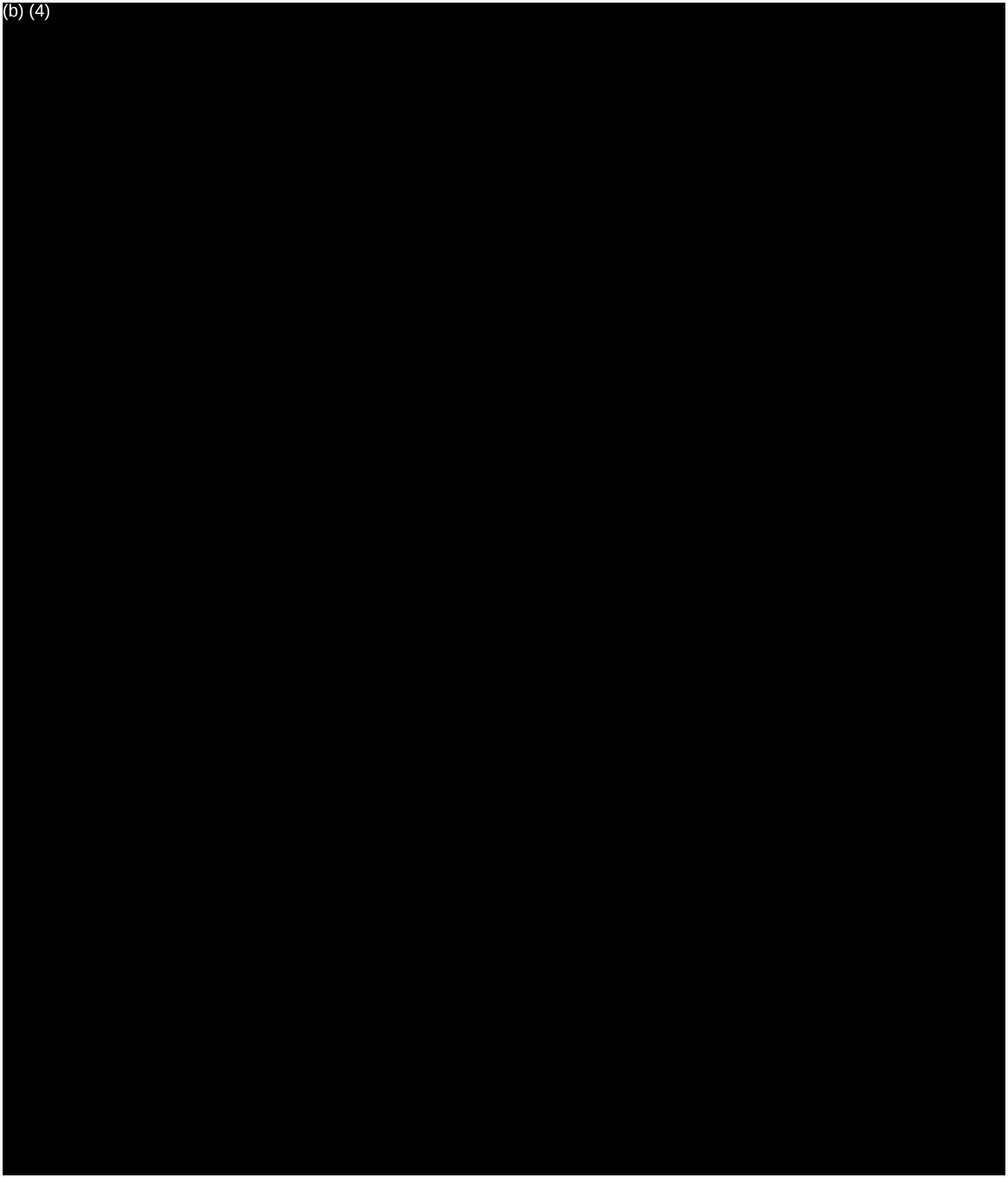
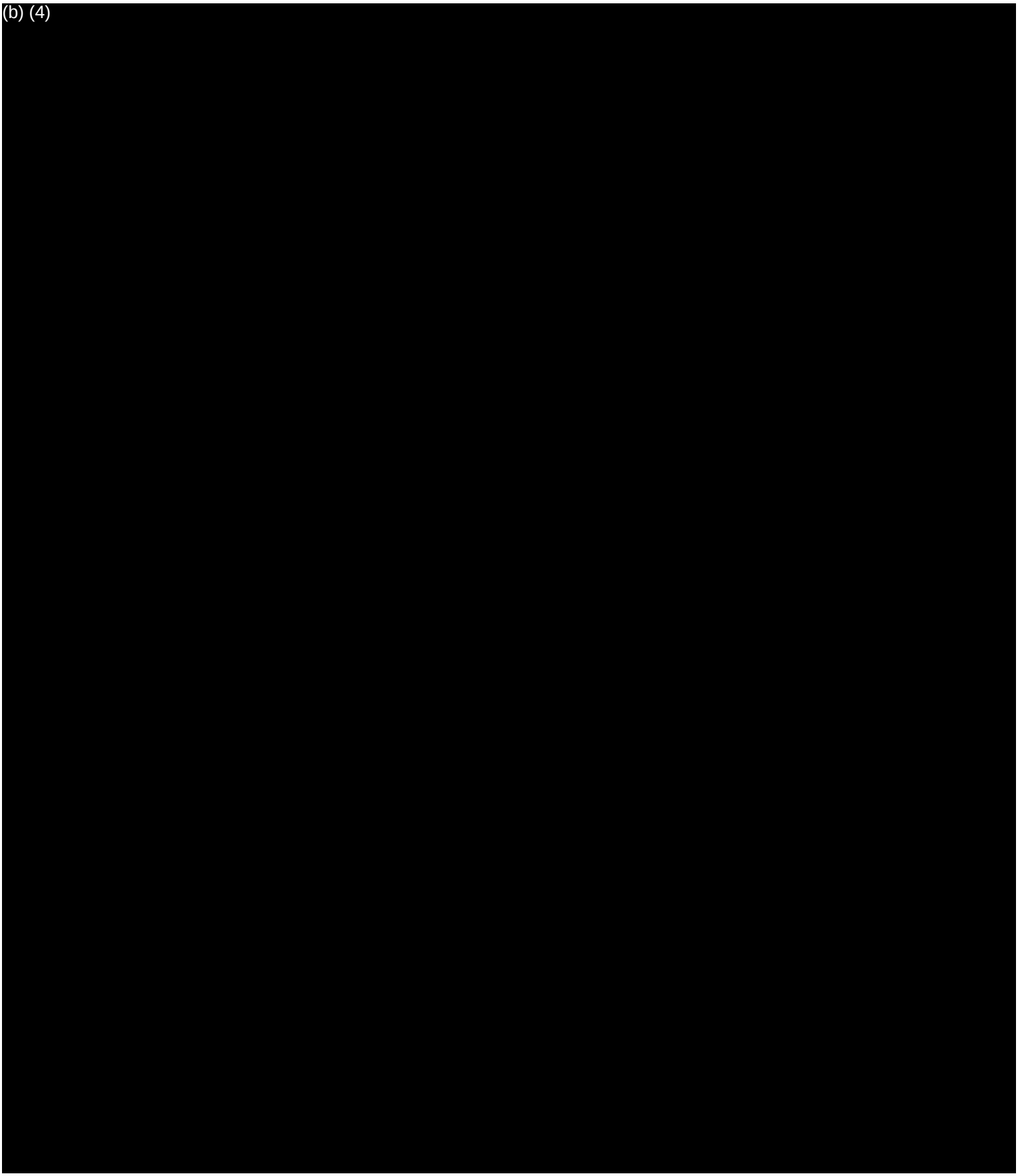


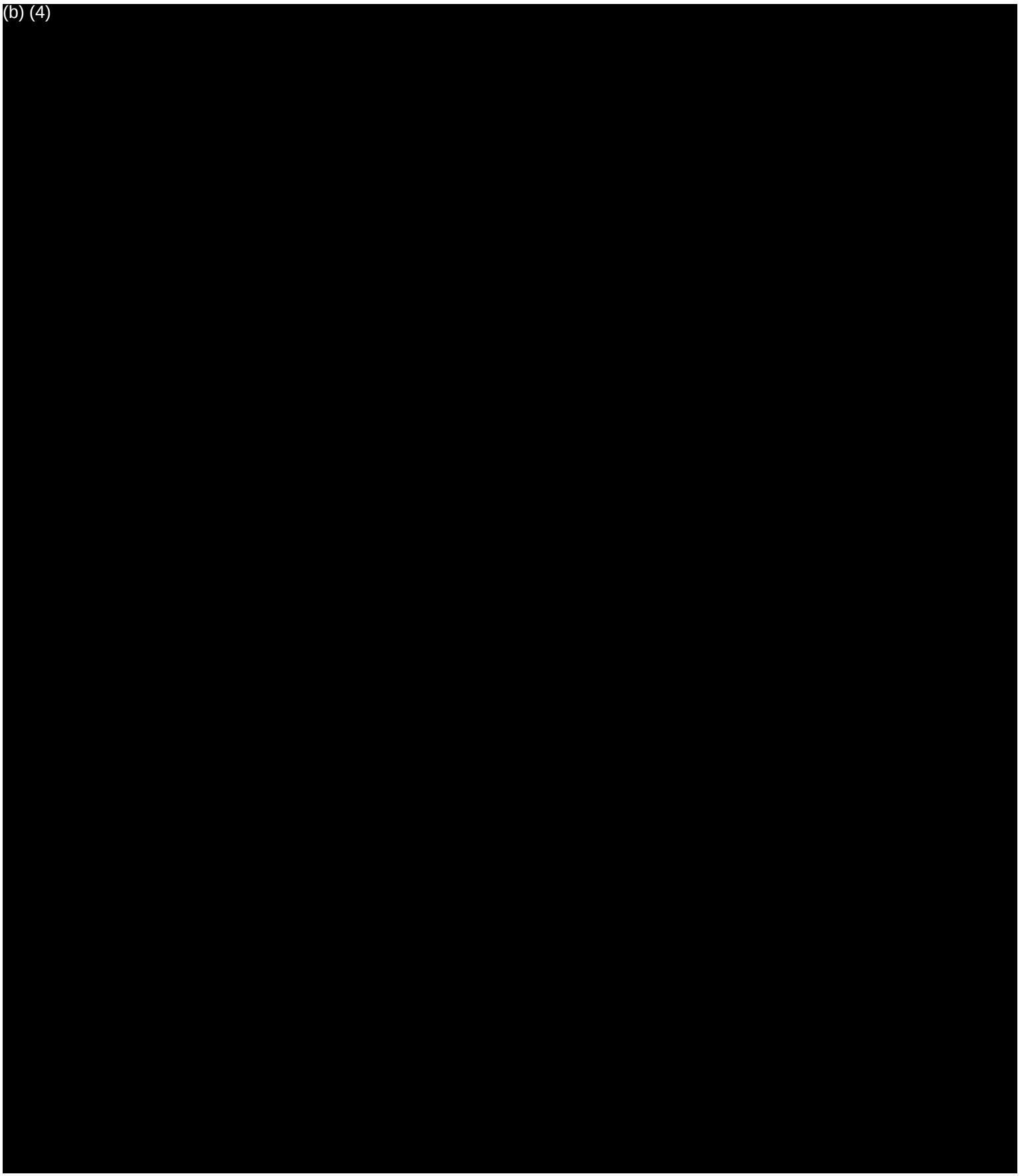
(b) (4)



(b) (4)



(b) (4)



(b) (4)

[redacted]

WBS 9.0- Novel Coronavirus EUA		
Phase	***Deliverables***	***Target Date 50% Confidence***
Concept/ Technical Feasibility Phase	*MEC Rev 1*	DONE
	DIR Rev 1	DONE
	R&D Analytical Study Test Plan	DONE
	Schedule	***DONE***
	FDA Application for EUA	***DONE***
	Clinical Plan Draft	DONE
	ROBAL Prototype	DONE
	Technical Feasibility Design Review	DONE
Design and Development Validation	*LoD, Analytical Inclusivity & Exclusivity studies*	DONE
	Design and Development Review	DONE
Validation and Launch	*Clinical report*	DONE
	FDA Submission Package	DONE
	Launch Kit Build	DONE
	Launch Readiness Review	DONE
WBS 10.0- Xpert® SARS-CoV-2/Flu/RSVAssay (EUA)		
Phase	***Deliverables***	***Target Date 50% Confidence***
Concept/ Technical Feasibility Phase	*MEC Rev 1*	*July 15, 2020*
	DIR Rev 1	*July 15, 2020*
	R&D Analytical Study Test Plan	*July 15, 2020*
	Schedule	*July 15, 2020*
	FDA Application for EUA	*July 15, 2020*
	Clinical Plan Draft	*July 15, 2020*
	ROBAL Prototype	*July 15, 2020*
	Technical Feasibility Design Review	*July 15, 2020*
Design and Development Validation	*LoD, Analytical Inclusivity & Exclusivity studies*	*August 15, 2020*
	Design and Development Review	*August 15, 2020*
Validation and Launch	*Clinical report*	*September 15, 2020*
	FDA Submission Package	*September 15, 2020*
	Launch Kit Build	*September 15, 2020*
	Launch Readiness Review	*September 15, 2020*

6.0 Milestone Schedule

Schedule is based on August 1 award and full staffing. Delivery dates, especially in early project phases, may shift due to staffing considerations.

Milestone No.	Engineering Deliverable Description	Estimated Due Date	Estimated Total Program Funds
Omni SW & FW-100688	**Roll-Up Software and Firmware Task. See SOW 4.1 and subsections for deliverables by development phase**		(b) (4)
1	Completion of Tech Feasibility Phase and Associated Deliverables		(b) (4)
2	Completion of Design and Development Phase and Associated Deliverables		(b) (4)
3	Completion of Validation Phase and Associated Deliverables		(b) (4)
4	Sustainment Phase Activities and Associated Deliverables		(b) (4)
Omni 10- Color - 100689	**Roll-Up for 10-Color Detection Task. See SOW 4.2 and subsections for deliverables by development phase**		(b) (4)
5	Completion of Tech Feasibility Phase and Associated Deliverables		(b) (4)
6	Completion of Design and Development Phase and Associated Deliverables		(b) (4)
7	Completion of Validation Phase and Associated Deliverables		(b) (4)
8	Sustainment Phase Activities and Associated Deliverables		
Omni Dev Accel - 100690	**Roll-Up for Omni Development Acceleration. See SOW 4.3 and subsections for deliverables by development phase**		(b) (4)
9	Completion of Tech Feasibility Phase and Associated Deliverables		(b) (4)
10	Completion of Design and Development Phase and Associated Deliverables		(b) (4)
11	Completion of Validation Phase and Associated Deliverables	3	(b) (4)
Cart A & Dev & Mfg - 100691	**Roll-Up for Next generation cartridge, Cart A+ Development Acceleration and Manufacturing Scale-up. See 4.4 and subsections.**		(b) (4)
12	Completion of Tech Feasibility Phase and Associated Deliverables		(b) (4)
13	Completion of Design and Development Phase and Associated Deliverables		(b) (4)
14	Completion of Validation Phase and Associated Deliverables		(b) (4)
15	Completion of Manufacturing Scale-Up Phase and Launch as well as Associated Deliverables		(b) (4)
16	Completion of Manufacturing Scale-Up Phase II		(b) (4)

17	Sustainment Phase Activities and Associated Deliverables	[redacted]	(b) (4) [redacted]
Hemorrhagic Fever Cartridge -100686	**Roll-Up for Hemorrhagic Fever Cartridge Development and Clearance. See Section 4.4 and subsections.**		(b) (4) [redacted]
18	Completion of Concept Phase and Associated Deliverables	[redacted]	(b) (4) [redacted]
19	Completion of Tech Feasibility Phase/Alpha Studies and Associated Deliverables	[redacted]	(b) (4) [redacted]
20	Completion of Design and Development Phase and Associated Deliverables	[redacted]	(b) (4) [redacted]
21	Completion of Validation Phase/Clinical Trials and Associated Deliverables	[redacted]	(b) (4) [redacted]
Tropical Fever Cartridge - 100685	**Roll-Up for Tropical Fever Cartridge Development and Clearance. See Section 4.5 and subsections**		(b) (4) [redacted]
22	Completion of Concept Phase and Associated Deliverables	[redacted]	(b) (4) [redacted]
23	Completion of Tech Feasibility Phase/Alpha Studies and Associated Deliverables	[redacted]	(b) (4) [redacted]
24	Completion of Design and Development Phase and Associated Deliverables	[redacted]	(b) (4) [redacted]
25	Completion of Validation Phase/Clinical Trials and Associated Deliverables	[redacted]	(b) (4) [redacted]
Bacterial vs. Host Response - 100687	**Roll-Up for Bacterial vs. Host Response Development. See Section 4.5 and subsections.**		(b) (4) [redacted]
26	Completion of Concept Phase and Associated Deliverables	[redacted]	(b) (4) [redacted]
27	Completion of Tech Feasibility Phase/Alpha Studies and Associated Deliverables	[redacted]	(b) (4) [redacted]
28	Cepheid Co-Investment		(b) (4) [redacted]
Bacterial Agents Cartridge- 100XXX	**Roll-Up for Bacterial Agents Cartridge Development and Clearance. See Section 4.5 and subsections**		(b) (4) [redacted]
29	Completion of Concept Phase and Associated Deliverables	[redacted]	(b) (4) [redacted]
30	Completion of Tech Feasibility Phase/Alpha Studies and Associated Deliverables	[redacted]	(b) (4) [redacted]
31	Completion of Design and Development Phase and Associated Deliverables	[redacted]	(b) (4) [redacted]
32	Completion of Validation Phase/Clinical Trials and Associated Deliverables	[redacted]	(b) (4) [redacted]
Novel Coronavirus EUA- 101000	***Roll-Up for Coronavirus-EUA Development and Clearance. See Section 4.5 and subsections (Phase 3)***		(b) (4) [redacted]
37	***Completion of Tech Feasibility Phase and Associated Deliverables***	[redacted]	(b) (4) [redacted]
38	***Completion of Design & Development and Associated Deliverables***	[redacted]	(b) (4) [redacted]
39	***Completion of Validation Phase and Associated Deliverables***	[redacted]	(b) (4) [redacted]

	Reports		(b) (4)
Xpert® SARS-CoV-2/Flu/RSV Assay (EUA)	***Roll-Up for SARS-CoV-2/Flu/RSV Assay (EUA) Development and Clearance***		(b) (4)
40	***Completion of Concept/Technical Feasibility Phase and Associated Deliverables***	[redacted]	(b) (4)
41	***Completion of Design & Development and Associated Deliverables***	[redacted]	(b) (4)
42	***Completion of Validation Phase and Associated Deliverables***	[redacted]	(b) (4)
43	Annual Report	30-Sep-18	(b) (4)
44	Quarterly Report	30-Dec-18	
45	Quarterly Report	30-Mar-19	
46	Quarterly Report	30-Jun-19	
47	Annual Report	30-Sep-19	
48	Quarterly Report	30-Dec-19	
49	Quarterly Report	30-Mar-20	
50	Quarterly Report	30-Jun-20	
51	Annual Report	30-Sep-20	
52	Quarterly Report	31-Dec-20	
53	Quarterly Report	31-Mar-21	
54	Quarterly Report	30-Jun-21	
55	***Annual Report***	***30-Sep-21***	
56	***Quarterly Report***	***31-Dec-21***	
57	***Quarterly Report***	***31-Mar-22***	
58	***Quarterly Report***	***30-Jun-22***	
59	***Annual Report***	***30-Sep-22***	
60	***Quarterly Report***	***31-Dec-22***	
61	***Quarterly Report***	***31-Mar-23***	
62	***Quarterly Report***	***30-Jun-23***	
63	***Annual Report***	***30-Sep-23***	
64	***Quarterly Report***	***31-Dec-23***	
65	***Quarterly Report***	***31-Mar-24***	
66	***Quarterly Report***	***30-Jun-24***	
67	***Annual Report***	***30-Sep-24***	
68	***Quarterly Report***	***31-Dec-24***	
69	Final Report	***30-May-25***	
		Total	**$86,564,949**

7.0 Shipping Provision

(b) (4) [redacted]

[redacted]

Separately, the Omni system has been tested according to the ASTM D642, ASTM D999, ASTM D4149 standards, and has been preconditioned per ASTM D4332.

Images of soft carrying case for Omni instrument:

8.0 Data Rights, Patent Rights and Copyrights

The Government claims Government Purpose Rights for all data developed under the OTA other than that asserted in the table below.

Technical Data or Computer Software or Hardware or Materials to be Furnished with Restrictions	Basis of Assertion	Asserted Rights Category (A,B,C)	Name of Organization Asserting Restrictions	Milestone # Affected
All rights in Cepheid patents and patent applications, both foreign and domestic whether issued, pending, in-licensed or abandoned *that exist before* the Effective Date of this OTA (except for any pre-existing U.S. Govt rights) *or that Cepheid independently develops outside of this OTA.*	Paid for by Cepheid	A* (except for any pre-existing Govt rights	Cepheid	NA
All trade secrets related to Omni or non-Omni hardware, software, manufacturing processes or procedures *that exist before the Effective Date of this OTA or that Cepheid independently develops outside of this OTA.*	Paid for by Cepheid	A	Cepheid	NA
All trade secrets related to design, manufacture or use of	Paid for by Cepheid	A	Cepheid	NA

any Gene Xpert cartridge that exist before the effective date of this OTA or that Cepheid independently develops outside of this OTA.				
All property rights of GeneXpert cartridges in production, design or development	Paid for by Cepheid	A	Cepheid	NA
All property rights to Omni and C360 software and firmware	Paid for by Cepheid	A	Cepheid	NA
All property rights to non-Omni Cepheid software and firmware	Paid for by Cepheid	A	Cepheid	NA
All non-Omni hardware including but not limited to designs and schematics	Paid for by Cepheid	A	Cepheid	NA
All pre-existing Omni hardware including but not limited to designs and schematics	Paid for by Cepheid	A	Cepheid	NA
Omni hardware and Omni software improvements made as part of this OTA	Mixed Funding	B	Cepheid	WBS 2, WBS 3
All chemical reagents and processes including but not limited to fluorescent dyes and quenchers used in Cepheid products	Paid for by Cepheid	A	Cepheid	NA
Omni Printed-Circuit Board Assembly (PCBA) documentation including schematics, layout and board fabrication details—to include all PCBA's *independently developed* prior to *or outside of* this OTA.	Paid for by Cepheid	A	Cepheid	NA
Omni Printed-Circuit Board Assembly (PCBA) documentation including schematics, layout and board fabrication detail for which the form, fit and function was changed to meet OTA deliverable requirements.	Mixed Funding	B	Cepheid	NA
All injection mold designs and tooling used in the Omni fabrication—to include all tooling developed prior to this OTA.	Paid for by Cepheid	A	Cepheid	NA
Injection mold designs and tooling used in the Omni fabrication for which the	Mixed Funding	B	Cepheid	NA

form, fit and function was changed to meet OTA deliverable requirements				
All property rights for cartridge A+ design	Paid for by Cepheid	A	Cepheid	NA
All property rights to manufacturing processes and equipment for all GeneXpert cartridges (including Cartridge A+)	Paid for by Cepheid	A	Cepheid	NA
Automation of Cartridge A+ manufacturing	Mixed Funding	B	Cepheid	NA
All property rights to pre-existing assay components and designs developed at private expense incorporated into *Government* panels[3]	Paid for by Cepheid	A	Cepheid	NA
Tropical fever assay customizations, development and validation needed to meet *Government* OTA requirements	Mixed funding	B	Cepheid	5.3-5.4
Hemorrhagic fever assay customizations, development and validation needed to meet *Government* OTA requirements	Mixed funding	B	Cepheid	6.3-6.4
Bacterial Agents assay customization, development and validation needed to meet *Government* OTA requirements	Mixed funding	B	Cepheid	7.3-7.4
Novel coronavirus assay primers and probe sequences are Cepheid trade secrets	Cepheid funded	A	Cepheid	37-39
Cepheid's Flu/RSV assay including all primers and probe sequences are Cepheid trade secrets	Cepheid funded	A	Cepheid	40-42
All property rights to Omni 10-color software/firmware/hardware	Cepheid funded	A	Cepheid	2.3
Omni 10-color software/firmware /hardware customizations needed to meet *Government* OTA requirements	Mixed Funding	B	Cepheid	NA
Omni-to-handheld non-radio connectivity software	Mixed funding	B	Cepheid	1.3

[3] When pre-existing assays are included into ***Government*** panels, assay primer and probe sequences will be provided to the ***Government*** in the event of a military or national emergency, and then solely to verify that the assay has suitable inclusivity and accuracy. Cepheid retains property rights to the assay design, and the Government will protect information as Cepheid-proprietary.

Dedicated C360 server for *Government* environment	Mixed funding	B	Cepheid	1.3
Study data and performance data generated under this OTA	Mixed Funding	B	Government	NA
None	Not contemplated	C	NA	NA

**Cepheid reserves the right to revise the above table.*

9.0 Security

- Cepheid shall not disclose ***Government***-generated developmental and operational test result data (i.e., cyber penetration and adversarial assessments and developmental and operational test results) without prior permission from the Agreement Officer (AO) or Agreement Officer's Representative (AOR).
- Cepheid shall not disclose ***Government***-specific software controls, security controls, user settings, and ***Government*** C360-related capabilities without prior permission from the Agreement Officer (AO) or Agreement Officer's Representative (AOR). However, they may be used generally by Cepheid in its commercial offerings.
- Cepheid shall not disclose target gene, primer or probe sequences, specific to the non-commercial, bacterial agent cartridge without prior permission from the Agreement Officer (AO) or Agreement Officer's Representative (AOR). Cepheid may disclose this information to the U.S. Food and Drug Administration to support regulatory activities and to ***Government***-designated agencies authorized to use the Bacterial Agent cartridge.
- Cepheid agrees to obtain facilities clearance and obtain personnel security clearance upon request. If requested, this statement of work will be modified to reflect the updated requirement, and Cepheid will provide a revised cost estimate to complete requisite security updates.
- Cepheid will employ best practices to hire U.S. Citizens for this project, but there may be exceptions where Cepheid may need to employ foreign suppliers and or foreign programmers. Cepheid agrees that core project team roles, as submitted in Volume 2, Appendix B and future C360 system administrator(s) will held by U.S. Citizens. C 360 System Administrator shall meet ***Government*** 8570.01-M requirements.
- Cepheid's Human Resources (HR) department is responsible for ensuring Cepheid policy is followed for all recruiting, hiring and terminating of Cepheid employees and Cepheid contract workers with positions on the project team. All job offers for Cepheid's project team members require a successful background check that includes employment verification, credential check and work authorization. HR utilizes E-Verify to provide Social Security Administration (SSA) and Homeland Security Administration with information from each new employee's Form I-9 to confirm U.S. citizenship or U.S. residency.
- On the first day of employment, project team members must attend New Hire Orientation that includes information on Cepheid Quality policies, safety protocols, standards of conduct, and regulatory compliance. Once per year, project team members must be certified on Danaher Integrity and Compliance training that reviews Federal Regulations and Danaher Standards of Conduct. Additional training for project team members is assigned by hiring manager to ensure conformance to specific departmental procedures and continued employee developmental growth.

10. Miscellaneous Requirements (Safety, Environmental, Etc.)

- Cepheid's quality system includes compliance to the FDA Quality System Regulation (QSR), 21 CFR Part 820, ISO 13485: 2016, Canadian Medical Devices Regulations CMDR SOR/98-282, DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 October 1998 on in vitro diagnostic medical devices (IVDD) and Taiwan Pharmaceutical Affairs Act.
- ISO Certificate, available upon request
- MSDS (Material Safety Data Sheet) will be generated for each assay developed under this effort.
- All relevant safety requirements, as outlined in the Base Agreement, shall apply to the effort.

11.0 Government Furnished Property/ Material/ Information:

11.1 Engineering Information Required:

- The ***Government*** shall provide additional information on data to transmit into dedicated ***Government*** C360. This impacts WBS 1.0 and must be provided within 1-2 months of the program start date.

- The ***Government*** shall provide additional input on usability demonstrations per WBS 1.0 and WBS 3.0 – items are each called out on the Microsoft project schedule, a total of 5 different demonstrations.

11.2 Government R&D Information Required:

- Input from the ***Government*** on final designs of the assay, which targets to include in each cartridge proposed. This needs to be provided within 1-2 months of program start date.

11.3 Government Clinical Required Input:

- Government laboratories will be used for the clinical trial testing of contrived specimens.
    a. Government will provide targets for select agents and where possible other targets (i.e., ideally virus or bacteria that can be used to spike human whole blood matrix for testing). Discussions for what can and cannot be provided should occur during Technical Feasibility or earlier if possible and prior to the Clinical Plan completion.
    b. Cepheid will need access to the site (not the BSL3-4 labs specifically) and personnel to perform the following procedures according to Cepheid Clinical Affairs standard operating procedures and the master validation plan:
        i. For execution of the clinical trial the following activities will be required: site qualification, site training on the assays, and site initiation of the study protocol, possibly an interim monitoring visit, and a final close out visit. (Note: the training on how to set up the systems and assays can be performed using non-infectious materials outside the BSL3/4 labs. Then the government personnel(s) can take the systems and place them in the BSL3/4 labs and conduct the study).
        ii. It will be expected that the clinical trial testing at each Government laboratory will be conducted in accordance with the study protocol, including responsibility for the maintenance and organization of the study documentation.
        iii. Where the protocol states that contrived specimens will be prepared, government will prepare the specimens according to an approved procedure using negative human whole blood matrix provided by Cepheid.
- Government clinical trial sites and laboratories may be requested to participate in the clinical trial to prospectively collect and test clinical specimens for subjects enrolled in the study.
    a. Cepheid will need access to the site and personnel to perform the following procedures according to good clinical practice guidelines, Cepheid Clinical Affairs standard operating procedures and the master validation plan:
        i. For execution of the clinical trial the following activities will be required: site qualification, site training on the assays, and site initiation of the study protocol, possibly an interim monitoring visit, and a final close out visit. (Note: the training on how to set up the systems and assays can be performed using non-infectious materials outside the BSL3/4 labs. Then, the government personnel(s) can take the systems and place them in the BSL3/4 labs and conduct the study).

    It will be expected that the clinical trial testing at each government laboratory will be conducted in accordance with the study protocol, including responsibility for the maintenance and organization of the study documentation.

11.4 Operations

- (b) (4) [redacted]

[1] https://www.cdc.gov/coronavirus/2019-ncov/summary html

[2] https://www.cdc.gov/media/releases/2020/p0130-coronavirus-spread.html

[3] https://coronavirus.jhu.edu/map html