Our vision is a U.S. Military Force that has a full medical countermeasure capability to fight and win in any CBRN battlespace worldwide.

Overview of the Department of Defense’s (DoD) Advanced Development and Manufacturing (ADM) Facility and Capabilities

Presented to:
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DISTRIBUTION STATEMENT A: Approved for public release; distribution is unlimited.
The DoD ADM is “Open for Business” for medical countermeasure development and manufacturing
Challenges in Medical Countermeasure Development

- “Big Pharma” is unwilling to develop DoD MCMs
  - Low profitability/return on investment, lack of long term DoD commitment
  - Intellectual Property concerns
  - Federal Acquisition Regulations (FAR)

- DoD relies on small innovator companies
  - Restarts a steep learning curve with each new product
    - Lack FDA regulatory experience, especially ‘animal rule’
    - Lack GMP process development/scale-up experience
  - Typically, product has a unique development path and manufacturing process
  - Limited access to stable manufacturing infrastructure

- Manufacturing issues a major cause of delays and cost increases

- Impact: Extended development schedules, increased costs

Solution: A dedicated, flexible and agile Advanced Development and Manufacturing (ADM) capability
DoD ADM Contract

• **Contract awarded to Nanotherapeutics, Inc., in Alachua, FL**
  – Base Period (Establishment)
  – Four 2-Year Option Periods (Sustainment)
  – Options for up to 3 additional manufacturing suites

• **Purpose-built biomanufacturing facility featuring:**
  – 180,000 ft² of development, manufacturing, laboratory, warehousing, and support space.
  – Biosafety Level 3 (BSL-3) manufacturing
  – Capability to support development from research through licensure and fielding
  – Capable of manufacturing scales from bench to large scale, including horizontal scaling for surge events
DoD ADM Facility
From Concept to Reality
• State-of-the-art Bio-manufacturing facility:
  – cGMP and BSL-3 compliant manufacturing
  – Four, independent manufacturing suites, segregated by dedicated HVAC systems
    • Allows for concurrent projects
    • Provides unidirectional flow of people & materials
    • Horizontal scaling
  – Utilizes stainless steel and single-use manufacturing technologies
  – Supports pilot through large-scale cGMP manufacturing
    • Up to 300L fermenter or 2,000L single-use bioreactor
  – All support capabilities “under one roof”
    • Process development, cell banking, and laboratory testing
    • 25,000 square feet of active GMP manufacturing space
  – Over 100 full time employees
Current DoD ADM Pipeline

- **Ricin vaccine (RVEc)**
  - Technology transfer, process development and engineering run production

- **Venezuelan Equine Encephalitis vaccine**
  - Assay and Manufacturing Technology transfer, Engineering runs

- **Tularemia Vaccine**
  - Process development and product manufacturing

- **Scopolamine**
  - Fill/finish product for clinical trial

- **Autoinjectors**
  - Development of alternative autoinjectors for 2-PAM and/or atropine
  - Regulatory assistance

- **Platform Technologies**
  - Technologies that can counter a variety of threat agents using standardized discovery, design, manufacturing, and/or testing processes to accelerate MCM delivery to the Warfighter
Summary

- DoD ADM is “Open for Business” to support DoD’s MCM requirements
- DoD ADM is a state-of-the-art development and manufacturing capability
  - Contractor-owned, contractor operated facility
  - Provides a full array of development and production services
  - Designed to support a wide range of product types at scales to meet DoD requirements
  - Multi-product, BSL-3 capable, hybrid manufacturing concept leverages single-use systems
- DoD ADM will implement lessons learned on each additional DoD product
  - Advancing new regulatory science, platforms, and manufacturing processes
  - Shortened development cycles and reduced life cycle costs
- Product development efforts underway at new facility
  - BOT A/B mAbs, and vaccines against ricin, WEVEE and Tularemia
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The DOD ADM: Overview and Capabilities
Facility Overview
Facility Infrastructure

Facility situated on 29 acres with a gated entry

Secured perimeter with infrared motion-activated cameras and 24/7 monitoring

Facility has room for expansion
- Internal expansion space
- Building can be further expanded externally in two directions if required

Separate passenger vehicle and truck entrances
Facility Layout

Area A (~ 23,000 ft²)
- Administration
- Training
- Conference Rooms
- Security Operations Center
- Secure Archived Document Storage

Area B (~ 24,000 ft²)
- QC Analytical and Release Testing
- Pilot Plant
- BSL-3 Labs
- Viral and Cell Banking
- Development Labs

Area C (~ 42,000 ft²)
- GMP / BSL-3 Manufacturing Core
- Future Expansion Area

Area D (~ 9,000 ft²)
- Central Utilities Plant

Area E (~ 30,000 ft²)
- Warehouse
- Flammable storage room
- Shipping / Receiving docks
- Waste Dock
- Cold Room

Mechanical Mezzanine (~ 52,000 ft²)
- Critical utilities
- Walkable ceilings
Vector Development
- Cloning
- Research cell bank

Pilot Plant
- Upstream Processing
- Downstream Processing
- Harvesting/Cell Separation

BSL-3 Development and QC Labs

cGMP ISO-7 Labs
- Viral Banking
- Cell Banking
- ISO-5 aseptic processing

Freezer Room
- Multiple -80°C Freezers
- Liquid N\textsubscript{2} Cryogenic Storage
Manufacturing Core

Four independent processing rooms
- Up to four products concurrently
- Independent AHUs (zoning)
- Unidirectional flow
- Media/Buffer Preparation

BSL-3 Containment Area
- Negative pressure cascades
- HEPA supply and return
- ClO₂ decontamination ports
- Spillage containment epoxy floors
- Sealed penetrations

Modular Cleanroom Design
- Impervious walls and ceilings
- Walkable ceiling

ISO-8 Processing Rooms with access to ISO-7 spaces containing ISO-5 BSCs to support:
- Aseptic processing
- Bulk drug substance fill
- Small fill-finish projects
The open ballroom and unidirectional flow concept allow for flexible and agile manufacturing of biologics (up to 2,000 L) based on the SUT and SS technologies.
Quality Control

Sample Handling and Stability Storage
- Incoming receipt
- Retains

Cell Assay Lab & Immunology Lab
- Plaque assays
- Enzyme-linked immunosorbent assay (ELISA)

Analytical Chemistry Lab
- Wet chemistry
- Product characterization

Microbiology Lab
- Environmental monitoring
- Bioburden
- Endotoxin
- Sterility
Capabilities and Services
Core Competencies

Process Development and Scale-up
- Technology Transfer
- Molecular and Cell/Vector development
- Process development and optimization
- Process Scale-up
- Non-cGMP production up to 200 L
- Small model qualification

cGMP Manufacturing
- Cell banking
- Virus banking
- Drug Substance-API production up to 2,000 L
- Process validation
- Product storage and shipment

Quality
- Analytical development and validation
- Quality Control testing
- Stability testing
- Quality Assurance
- Product release
- Validation
- Training

Bioanalytical
- Bioanalytical method development
- Method transfer and optimization
- Nonclinical and clinical sample analysis
- Sample handling and management

Regulatory
- Product development plans
- Regulatory strategy
- Life cycle management of regulatory submissions
- Electronic submissions
- Target Product Profile

Program Management
- Project Planning
- Schedule Integration
- Client communication
- Budgeting
- Subcontractor management
Experience with Expression Systems

Mammalian Cell Culture
- Vero, CHO, HEK293, BHK, PerC6, MDCK for recombinant proteins, antibodies, inactivated or live viral vaccines, VLPs, VRPs.
- Nanotherapeutics’ proven Vero cell technology (DMF 10336, Master and Working Cell banks) has been used in production of commercial and clinical vaccines (influenza, Chikungunya virus, Ross River virus and many others)
- CHO production of monoclonal antibodies

Microbial Systems
- Bacterial systems (e.g., E. coli fermentation) including experience with ricin subunit vaccine production
- Yeast (Pichia pastoris) including experience with recombinant botulinum toxin protein vaccine

Insect cells (Sf9) using baculovirus system
- Production of norovirus GI and GII.4 recombinant VLPs
Process Development

Upstream Process Development
- Culture expansion parameters, MOI, time of harvest
- Establish scalable process
- Productivity strategies for protein-free and serum-free production processes
- Single-use technologies

Purification Development
- cGMP processes developed and scaled up for a variety of products
- Scalable and Disposable Technologies
- Filtration
- Chromatography

Process Technology Transfer to pilot plant or cGMP manufacturing suites
Cell and Virus Banking

Dedicated Cell Banking Suite
Dedicated Virus Banking Suite
  ▪ Plaque purification
  ▪ Up to BSL-3 material

Controlled Rate Freezers

cGMP Storage Freezers
  ▪ Monitored and alarmed
  ▪ -80°C
  ▪ Vapor phase liquid nitrogen
Manufacturing

Inoculum Prep
- CO₂ Incubators
- Biosafety Cabinets Class II Type B1

Cell Culture Processing
- Single-Use Bioreactors
  - Roller bottles, NCF, Hyperstack
  - 25 L GE Wave Reactor
  - 50 L, 200 L, and 500 L SUB

Stainless Steel Fermentors
- 75 L and 150 L Eppendorf

Stainless Steel cell disrupter
- 200 L/hr GEA Westfalia

Bulk Filling
- Biosafety cabinets
- Aseptic Filling Machine
  - 5mL to 5 L fill volumes
  - ± 0.5% accuracy
Quality Systems
Quality Assurance (QA) organization provides:
- Operational oversight
- Management and administrative support for the QMS functions

ISO 9001 Certified Quality Management System (QMS)
- 21 CFR Part 211, Part 600 and Part 820.
- ICH Q8, Q9, Q10, and Q11

Risk Management
- Well-defined, systematic, iterative process to identify, assess, mitigate and respond to areas that could prevent from meeting objectives within the defined requirements.
Quality Management Systems

QMS is supported by validated software systems providing management of key Quality Systems Elements

- NextDocs
  - Document Management and Control

- MODA
  - LIMS-Environmental Monitoring

- Trackwise
  - Deviation, CAPA, Change Control, Investigations, Audit Management

- LabVantage
  - Laboratory Information Management System (LIMS)

- QAD
  - ERP Inventory Management and Control

- Compliance Ware
  - Training Management

- Procal
  - Equipment Calibration and Maintenance Management

- LabVantage
  - Laboratory Information Management System (LIMS)
Quality Control Capabilities
Microbiology

- Environmental and Utility Monitoring (MODA)
- Disinfectant Efficacy Program
- BSL3 QC laboratory
- 60 SOPs (methods and O&M)
Analytical Chemistry

- Includes Stability and Sample Management (LabVantage)
- 45 SOPs (methods and O&M)
Cell Assay

- PCR Suite
- Mammalian and non-mammalian spaces
- 38 SOPs (methods and O&M)
Regulatory Capabilities
### Regulatory Support Tiers

<table>
<thead>
<tr>
<th>Tier</th>
<th>Description</th>
<th>Example Deliverables</th>
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<tbody>
<tr>
<td>Tier 1 – Source Document Only</td>
<td>Review master and executed documents planned for delivery to the client to ensure documents are adequate to support product intended use. Review applicable change controls related to the facility and program for regulatory impact.</td>
<td>▪ Source document deliverables in accordance to SOW.</td>
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<td>▪ No regulatory deliverables.</td>
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<td>Tier 2 – CMC Technical Writing - Module 3 Only</td>
<td>Module 3 Quality CMC technical writing only, CMC consultation and guidance limited to products manufactured in the ADM facility or by ADM subcontractors;</td>
<td>▪ Word Documents (Module 3 CTD Templates)</td>
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<td>▪ Scope well defined via a Regulatory Support Services Agreement (RSSA)</td>
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<td>▪ Includes Tier 1 support</td>
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<td>Tier 3 – Regulatory Application Writing</td>
<td>Regulatory writing to include all applicable forms and CTD sections as defined in the RSSA.</td>
<td>▪ Word Documents (CTD Templates)</td>
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<td>▪ Specific to scope in RSSA</td>
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<td>▪ Clinical document writing and oversight</td>
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<td>▪ Includes Tier 1 &amp; 2 support</td>
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<tr>
<td>Tier</td>
<td>Description</td>
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| Tier 4 – Formal Meeting Support     | Regulatory strategic guidance and support to support meeting objectives, including providing subject matter experts in discipline of meeting focus, authoring and preparation of meeting scope, and leadership during the meeting process. | ▪ Letter of request with targeted questions  
▪ Briefing package / meeting materials  
▪ Meeting preparation tracking tool  
▪ Meeting summary |
Project Initiation and Management
New Product Introduction

Assess the risk of introducing a new product into the facility
Initial assessment to identify BSL level and any exclusion category
Introduction of new product initiated using TrackWise Change Request
Risk assessment which includes risks and mitigation strategies including:
- Concurrent work/adjacencies
- Prior manufacturing campaign and changeover
- Adventitious agents
- Disinfectant/decontamination efficacy and cleaning validation requirements
- Personnel/material/waste flows

Internal Biosafety Committee assesses biosafety risks
Quality Review Board assess cGMP risks and requirements
**CORE PDT MANAGEMENT**

- **Program Manager**
  - Responsible for all aspects of team performance and project success
  - Responsible for technical development plan and execution
  - Provides scientific expertise and leadership in product development

- **Principal Investigator**
  - Responsible for sound business and financial management of the project
  - Provides support in finance and EVM (as appropriate)

- **Financial Manager**

**FUNCTIONAL TEAM**

- **Quality Systems**
- **Regulatory Affairs**
- **Research & Development/Process Development**
- **Analytical Development/Quality Control**
- **Clinical Research**
- **Non-clinical Research**
- **cGMP Mfg.**
- **Contract and Subcontract Management**

**ADDITIONAL STAKEHOLDERS**

- **Client**
  - Technical requirements
  - Contract requirements
  - Program oversight
  - Funding

- **Subcontractors**
  - Non-clinical testing
  - Clinical trials
  - Manufacturing
  - Product support

- **External experts**
  - Consultants
  - Strategic collaborators
  - Academia

**PRODUCT DEVELOPMENT TEAM**

**INTEGRATED PROJECT TEAM**
Nanotherapeutics uses a well-defined, systematic, iterative process to identify, assess, mitigate and respond to areas that could prevent us from meeting project objectives within the defined requirements.

High-level methodology includes:
- Risk identification
- Risk assessment and quantification
- Risk response development
- Risk response control

Risk management is built into our program to protect our Clients’ investment.