Accelerating Medical Countermeasures from R&D to Clinical Trials via GMP Manufacturing at the Walter Reed Army Institute of Research

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Defense Health Agency
RESEARCH & DEVELOPMENT ®

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WRAIR: A Global Organization with Expertise in Infectious Disease Research and Product Development

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PILOT BIOPRODUCTION FACILITY

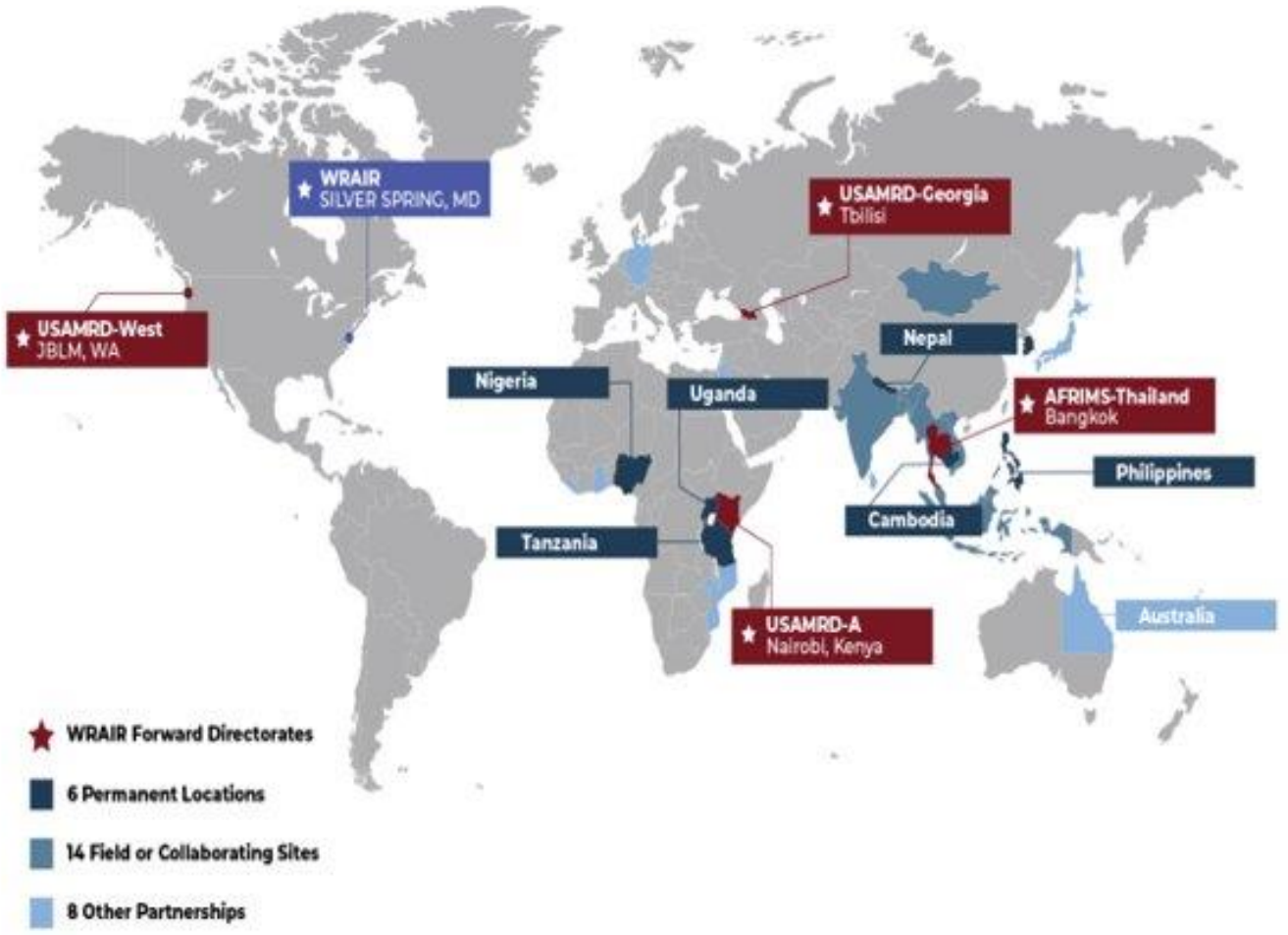
WRAIR
Walter Reed Army Institute of Research
Defense Health • Global Health

Mission

Discover, design, develop and deliver globally impactful solutions for military relevant infectious diseases, brain health, and performance optimization through innovative research.

Vision

The DoW's premier research enterprise for infectious diseases, brain health, and performance optimization.



Pilot Bioproduction Facility

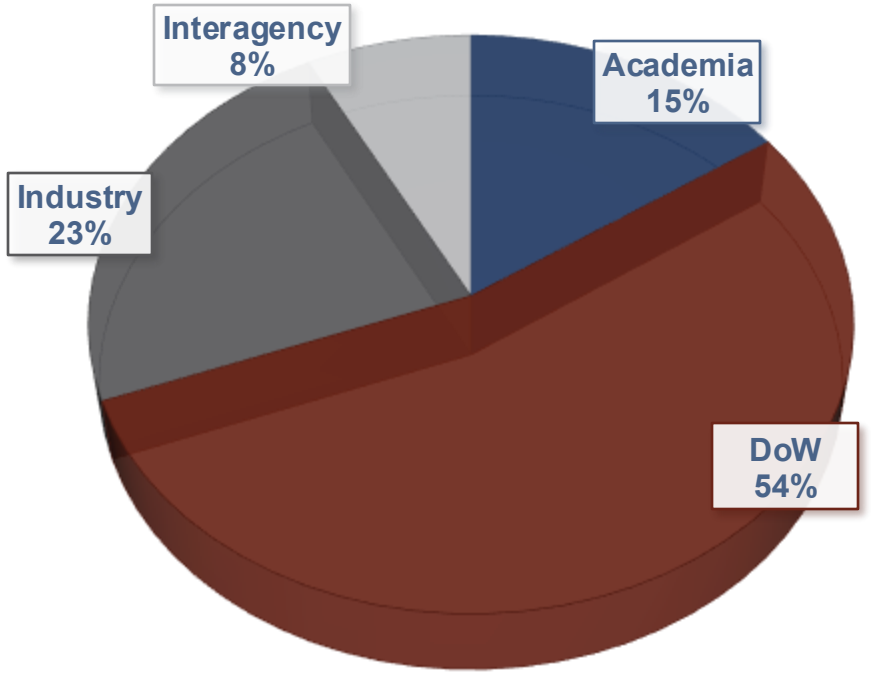
- Established in 1953 as the Department of Biologics Research, manufacturing GMP material since 1993
- Newly renovated ***Government Owned/Government Operated*** facility re-opened in 2020 with modernized state-of-the-art equipment
- Vertical integration within WRAIR and DHA R&D enterprise enables ***cost, schedule and performance risk reduction*** for medical countermeasure development
- ***One-stop shop*** providing process development, drug substance and final drug product production, testing, and stability

Your critical early Phase manufacturing partner in vaccine and biologic product development to readily transition products from R&D to clinical trials

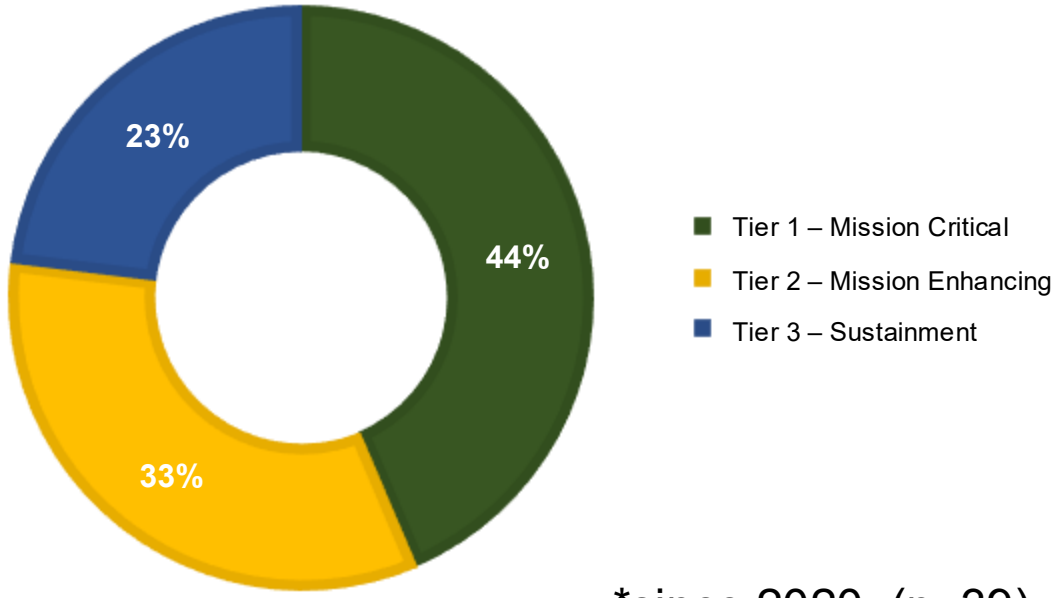
Enabling DoW and USG Mission Critical Priorities and Sustaining Partnerships to Deliver Medical Countermeasure Solutions

- Tiered prioritization of projects based on mission relevance with enhanced schedule prioritization, operational flexibility, and cost benefits for DoW and USG products
- Collaborations with external clients through Cooperative Research and Development Agreements (CRADAs) and Interagency Agreements (IAAs) to support mission enhancing and sustainment efforts
- Fee-for-service business model with market competitive costs and reduced rates for government projects

DISTRIBUTION BY PARTNER CLASSIFICATION



PROJECT DISTRIBUTION BY TIER



*since 2020 (n=39)

GMP manufacturing capabilities

- **GMP Clean Core:**

✓ "Suite" design based on unit operations
  - Viral production (upstream & downstream)
    - Suspension culture (wave reactor)
    - Adherent culture (cell-stacks, rollerbottles, fixed bed bioreactor)
    - single-use technology for purification and TFF
  - Non-viral Upstream
    - Microbial: 1-3L single-use, 45-400L stainless steel
    - Mammalian: 40L suspension culture
  - Downstream purification & mRNA production
  - Fill/Finish
    - Liquid or lyophilized products

✓ Separate ISO-7, -8, and -9 areas with ISO-5 BSCs for open work

✓ BSL-1 and BSL-2 manufacturing:
  - Master/Working cell banks (200-300 vials)
  - Master/Working viral seeds (200-300 vials)
  - Bulk Drug Substance
  - Drug Product (up to 2,000 vials/lot)

- **Quality System designed to meet requirements for early-phase clinical trials**
  ✓ "Guidance for Industry: CGMP for Phase 1 Investigational New Drugs"

- **Quality Control**
  ✓ Environmental monitoring – air, surfaces, water, process gasses, etc.
  ✓ In-process product testing
  ✓ Release testing
    - Compendial (USP) testing: appearance, pH, endotoxin, bioburden, SDS-PAGE, etc.
    - Product specific test development available via ASAT
  ✓ Drug Substance & Drug Product stability plan management and testing

Multi-product facility with experience in a wide range of product types

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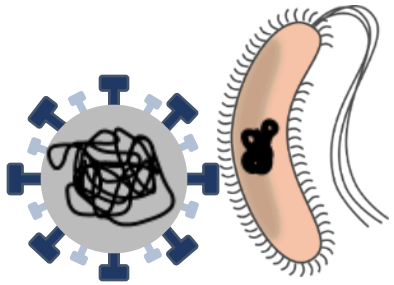
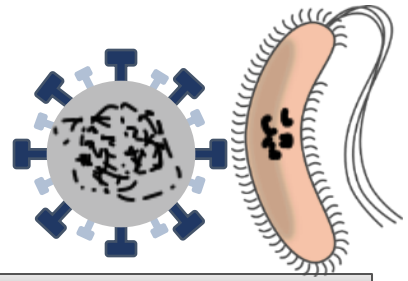


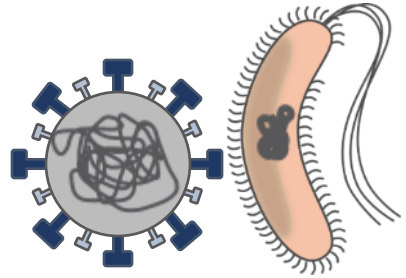
Clinical Challenge Strains (BSL-2)

- ✓ **Dengue***
- ✓ **Malaria***
- ✓ ETEC
- ✓ **Shigella***
- ✓ **Salmonella***



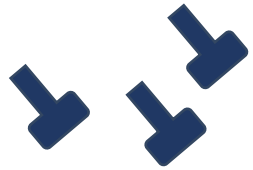
Whole Inactivated Vaccines

- ✓ Japanese Encephalitis
- ✓ **Zika***
- ✓ **CHIKV-181***
- ✓ ETEC
- ✓ Shigella
- ✓ Dengue
- ✓ Hepatitis A
- ✓ Campylobacter
- ✓ **Rotavirus***
- ✓ **Sindbis virus chimera vaccines***



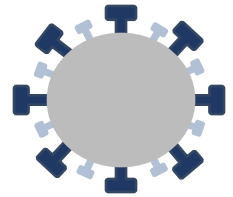
Live Attenuated Vaccine Platforms

- ✓ VSV
- ✓ MVA
- ✓ Adenovirus
- ✓ AAV
- ✓ Dengue
- ✓ **Shigella***
- ✓ ETEC
- ✓ **Salmonella***
- ✓ **F. tularensis (ΔClpB)***
- ✓ **Cholera***
- ✓ **Rotavirus***



Recombinant Proteins

- ✓ **Malaria***
- ✓ Botulinum
- ✓ Rotavirus
- ✓ Shigella
- ✓ mAb (*in development*)



Nanoparticle/Viral Like

- ✓ **Malaria***
- ✓ **COVID-19***
- ✓ **Lipid nanoparticle formulations***

Other

- ✓ **Substance abuse conjugate vaccine***
- ✓ **mRNA***

***GMP produced since 2020**

Capability modernization – mAb manufacturing

Vector & Product Design

Stable Cell Line Development (Stable Pool) ~4-8wks

Clonal Selection (RCB) ~14wks

RCB provided to PBF by product owner

Process Development/Optimization
Platform process establishment
DOE Media & feed optimization
Resin screening

Platform Process: in development
High throughput DOE: pending equipment installation

Testing: product specific assay development and qualification may be required

cGMP Cell Bank (MCB/WCB) [200 vials]

~4 wks

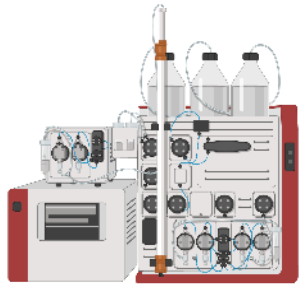
Existing PBF capability – up to 300 vial bank

GMP Upstream Production

~6-8 wks

40L scale (FY27)
500L scale (FY28-29)

Equipment: **on track**
Process: in development



GMP Downstream purification (Bulk Drug Substance)

~2 wks

40L scale (FY27)
500L scale (FY28-29)

Equipment: **Ready**
Process: in development

Viral clearance testing outsourcing required

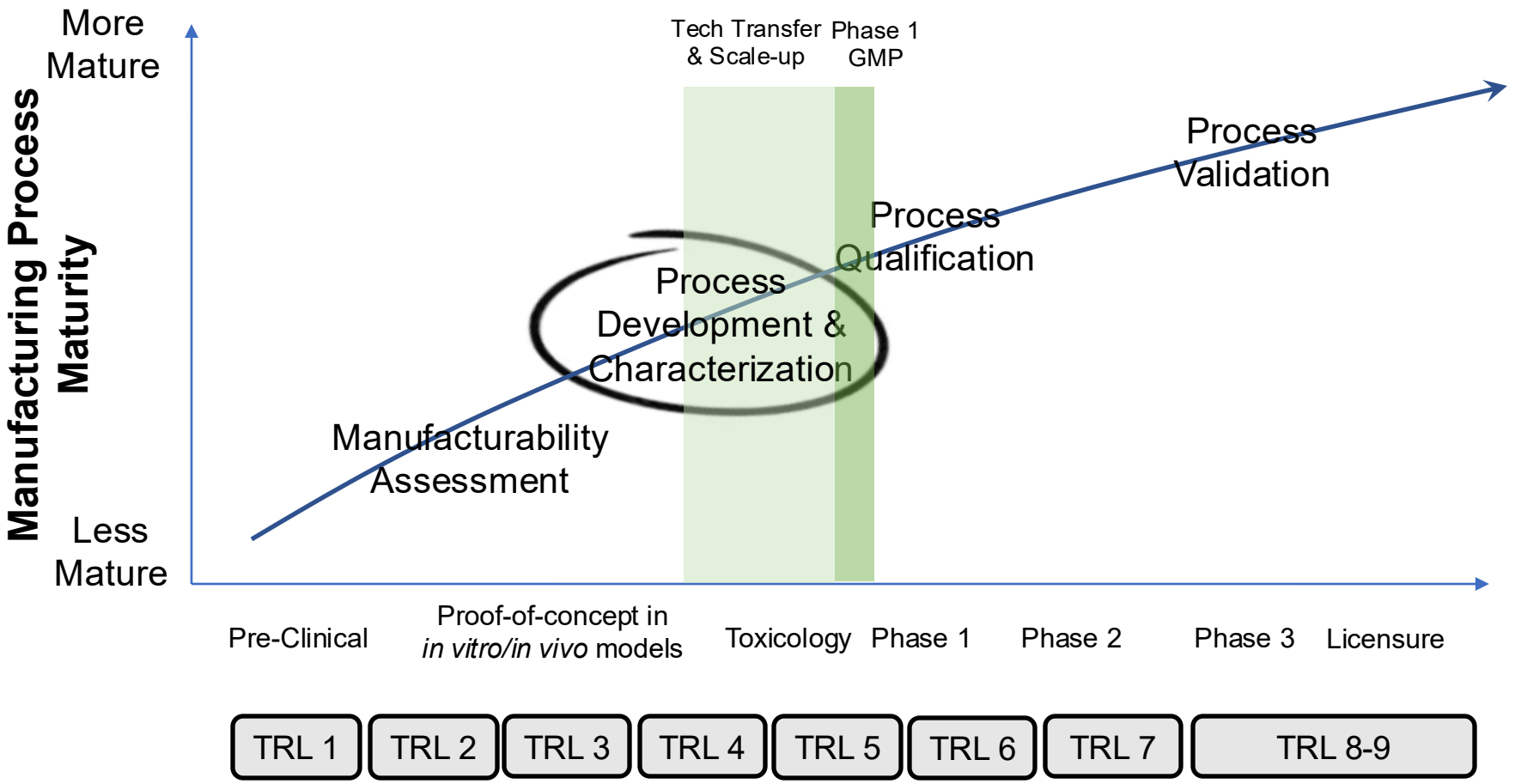
Drug Product Vialing

~1 wk

Drug Product fill/finish up to 2,000 vials – Existing capability

Testing: product specific assay development and qualification may be required

Enabling Product Advancement Though Manufacturing Process Development



Risks to Cost, Schedule & Performance during tech transfer & scale-up in the "Valley of Death":

- Poor understanding of product critical quality attributes (CQAs) and critical process parameters (CPPs)
- Gaps in documentation – "secret sauce"
- Differences in:
  - equipment
  - materials
  - Mixing times/speeds, column size, flow rates, etc.

Product Development Stage

Defense Acquisition Tech Readiness Levels

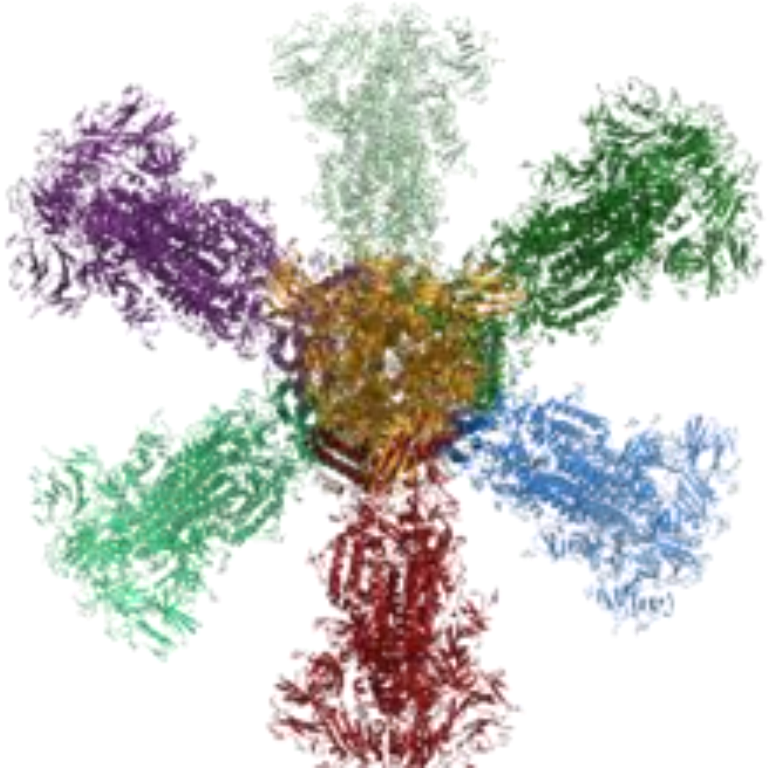
PBF Manufacturing Sciences & Technology (MSAT) Reduces Schedule and Performance Risk

- Process suitability & scalability assessments
- Process familiarization & technology transfer packages
  - Verify performance of your process in our hands
  - Tech Transfer documentation packages to aid transfer-in/out
- Process development to support scalability and transfer to advanced development
  - Equipment harmonization with GMP capabilities for smooth transition
  - Production platforms aligned with large-scale GMP manufacturers
- Product specific assay analytical transfer, development and phase-appropriate qualification

Case Study: Acceleration of development for WRAIR's COVID-19 Vaccine (SpFN)

Vertical integration of GMP manufacturing allows for parallel development pathways, flexibility and prioritization of WRAIR products. As a result, SpFN manufacturing was initiated at least 6-9 months earlier than other industry manufacturers

- **Apr 2020:** Agreement and funding awarded to WRAIR EID and WRAIR PBF to begin SpFN development
- **Jun 2020:** WRAIR completes antigen downselection, PBF receives cell line licensing rights and new equipment required for SpFN manufacturing
- **Aug 2020:** PBF receives critical raw material and initiates engineering run
- **Sep 2020:** PBF initiates cGMP production in parallel to engineering run
- **Dec 2020:** PBF completes cGMP production with sufficient material for Phase 1/2
- **Jan 2021:** SpFN released and Phase 1 activities begin



Summary

- WRAIR Pilot Bioproduction Facility is a Phase 1 GMP-compliant vaccine and biologics manufacturing facility, building new capabilities to support modern prevention and therapeutic modalities to enable medical countermeasure development
- Common risks and challenges during scale-up and tech transfer can be mitigated through manufacturing process development early during R&D bridging the product development valley of death

Acknowledgements

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  - NIH Division of AIDS

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