The Vaccine Pilot Plant: Use of FFRDC for Urgent National Need

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Vaccine Research Research Center

John Gilly, Ph.D.
Director VCMP
SAIC
The VRC, VPPL and VCMP
Vaccine Research Center

• VRC mission involves the rapid advancement of promising vaccine candidates from the laboratory to the clinic
  – Basic and applied virology and immunology
  – Pre-clinical immunology – animal models
  – Translational research & development
  – Clinical trial vaccine testing
  – Collaboration with other USG agencies and NGOs for advanced clinical evaluation
VRC Translational Research Programs

**HIV**
- Gene-based vaccines
- Protein-based vaccines
- Broadly Neutralizing mAb

**Emerging Diseases**
- Chikungunya vaccine

**Biodefense**
- Filovirus (Ebola and Marburg) vaccine
- Alphaviruses (V, E and WEEV) vaccine

**Influenza**
- Seasonal vaccine
- Universal vaccine
Overview of the Vaccine Production Program Lab (VPPL)

• VPPL is responsible for translation of research ideas/products through development and production for all VRC clinical products

• Organization includes resources for:
  – Process (~22 FTE), analytical (~12 FTE) and formulation development (~3 FTE)
  – Project management (~2-3 FTE)
  – Regulatory Affairs (~2 FTE)

• Designed for the concurrent development of 2 new clinical products
Overview of the Vaccine Clinical Materials Program (VCMP)

- Contractor responsible for GMP production of all VRC clinical products
  - Internal production at Vaccine Pilot Plant (VPP)
  - Subcontract production when more effective

- Organization includes resources for:
  - Manufacturing (~40 FTE)
  - QC (~25 FTE)
  - QA (~23 FTE)
  - Management (~9 FTE)
  - Facilities (~19 FTE)

- Staffed for the concurrent production of 2 clinical products and maintenance of on-going trials
The Need for the VCMP at the VRC
The VRC’s Need for the VCMP

• VRC mission involves the rapid advancement of promising vaccine candidates from the laboratory to the clinic

• Necessitates the development of a vaccine production infrastructure that includes the capacity for cGMP production of materials for Phase I/II clinical trials

• Two strategies are possible for obtaining the requisite cGMP capacity:
  – contracting with commercial firms
  – building a government financed manufacturing facility
Contracting vs Internal Production

• Time:
  – Commercial manufacturers typically require up-front commitment of products and processes up to a year in advance; making it difficult, if not impossible, to drive new vaccine candidates forward on accelerated timelines

• Cost:
  – Commercial manufacturers are very expensive (~$8M for partial VRC01 Phase I clinical material)

• Technology:
  – Technology unique to VRC products is extremely difficult and time intensive to transfer to external manufacturers
Why the VCMP via the FFRDC at NCI?

- Government-controlled GMP production capacity is a critical component for expediting the introduction of vaccine candidates into the clinic.
- Realization that NIAID could not manage a GMP facility based on contracting resources and timeframes required to effectively run a pilot plant.
- The FFRDC at NCI-F provided the best mechanism for operation of a contractor-operated pilot plant for the VRC.
- Facility Approval Timelines
  - Facility approvals initiated in Jan 2003
  - D&F approved in June 2003
  - Oct 2003 final HHS comments to NIH for award of task to SAIC
Expansion of the VRC & VCMP Mission

• After 9/11 attacks, the mission of the VRC & VCMP expanded from providing clinical lots of HIV vaccines to expeditiously developing, manufacturing and testing vaccines against potential bioterrorism agents.

• To implement this enhanced mission, the scope, and subsequently the size, of the facility expanded to include adequate processing capacity for potential biodefense vaccine candidates.
The VPP Facility

Facility Scope

- Increased scope for biodefense and emergency*use
  - From: initial design of 1 small (100L) and 2 medium-scale (400L)
  - To: 2 small, 1 medium and 1 large (2000L) bulk production suites
- Drug product filling capacity up to 30K vials/lot (15K current)
- Multiple locations considered during facility planning
- Meeting with FDA for facility design prior to construction
- Full GMP utilities and Equipment
  - SS bioreactors
  - Disposable media prep and fluid handling equipment utilized
Current Projects in the VPPL and VCMP
# Projects in the VPPL and VPP

<table>
<thead>
<tr>
<th>Disease</th>
<th>pDNA</th>
<th>Adeno</th>
<th>VLP</th>
<th>mAb</th>
<th>rProtein</th>
<th>MVA-Pox</th>
<th>AAV</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>X</td>
<td>X, IP</td>
<td>IP</td>
<td>IP</td>
<td>TBD</td>
<td>IP</td>
<td>IP</td>
<td>IP</td>
</tr>
<tr>
<td>Filovirus</td>
<td>X</td>
<td>X, IP</td>
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<td>IP</td>
<td>IP</td>
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<td></td>
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</tr>
<tr>
<td>CHIKV</td>
<td>X</td>
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<td></td>
<td></td>
<td></td>
<td>IP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WEVEE</td>
<td>IP</td>
<td></td>
<td>IP</td>
<td>IP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Universal Influenza</td>
<td>X, IP</td>
<td></td>
<td>IP</td>
<td>IP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **X**: Complete
- **IP**: In-progress
Production of Products by the VCMP

- VCMP has the ability to manufacture products at VPP or via subcontract

- **Make (VPP) – Buy (Subcontract) Product Decision**
  - Products developed in the VRC research labs utilizing new technology will be developed within the VPPL and produced at VPP (VLP, nanoparticle, rProtein)
  - Products developed in the VRC research labs utilizing platform or collaborator technology may be produced at VPP or via subcontract (pDNA, Ad5, mAb, ChAd3)
  - Products developed in the VRC research labs utilizing commercially available technology will be considered for production via subcontract (large-scale mAb, MVA, AAV, reagent production, CLD & formulation development)
# Production at VPP or Subcontractor

<table>
<thead>
<tr>
<th>Disease</th>
<th>pDNA</th>
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<th>VLP</th>
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<th>rProtein</th>
<th>MVA-Pox</th>
<th>AAV</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>VPP</td>
<td>Sub &amp; VPP</td>
<td>Sub &amp; VPP</td>
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<td>Sub</td>
<td>Sub</td>
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<tr>
<td>Filovirus</td>
<td>VPP</td>
<td>Sub &amp; VPP</td>
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<td>Sub</td>
<td>Sub</td>
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<tr>
<td>CHIKV</td>
<td>VPP</td>
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<td>VPP</td>
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<tr>
<td>WEVEE</td>
<td>VPP</td>
<td></td>
<td>VPP</td>
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</tr>
<tr>
<td>Universal Influenza</td>
<td>VPP</td>
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<td>VPP</td>
<td></td>
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<td>VPP</td>
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</table>
VPPL Development and VCMP Production - Actual Success Stories

2009 Pandemic Influenza Vaccine

A Chikungunya VLP Vaccine
DNA Vaccine Development Timeline - An Example
Swine-Origin Influenza A (A/California/04/2009 (H1N1))

- **April 1, 2009**: La Gloria, Veracruz Mexico, 60% population sickened by Respiratory illness
- **Late March 2009**: First case in USA
- **April 1, 2009**: 1st isolate completely sequenced (A/California/04/2009 (H1N1))
- **April 25, 2009**: VRC received the flu sequence
- **May 15, 2009**: 2nd Gen Codon optimized plasmids received at VRC
- **May 20, 2009**: First mice studies initiated at VRC
- **May 28, 2009**: Plasmid received at Pilot Plant
- **June 4, 2009**: cGMP MCB Complete
- **June 9, 2009**: cGMP Bulk Complete
- **June 10, 2009**: cGMP Filled Drug Product Complete
- **June 21, 2009**: VRC Vaccine Pilot Plant Releases Vaccine
- **July 21, 2009**: cGMP Filled Drug Product Complete
- **August 5, 2009**: FDA Release of VRC Product
- **August 24, 2009**: Influenza Phase I Clinical Trial Initiated at VRC/NIAID
Chikungunya VLP-Based Vaccine
CHIKV Genome & Production Plasmid

Chikungunya genome

<table>
<thead>
<tr>
<th>NS1</th>
<th>NS2</th>
<th>NS3</th>
<th>NS4</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
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</table>

nonstructural

C  E3  E2  6K  E1

core  envelope

VLPs constructs: C-Env

<table>
<thead>
<tr>
<th>C</th>
<th>E3</th>
<th>E2</th>
<th>6K</th>
<th>E1</th>
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<tr>
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</tr>
</tbody>
</table>
CHIKV cGMP Development and Production

VPPL Development
- Serum-free HEK-293 cell line
- Upstream process development
- Downstream process development
- Analytical development
- Formulation development (contracted by SAIC-F)

VPP Manufacturing
- Tech transfer from VPPL to VPP of process and assays
- Bulk manufacturing
- Drug product manufacturing
- Lot release testing
- On-going stability testing
Chikungunya Virus Vaccine Program

2009/2010
- CHIKV VLP vector development
- CHIKV VLP vector development
- CHIKV VLP vector development
- CHIKV VLP vector development

2011
- CHIKV VLP cGMP Production
- CRADA and License with Merck for Phase II and further development
- CHIKV VLP cGMP Tech Transfer
- CHIKV VLP cGMP Tech Transfer

2012 (and beyond)
- CHIKV Vaccine Phase I Trial
- Expand VLP model to additional alphaviruses (WEVEE)
- CHIKV VLP platform for vaccine delivery
- CHIKV VLP platform for vaccine delivery

Vaccine Candidates

Research Studies

Technology and Resources

VRC293 Cell Line for cGMP Production

CHIKV VLP platform for vaccine delivery
Examples of VCMP Sourcing for Specific Needs
<table>
<thead>
<tr>
<th>Name</th>
<th>Purpose</th>
<th>LTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access Bio</td>
<td>Tox/PK Consulting</td>
<td>$6,000</td>
</tr>
<tr>
<td>Bavarian Nordic</td>
<td>CMO (MVA)</td>
<td>$3,336,000</td>
</tr>
<tr>
<td>California Institute of Technology</td>
<td>rAAV Research</td>
<td>$4,528,530</td>
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<tr>
<td>GenVec</td>
<td>CMO (rAd)</td>
<td>$5,667,685</td>
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<tr>
<td>Lampire Biological Laboratories, Inc.</td>
<td>Reagent Development</td>
<td>$101,388</td>
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<tr>
<td>Lonza Sales AG</td>
<td>CMO (bnMAb)</td>
<td>$8,457,510</td>
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<tr>
<td>Science Applications International Corp</td>
<td>Regulatory</td>
<td>$238,137</td>
</tr>
<tr>
<td>SRI International</td>
<td>Preclinical Tox</td>
<td>$545,710</td>
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<tr>
<td>TBD - Pending Selection</td>
<td>CMO (rAAV)</td>
<td>$2,000,000</td>
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<tr>
<td><strong>Grand Total</strong></td>
<td></td>
<td><strong>$24,880,961</strong></td>
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## VRC Active Subcontracts Through VCMP

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<thead>
<tr>
<th>Name</th>
<th>Purpose</th>
<th>LTD</th>
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<tbody>
<tr>
<td>Beth Israel Deaconess Medical Center</td>
<td>Lab Animal Medicine</td>
<td>$1,200,000</td>
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<tr>
<td>BioQual</td>
<td>Lab Animal Medicine</td>
<td>$2,375,362</td>
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<tr>
<td>Dr. Lynn Morris (University of Witswatersrand)</td>
<td>VRC Structural Biology</td>
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<tr>
<td>Duke University Medical Center</td>
<td>Lab Animal Medicine</td>
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<tr>
<td>Full Spectrum Genetics, Inc.</td>
<td>VRC Structural Biology</td>
<td>$150,000</td>
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<tr>
<td>Kansas State</td>
<td>Lab Animal Medicine</td>
<td>$115,000</td>
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<tr>
<td>Tulane National Primate Research Center (TNPRC)</td>
<td>Lab Animal Medicine</td>
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<tr>
<td>University of Kentucky Research Foundation</td>
<td>Lab Animal Medicine</td>
<td>$51,782</td>
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<td>University of Michigan</td>
<td>Lab Animal Medicine</td>
<td>$200,000</td>
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<td>University of Texas Medical Branch</td>
<td>Lab Animal Medicine</td>
<td>$418,415</td>
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<tr>
<td></td>
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<td><strong>Grand Total</strong></td>
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Tracking In-House Project Costs to the Value of the Delivered Products
Cost Efficiency of VCMP

VCMP Cost and Output Product Value by Fiscal Year
2007 - 2011
Cost Efficiency of VCMP

Expense Cash Flow of the VCMP
(Product Value Determined from Available CMO Sources)

FY2007 - FY2011

Fiscal Year

2006 2007 2008 2009 2010 2011 2012

Net Cash Flow ($ million)

$0 $50 $100 $150

$70 $103 $105 $107 $99

FY2007 - FY2011
Cost Efficiency of VCMP

Example of Single Year Analysis

<table>
<thead>
<tr>
<th>FY2011 Products</th>
<th>Bulk (g or L)</th>
<th>Vials</th>
<th>Value</th>
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<tbody>
<tr>
<td>ChikV VLP Tox Lot</td>
<td>16</td>
<td></td>
<td>$1,153,679</td>
</tr>
<tr>
<td>ChikV VLP GMP1</td>
<td>16</td>
<td></td>
<td>$1,153,679</td>
</tr>
<tr>
<td>ChikV VLP GMP2</td>
<td>16</td>
<td></td>
<td>$1,153,679</td>
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<tr>
<td>ChikV VLP GMP3</td>
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<td>$1,153,679</td>
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<tr>
<td>ChikV VLP GMP4</td>
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<td>$1,153,679</td>
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<tr>
<td>FluPerth Fill</td>
<td>2665</td>
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<td>$1,037,446</td>
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<tr>
<td>ChikV Fill</td>
<td>782</td>
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<td>$304,421</td>
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<td>ChikV Fill</td>
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<td>ChikV Fill</td>
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<td>$119,900</td>
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<tr>
<td>VLP Tech Transfer</td>
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<td></td>
<td>$600,000</td>
</tr>
<tr>
<td>HIV mosaic pDNA9663</td>
<td>4.6</td>
<td></td>
<td>$1,334,000</td>
</tr>
<tr>
<td>Flu Perth pDNA 2439 mosaic DNA</td>
<td>24</td>
<td></td>
<td>$6,960,000</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td></td>
<td></td>
<td><strong>$16,336,713</strong></td>
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Tracking Responsiveness to Critical VRC Deadlines
# In-House – Outsource Comparison

## VRC01 GMP Production

<table>
<thead>
<tr>
<th>Key Activity</th>
<th>Original Target</th>
<th>Actual Completion</th>
<th>Difference</th>
<th>Yield (g)</th>
<th>Target</th>
<th>Actual</th>
</tr>
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<tbody>
<tr>
<td>MCB Production*</td>
<td>26-Dec-11</td>
<td>15-Dec-11</td>
<td>-11d</td>
<td></td>
<td>188.0</td>
<td>55.2</td>
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<tr>
<td>130L Pilot Bulk #1 (Tox)**</td>
<td>5-Feb-12</td>
<td>15-Dec-11</td>
<td>-52d</td>
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<td>188.0</td>
<td>110.6</td>
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<tr>
<td>130L Pilot Bulk #2</td>
<td>14-Jun-12</td>
<td>14-Jun-12</td>
<td>0</td>
<td></td>
<td>188.0</td>
<td>110.6</td>
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<tr>
<td>GMP Documentation</td>
<td>9-Feb-12</td>
<td>14-Jun-12</td>
<td>+130d</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GMP Batch Bulk Production**</td>
<td>12-Mar-12</td>
<td>16-Aug-12</td>
<td>+157d</td>
<td>2,880.0</td>
<td>1,268.0</td>
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</tr>
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</table>

* Duration of 18 months from start of cell line development to MCB production

** Pilot #1 process deviations required Pilot #2 to be produced. The GMP batch included significant process deviations resulting in product loss and reprocessing.

## 2012-2013 Seasonal Influenza pDNA Trivalent Vaccine Production

<table>
<thead>
<tr>
<th>Key Activity</th>
<th>Original Target</th>
<th>Actual Completion</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Strain Announcement</td>
<td>23-Feb-12</td>
<td>N/A</td>
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<tr>
<td>Plasmid Construct Avail.</td>
<td>6-Mar-12</td>
<td>30-Jan-12</td>
<td>-28d</td>
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<tr>
<td>B/Wisconsin GMP Bulk</td>
<td>16-Mar-12</td>
<td>2-Mar-12</td>
<td>-10d</td>
</tr>
<tr>
<td>A/Victoria GMP Bulk</td>
<td>23-Mar-12</td>
<td>21-Mar-12</td>
<td>-3d</td>
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<tr>
<td>Final Vaccine fill</td>
<td>4-Apr-12</td>
<td>22-Mar-12</td>
<td>-9d</td>
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<tr>
<td>Ship to Clinical Sites</td>
<td>29-May-12</td>
<td>23-May-12</td>
<td>-4d</td>
</tr>
<tr>
<td>Protocol Activated/First enrollment</td>
<td>7-Jun-12</td>
<td>4-Jun-12</td>
<td>-3d</td>
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</tbody>
</table>
Summary
VCMP – Contract Responsibilities

Support to the NIAID Vaccine Research Center (VRC)

The VRC cGMP pilot plant shall be leased and operated by the Contractor with major responsibilities to include, but are not limited to:

- **Support** all aspects of GMP development,
- **Establish and manage** the production, testing, and QA release for Phase I/II products;
- **Establish** manufacturing processes suitable for eventual manufacture by VRC partners;
- **Comply** with U.S. Food and Drug Administration regulations as is appropriate to meet compliance-level requirements for each product manufactured.
- **Manufacture** Phase I/II clinical lots of candidate vaccines utilizing appropriate cGMP standards;
- **Support** the development activities at the VPPL;
- **Maintain** Quality Systems to support manufacturing of candidate vaccines by other VRC Contractors;
- **Participate** in technology transfer of manufacturing processes as projects are transferred from VPPL to the VCMP
- **Develop and maintain** regulatory Master Files and CMC sections to support all active INDs

**Track record for products from the VCMP since 2006:**
- 28 INDs.
- Supporting 54 clinical protocols
- With 22 drug product types (plus 4 placebo types)
- Produced and released 46 drug product lots and 17 placebo lots