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

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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 Neutalizing 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

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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

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Current Projects in the VPPL and VCMP

Projects in the VPPL and VPP

Disease	Product Type							
	pDNA	Adeno	VLP	mAb	rProtein	MVA -Pox	AAV	NP
HIV	X	X, IP		IP	TBD	IP	IP	
Filovirus	X	X, IP				IP		
CHIKV	X		X					
WEVEE	IP		IP					
Universal Influenza	X, IP				IP			IP

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

Disease	Product Type Produced at (VPP) or Subcontractor (Sub)							
	pDNA	Adeno	VLP	mAb	rProtein	MVA-Pox	AAV	NP
HIV	VPP	Sub & VPP		Sub & VPP	VPP	Sub	Sub	
Filovirus	VPP	Sub & VPP				Sub		
CHIKV	VPP		VPP					
WEVEE	VPP		VPP					
Universal Influenza	VPP				VPP			VPP

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VPPL Development and VCMP Production

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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))

2009

Mid March 2009

La Gloria, Veracruz Mexico 60% population sickened by Respiratory illness

Late March 2009

First case in USA

April 1, 2009

First 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

Jun 4, 2009

cGMP MCB Complete

Jun 9, 2009

cGMP Bulk Complete

Jun 10, 2009

cGMP Filled Drug Product Complete

July 21, 2009

VRC Vaccine Pilot Plant Releases Vaccine

August 5, 2009

FDA Release of VRC Product

August 24, 2009

Influenza Phase I Clinical Trial Initiated at VRC/NIAID

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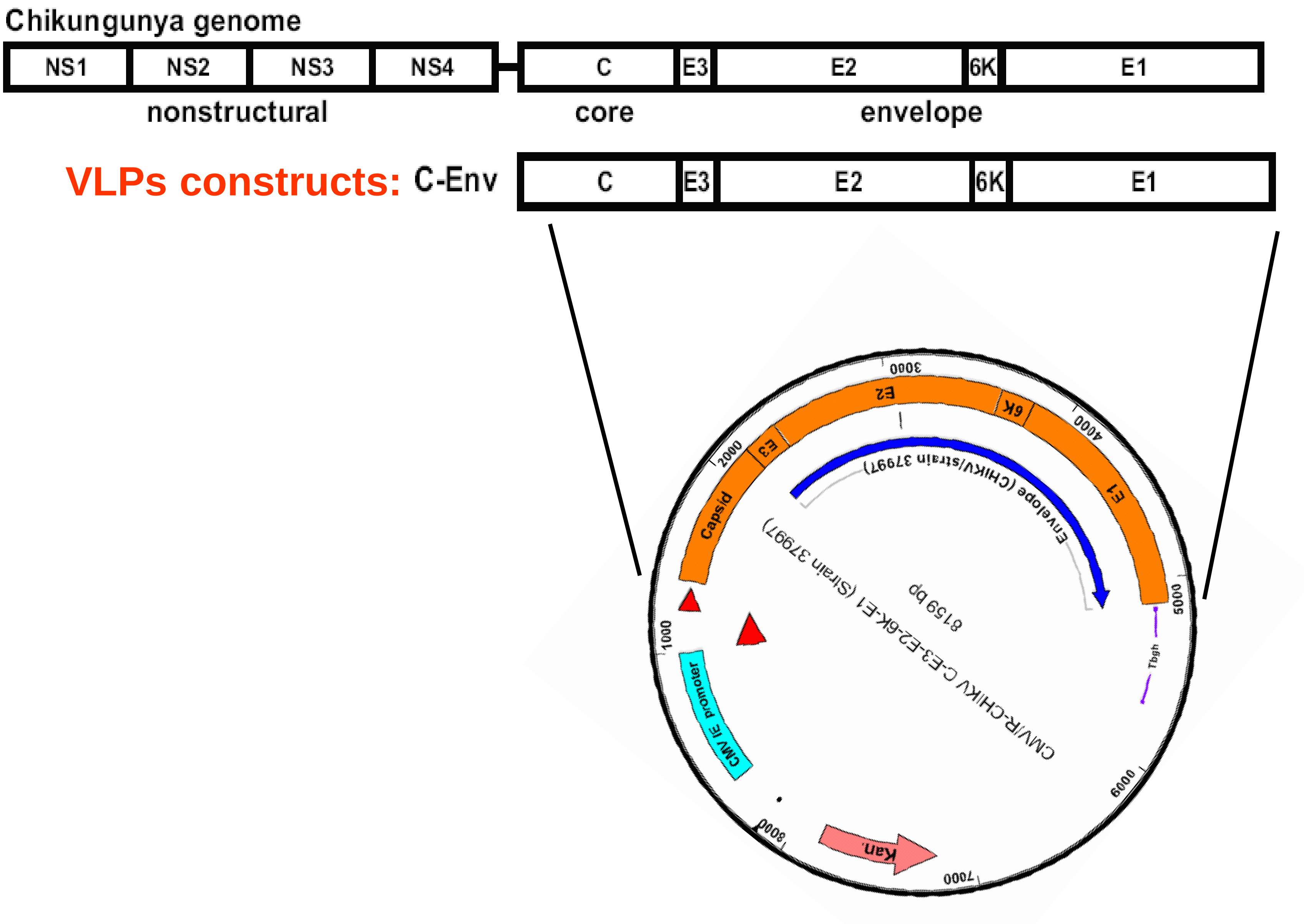
Chikungunya VLP-Based Vaccine

CHIKV Genome & Production Plasmid



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	2011	2012 (and beyond)

Vaccine Candidates

- CHIKV VLP vector development
- CHIKV VLP cGMP Production
- CHIKV Vaccine Phase I Trial
- CHIKV VLP cGMP Tech Transfer
- CRADA and License with Merck for Phase II and further development

Research Studies

- Expand VLP model to additional alphaviruses (WEVEE)

Technology and Resources

- VRC293 Cell Line for cGMP Production
- CHIKV VLP platform for vaccine delivery

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Examples of VCMP Sourcing for Specific Needs

VRC Active Subcontracts Through VCMP

Name	Purpose	LTD
Access Bio	Tox/PK Consulting	$6,000
Bavarian Nordic	CMO (MVA)	$3,336,000
California Institute of Technology	rAAV Research	$4,528,530
GenVec	CMO (rAd)	$5,667,685
Lampire Biological Laboratories, Inc.	Reagent Development	$101,388
Lonza Sales AG	CMO (bnMAb)	$8,457,510
Science Applications International Corp	Regulatory	$238,137
SRI International	Preclinical Tox	$545,710
TBD - Pending Selection	CMO (rAAV)	$2,000,000
Grand Total		**$24,880,961**

VRC Active Subcontracts Through VCMP

Name	Purpose	LTD
Beth Israel Deaconess Medical Center	Lab Animal Medicine	$1,200,000
BioQual	Lab Animal Medicine	$2,375,362
Dr. Lynn Morris (University of Witswatersrand)	VRC Structural Biology	$50,000
Duke University Medical Center	Lab Animal Medicine	$547,332
Full Spectrum Genetics, Inc.	VRC Structural Biology	$150,000
Kansas State	Lab Animal Medicine	$115,000
Tulane National Primate Research Center (TNPRC)	Lab Animal Medicine	$1,061,440
University of Kentucky Research Foundation	Lab Animal Medicine	$51,782
University of Michigan	Lab Animal Medicine	$200,000
University of Texas Medical Branch	Lab Animal Medicine	$418,415
Grand Total		**$6,169,331**

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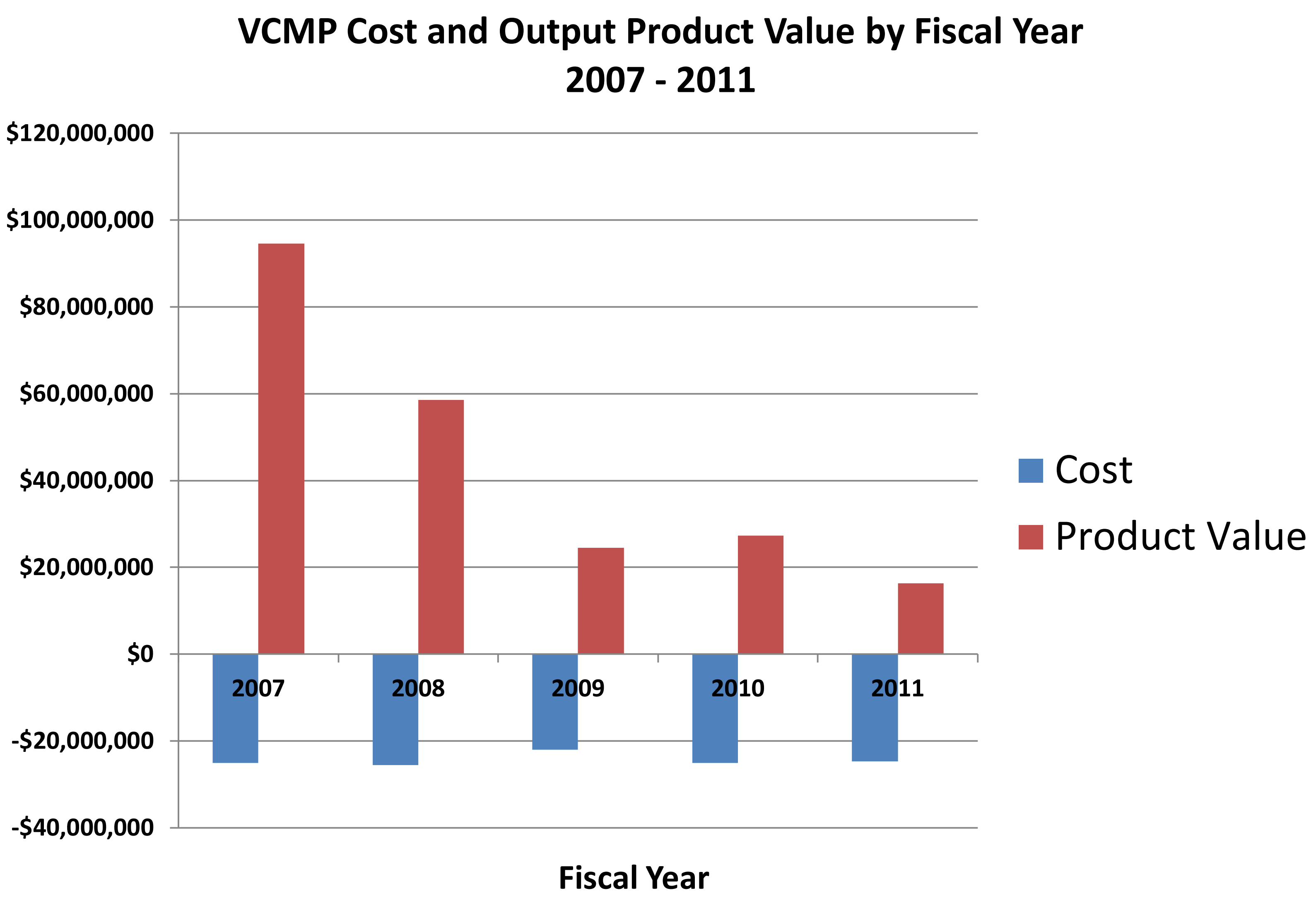
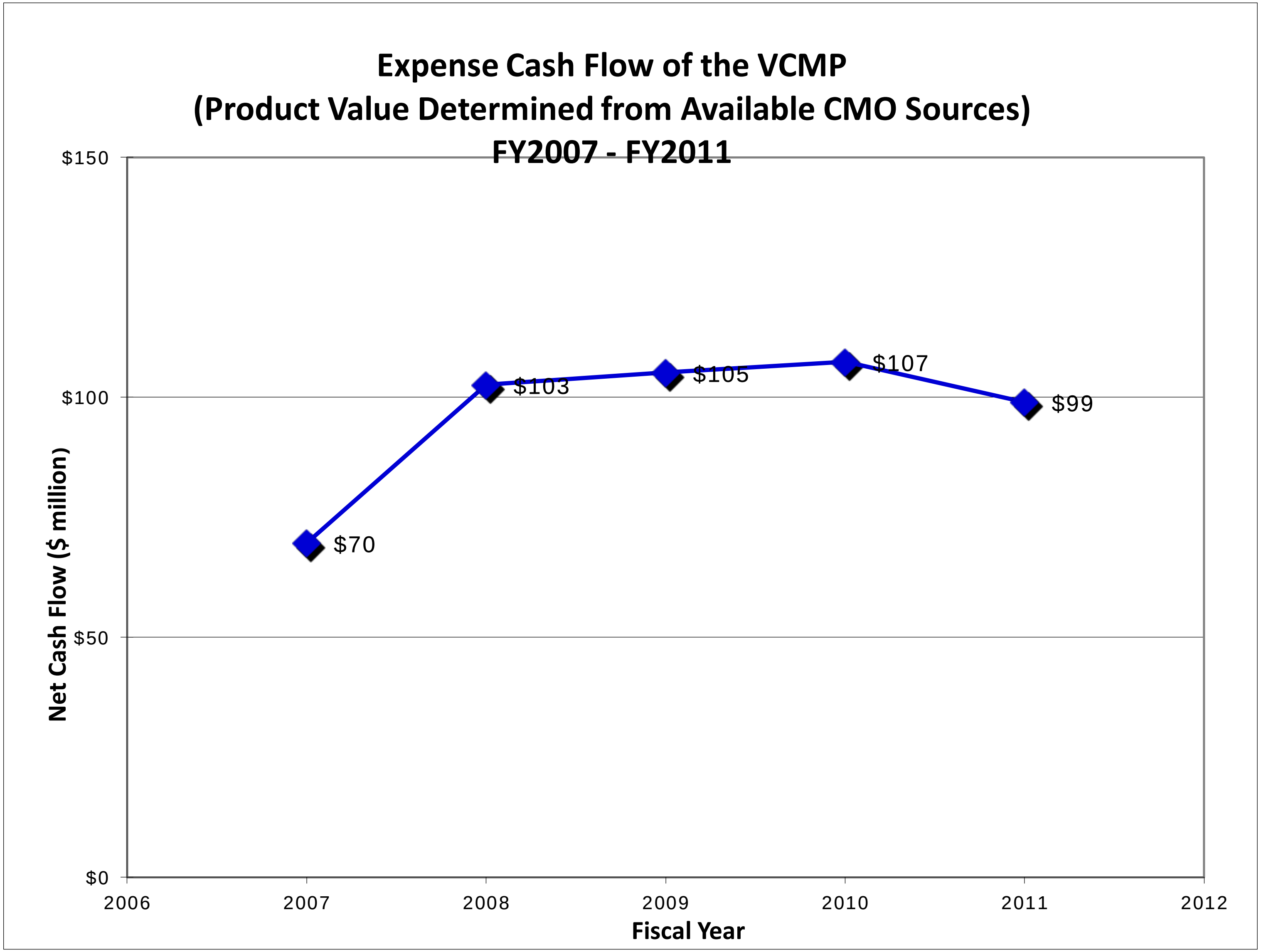
Tracking In-House Project Costs to the Value of the Delivered Products

Cost Efficiency of VCMP



Cost Efficiency of VCMP



Cost Efficiency of VCMP

Example of Single Year Analysis

FY2011 Products	Bulk (g or L)	Vials	Value
ChikV VLP Tox Lot	16		$1,153,679
ChikV VLP GMP1	16		$1,153,679
ChikV VLP GMP2	16		$1,153,679
ChikV VLP GMP3	16		$1,153,679
ChikV VLP GMP4	16		$1,153,679
FluPerth Fill		2665	$1,037,446
ChikV Fill		782	$304,421
ChikV Fill		546	$212,550
ChikV Fill		308	$119,900
VLP Tech Transfer			*$600,000*
HIV mosaic pDNA9663	4.6		$1,334,000
Flu Perth pDNA 2439 mosaic DNA	24		$6,960,000
		Total:	$16,336,713

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Tracking Responsiveness to Critical VRC Deadlines

In-House – Outsource Comparison

VRC01 GMP Production

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

** 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

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

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***