Overview of the One Health Plus Biocorridor

Integrated Advanced Development and Manufacturing of Vaccines and Therapeutic

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Assoc. PI- TAMUS Center for Innovation

One Health PLUS™ Biocorridor

The Texas A&M Center for Innovation in Advanced Development & Manufacturing
Biomedical Objective

Radically accelerate translation of life saving therapeutics and devices “from the bench to the patient”

- Integrated, multidisciplinary, holistic enterprise
- Research and innovation driven
- Emphasizes veterinary, agriculture, and engineering aspects of therapeutics, global health, and biosecurity
One Health Plus Biocorridor™ Map

- Emphasis on plant, animal, human health and clean water
- Encompasses research and discovery, preclinical studies, manufacturing and clinical studies
- Connects academia with small innovative biotech industry, pharmaceutical partners and leading non profit institutions
The New Reality of Emerging Diseases

The Natural Threat

Emergence of new, virulent pathogens
(50 appeared since 1973)

H5N1  SARS

Transportation assures rapid global spread of emerging diseases

The world’s deadliest bioterrorist
Nature likes biological weapons more than human villains do

April 28, 2012
The Escalating Threat of Bioterrorism

Bioterrorism Report Card: U.S. unprepared

October 12, 2011

Bio-Engineered Threat

Synthetic Biology: Microbes Made to Order

Science
29 February 2008

November 2011

Should a New Recipe for Engineered Bird Flu, Potent Enough to Kill Millions, Be Published?

Terrorists try to infiltrate UK's top labs

The security services have intercepted up to 100 suspects posing as postgraduate students who aim to acquire weapons material and expertise
The Pandemic Wake-Up Call

April 27, 2009
U.S. Declares Public Health Emergency
Over Swine Flu

Edgar Hernandez
Patient Zero - March 2009

Pandemic Declared- June 11, 2009

1918

H1N1, US, 2009-2010
• 60.8 million cases
• 274,000 hospitalizations
• 12,469 deaths
“Vaccine stockpiles are not merely impractical, they are hubristic. Future biological threats are likely to be unannounced and unfamiliar.... Furthermore, epidemiological forecasts and threat assessments are notoriously unreliable.”

Dr. Kendall Hoyt
Long Shot: Vaccines for National Defense
Objective: Develop technologies that would allow the deployment of 100 million doses of a safe and effective vaccine/therapeutic within 16 weeks of a new pathogen emergence
**The New York Times**

Friday, November 26, 2010

**Texas A&M Stakes Claim as Leader in Pharmaceuticals**

“...a confluence of factors had primed Bryan and neighboring College Station... to be the country’s “third coast” of pharmaceutical manufacturing, with dozens of companies cropping up in the next 5 to 10 years ...”

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**Austin American-Statesman**

Saturday, April 2, 2011

**Biotechnology is new breed of business at Texas A&M**

"They are building a little Sunnyvale down there," Callahan said, referring to a city at the center of California’s Silicon Valley. "I don't find that kind of sparkle anywhere else. That is what we need for this big, big problem."
“And we are launching a new initiative that will give us the capacity to respond faster and more effectively to bioterrorism or an infectious disease - a plan that will counter threats at home and strengthen public health abroad.”

President Barack Obama
State of the Union
January 2010

“Our Nation must have the nimble, flexible capacity to produce MCMs rapidly in the face of any attack or threat, known or unknown, including a novel, previously unrecognized, naturally occurring emerging infectious disease.”

U.S. Department of Health and Human Services
The Public Health Emergency Medical Countermeasures Enterprise Review
August 2010
Centers for Innovation in Advanced Development and Manufacturing

Objectives

- Develop a national response capability to manufacture pandemic influenza vaccines for the U.S. population
  (50 million doses in 4 months: implies new cell-based or recombinant vaccine; Global pharmaceutical partner must be “anchor tenant”)

- Manufacture biothreat vaccines and medical countermeasures for the U.S. Strategic National Stockpile (SNS)
  (CBRN: Current requirements are for 17 products)

- Lead the development of new vaccines and countermeasures from ~Pre-IND through licensure
  (animal models, pivotal animal studies, clinical trials, regulatory submissions, etc.)

- Train the U.S. workforce in all aspects of vaccine and MCM development
TAMUS: CIADM Prime Contractor

TAMUS is the central administrative office responsible for management, oversight, and coordination of all nineteen System components

- Develops and approves the System budget: currently >$3.3 billion annually
- Manages all major construction projects: >$1 billion average ongoing projects
- Co-Manages State of Texas Permanent University Fund: ~$12 billion market value exclusive of land
- Additional responsibilities
  - Approves all academic programs, degrees, tenure decisions, etc.
  - Hires CEOs and academic leadership
  - Manages intellectual property, technology commercialization, legal affairs, research administration
  - Establishes policy framework and guidance
  - Provides leadership for Research Institutes of critical importance and high complexity
Why is TAMUS the Prime?

**Translational Life Sciences Initiatives Anticipated CIADM Requirements**

- Focused on *intermediate and advanced development* of vaccines, therapeutics, devices, and diagnostics
- Integrated, multidisciplinary, innovation-driven enterprise

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**Texas A&M Institute for Preclinical Studies (2007)**

Dedicated large animal GLP R&D program emphasizing model development, validation, and imaging: academic, commercial, USG customers

**National Center for Therapeutics Manufacturing (2009)**

First-in-class, flexible, multi-product, surge ready, cGMP biomanufacturing using mobile, modular clean rooms: the proof of concept for the CIADM flexible facilities

**DARPA “Blue Angel Program” and DoD “Vaccine Rapid Response Center” (2010)**

World’s largest “Next Generation” capability; industrialized and scaled Plant Made Vaccines and Pharmaceuticals
The leading national program to conduct comprehensive preclinical/GLP large animal studies to markedly enhance the quality and speed of drug and device development.

Opened: December 3, 2009
Texas A&M Institute for Preclinical Studies
Facilities and Equipment

- Primary focus on CV and oncology; BSL-2
- Entire College of Veterinary Medicine for “reach back”
- 4 OR suites, cardiac cath lab, ICU
- GLP Clinical Pathology
- 3T MRI with XMR
- 128 Slice PET/CT/cyclotron
- PET-MRI in development
- Sponsor workspaces; incubator space for start-ups

'Hibernation' research could help on battlefield, at home (12/20/2009)
Objective: Perform the research and development required to deliver a *candidate pandemic influenza bulk antigen*, expressed in plants, at a scale of 1 kilogram per month (scalable to 10 kg per month)

- Texas Plant Expressed Vaccine Consortium (TAMUS and G-Con, LLC)
- 2.2M *N. benthamiana* plants
- Downstream purification and fill/finish in MBUs
- Fully operational 15 months post-award
Biopharmaceutical manufacturing research, development, and production facility

- Flexible-by-design, multi-product, multi-technology architecture; mobile clean-room MBUs
- Accommodates all “best of breed” flexible bioprocess technologies
- Personalized therapeutics to moderate scale bioreactors (1000 L)
- Lowers initial capital outlay by ~5X and reduces operational costs
- Facilitates surge or product changeover
- Phase 1, Phase 2, and Phase 3 transition studies
- Educational programs for workforce training
- Supported by a $50 million competitive award from State of Texas Emerging Technologies Fund
The National Center for Therapeutics Manufacturing (NCTM)
Schematic Design Completed April 2010

- cGMP Wing: ~104,000 ft²
- Academic Wing: ~48,000 ft²
Aerial View (June 2011) of the NCTM

Construction Completed August 2011
Modular Biomanufacturing Units (MBU)

Class 1,000 - 10,000 (BSL-1 to BSL-3)

- Requires only electrical hook-up and chilled water
- Air-bearings allow pod to be pushed onto flat bed truck for transport
- Superstructure 42 x 18 feet
- Redundant core systems with automatic failover
“Gray Space”
MBU Utility Access (from inside gray space)
FDA Formal Type C Meeting – August 18, 2010
All NCTM concepts feasible and appropriate
Kalon Biotherapeutics, LLC

- **Kalon Biotherapeutics, LLC** is a private, limited liability company owned by The Texas A&M University System (the “System”)
  - Formed in 2011 to serve as the “corporate operator” of the cGMP portion of the National Center for Therapeutics Manufacturing (NCTM)
  - 10-year commercial facility operation and use agreement for exclusive use of the NCTM cGMP space and portions of academic space
  - Preparing the NCTM for cGMP compliant manufacturing by April 2012 in support of Phase 1 and Phase 2 clinical trials
    - Preparing for client-specific IND filing and Phase 1 work in May 2012
  - National recruitment of highly skilled and talented professionals with substantial cGMP experience for key executive and managerial positions
Kalon Business Model to Support Large and Small Scale Customers
Academic to Large Pharmaceutical Companies

Kalon Business Model

- Serve as an “integrator” of services starting from drug discovery through clinical trials
  - Process development
  - Regulatory, IND filings
  - Phase 1, 2 and 3 “run in” manufacturing

- Contract manufacturing (“Option A”) – provide turnkey contract manufacturing services for therapeutics at the NCTM

- Facility access and use (“Option B”) – lease of space/MBUs within NCTM and core support services

- Additional services
  - MBU and equipment procurement, commissioning, qualification and validation
  - Supply chain, materials management, cold chain, quality control, assays and testing, high purity utilities
Trained workforce critical for biopharmaceutical industry

Adjacency of academic and cGMP areas designed to foster to intermingling of industry and government experts with students.

The academic wing of the NCTM has >50,000 sq.ft. of training space, including:

- Two teaching wet labs (40 students each)
- Cell culture facility
- Computer laboratory with 50 work stations
- 3,500 sq. ft. cubicle study and teaming area
- Locker facilities for 100 students
- “Mock cGMP” process suite with gowning facilities, Sartorius and GE bioreactors and AKTA skids to simulate an commercial environment
- Two large lecture halls for students and conferences
- Foyer can be used for conferences, events
TAMUS is the Prime Contractor / System Integrator

Final Proposal Team

INTEGRATED BIOPHARMACEUTICAL COMPANIES
- GlaxoSmithKline Biologicals (Belgium)

ACADEMIC INSTITUTIONS
- Baylor College of Medicine (Texas)
  - Sabin Vaccine Institute
  - Vaccine Research Unit
  - Texas Children’s Hospital
- UTMB-Galveston National Laboratory
- University of Florida
- Blinn College (Texas)

BIOPROCESS TECHNOLOGY PROVIDERS
- Sartorius (Germany)
- GE Healthcare (Sweden)
- deltaDOT (UK)

TAMUS COMPONENTS
- Texas A&M University
  - TAMU Institute for Preclinical Studies (TIPS)
- Texas Engineering Experiment Station (TEES)
- Texas Engineering Extension Service (TEEX)
- Texas Veterinary Medical Diagnostic Laboratory (TVMDL)
- Texas A&M Research Foundation (TAMRF)

NON-PROFIT RESEARCH INSTITUTES
- Lovelace Biomedical and Environmental Research Institute (New Mexico)
- Texas Biomedical Research Institute (Texas)
- Mary Crowley Research Center (Texas)

COMMERCIAL PARTNERS
- Kalon Biotherapeutics (Texas)
- Lonza Houston (Texas)
- PPD, Inc. (North Carolina)
- NDA Partners (California)
- Caliber Biotherapeutics (Texas)
- Noesys Data (Texas)
Workforce Development

Biotherapeutics Manufacturing and Advanced Development Training Programs
Texas Workforce Commission Grant Awarded
Began Phase I: Curriculum Assessment & Industry Surveys

DECEMBER

Began Phase II: SME Kick-off & Course Pre-Work

MARCH

Begin Phase III: Curriculum Development

JUNE

Phase IV: Course Finalization & Submission
COE courses begin in NCTM

JANUARY

Ini.ated Internship Program

FEBRUARY

Begin Phase II: SME Kick-off & Course Pre-Work

MARCH

Initiated Internship Program

MAY

Initiated Development of Marketing Materials

OCTOBER

All levels of curricula complete

MARCH

Inaugural STEM Summer Camp begins

JUNE

All Therapeutics Manufacturing courses scheduled to begin

SEPTEMBER

2010

Established Program Advisory Board

FEBRUARY

2011

2012

2010

2011

2012

NATIONAL CENTER FOR THERAPEUTICS MANUFACTURING EDUCATION PROGRAMS TIMELINE
### EXISTING THERAPEUTICS MANUFACTURING EDUCATION PROGRAMS

<table>
<thead>
<tr>
<th>Program Type</th>
<th>Courses</th>
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</thead>
<tbody>
<tr>
<td><strong>Associate-Level Certificate</strong></td>
<td>Intro to Biotechnology, Intro to Therapeutics Manufacturing, Good Manufacturing Practices, Cell Culture Techniques, Drug Substance Manufacturing, Drug Product Manufacturing, Facility Operations &amp; Safety, Quality Systems for TM Lab Instrumentation, etc.</td>
</tr>
<tr>
<td><strong>Bachelor-Level Certificate</strong></td>
<td>Biosafety, Bioreactors &amp; Bioprocessing, Bioprocess Control, Bioseparations, Designing for Flexibility, Lean Thinking/Lean Manufacturing in Biotechnology, Safety in Pharmaceutical and Biotechnology Industries</td>
</tr>
<tr>
<td><strong>Master-Level Degree (PPiB)</strong></td>
<td>Biotechnology Principles &amp; Techniques, Molecular Biotechnology, Biotech Writing, Special Topics, Directed Internship, Technology Commercialization, Strategic Entrepreneurship, etc.</td>
</tr>
<tr>
<td><strong>Short Courses &amp; Workshops</strong></td>
<td>Customized training programs based on existing modules and/or new material/curriculum</td>
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### EXISTING ADVANCED DEVELOPMENT EDUCATION PROGRAMS

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Centers for Innovation in Advanced Development and Manufacturing
Announced June 18, 2012
• Three contracts awards: TAMUS/GSK, Novartis/NCSU, and Emergent/UMCP.
• Base period awarded for 5.5 years to establish readiness in the CIADM centers.
• Task orders to be issued for the next 25 years in response to BARDA/DHHS needs.
• Task orders may be in R&D, advanced development, manufacturing, and training/education.
• Task orders open only to CIADM awardees.
Opportunities for ISEN

- Near future: workshops and short course development and implementation
  - Lean thinking/lean manufacturing
  - Supply chain management
  - Process optimization
  - Risk analysis
- Future: R&D contracts
Challenges: Egg based production

EGG PRODUCTION

- Adaptation and incubation
- Harvesting
- Purification
- Inactivation
- Formulation and vialing

6 months

9–10 months

US ~60+ million doses
Challenges: seasonal occurrences of influenza
Challenges: Egg based production

- The pandemic could occur off cycle when not enough eggs are available.
- The virus could mutate sufficiently to nullify the potency (immunogenicity) of a vaccine already prepared and stockpiled (i.e., start over).
- H5N1 may not be the ultimate cause of the pandemic (i.e., start over).
- If the pandemic is rapidly contagious, there may not be enough time to produce an adequate supply of vaccine (e.g., difficult to start over).
- Increased worldwide demand from a pandemic, combined with the requirement for seasonal influenza vaccine, would completely overwhelm the programmed seasonal influenza vaccine manufacturing capacity.
- If an avian influenza infected the population of chickens that produce eggs for seasonal influenza vaccine, egg production would cease.
Impediments to change (ISEN related)

- Complex and costly regulatory requirements for new and modified vaccines and their associated manufacturing processes
- Inadequate government funding and/or incentives for innovation in vaccine manufacturing
- Economic and political structures that inhibit cooperation and collaboration, including inadequate protections for manufacturers (e.g., with regard to intellectual property, liability, and cost recovery)
- High production costs of clinical trial materials that limits translation of vaccine research to clinical development
- The global nature of disease and the need for integration of multinational vaccine development, manufacturing, and distribution systems
- Insufficient built-in surge capacity, production agility, adaptability, and modularity to enable sufficiently responsive vaccine manufacturing in case of emergency or unanticipated needs
Improvements Needed (ISEN related)

- Miniaturization, automation, and process integration
- Transfer of materials in a sterile contained and controlled system (particularly lyophilization) with assured security and validation
- Improved waste collection, handling, and disposal
- Improvements in delivery of the vaccine to the patient
- Improvements in product packaging and shipping
- Single-use and disposable equipment for batch production
- Further application of microprocessing technologies and use of integrated microfluidic quality control processes as validated inline test and validation systems
- Storage facilities to bank both master cultures and seed cultures with appropriate safety systems to prevent contamination; more rapid methods for culture expansion
Implementation of FDA cGMP guidance - QbD (other R&D opps)

- To facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- To encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- To ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science
- To enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities
### What was the perceived need?

<table>
<thead>
<tr>
<th>Sigma</th>
<th>ppm Defects</th>
<th>Yield</th>
<th>Cost of Quality</th>
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<tbody>
<tr>
<td>2σ</td>
<td>308,537</td>
<td>69.2%</td>
<td>25-35%</td>
</tr>
<tr>
<td>3σ</td>
<td>66,807</td>
<td>93.3%</td>
<td>20-25%</td>
</tr>
<tr>
<td>4σ</td>
<td>6,210</td>
<td>99.4%</td>
<td>12-18%</td>
</tr>
<tr>
<td>5σ</td>
<td>233</td>
<td>99.98%</td>
<td>4-8%</td>
</tr>
<tr>
<td>6σ</td>
<td>3.4</td>
<td>99.99966%</td>
<td>1-3%</td>
</tr>
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6 σ - World class
5 σ - Superior
4 σ - Healthy
3 σ - Average
2 σ - Not capable
1 σ - Not competitive

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PWC, 2001, *Productivity and the Economics of Regulatory Compliance in Pharmaceutical Production*
New Quality Paradigm - Regulator view of benefits to Industry

- Ensures better design of products with less problems in manufacturing
- Reduces number of manufacturing supplements required for post market changes – rely on process and risk understanding and risk mitigation
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny
- Allows for possible reduction in overall costs of manufacturing – less waste
- Ensures less hassle during review – reduced deficiencies – quicker approvals
- Allows for continuous improvements in products and manufacturing process
- Allows for better understanding of how APIs and excipients affect manufacturing
- Relates manufacturing to clinical during design

Helen Winkle CDER 2007
Flexible manufacturing: F3 initiative in Europe

Consortium of 25 European companies and EU research institutions

**Aims**
- to deliver radically new ‘plug and play’ modular chemical production technology, capable of widespread implementation throughout the chemical industry
- to deliver holistic process design methodology applying process intensification concepts and innovative decision tools

**Objectives**
- design and develop a modular continuous plant (the F³ Factory ‘backbone’ plant in Leverkusen) standardize processes and their interfaces by developing methodologies for whole process design focused on modular plant
- demonstrate the capabilities of the F³ Factory with existing products via seven case studies with the key industrial partners
Questions?