

# **After the License Approval: How Analytics Can Keep You in the Market**

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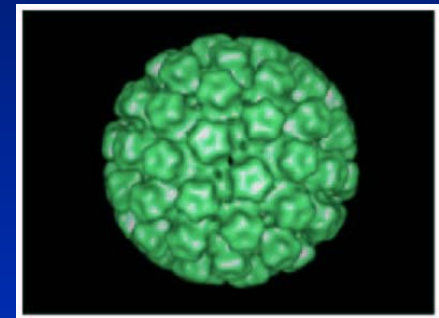
**Vaccine Technology III**  
**June 8, 2010**  
**Nuevo Vallarta**

# Outline

- **Analytical Comparability to accelerate transition from launch to larger facility**
- **Modernization of Assay Procedures for Legacy Vaccines**

# Gardasil<sup>®</sup>: Merck's Recombinant Quadrivalent HPV Vaccine

- L1 major capsid proteins (Types 6,11,16,18) each self-assemble into virus-like particles (VLPs)
- VLPs produced intracellularly in *Saccharomyces cerevisiae*
- VLPs do not contain viral DNA (non-infectious)
- Approved world wide in 2006 to prevent cervical cancer and warts

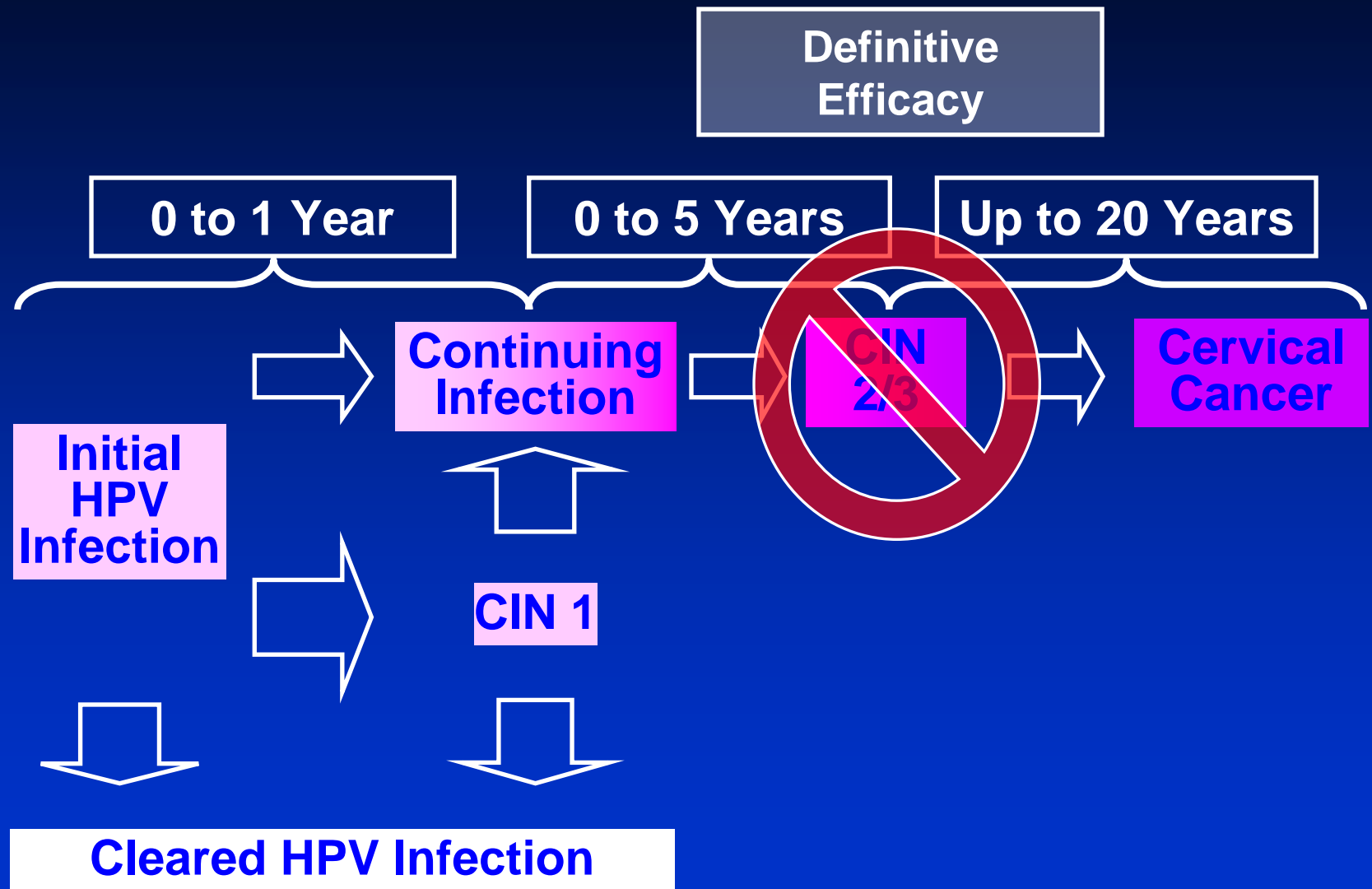


Type 18 VLP

# What Did We Know Early On?

- Animal models
- Early dose ranging looking at antibody response
- No accepted correlate
- Do we have a product?
- What to test in Phase III
- Should we invest in a factory?
- How could we compress the timeline?

# How Do We Show Cancer Efficacy?



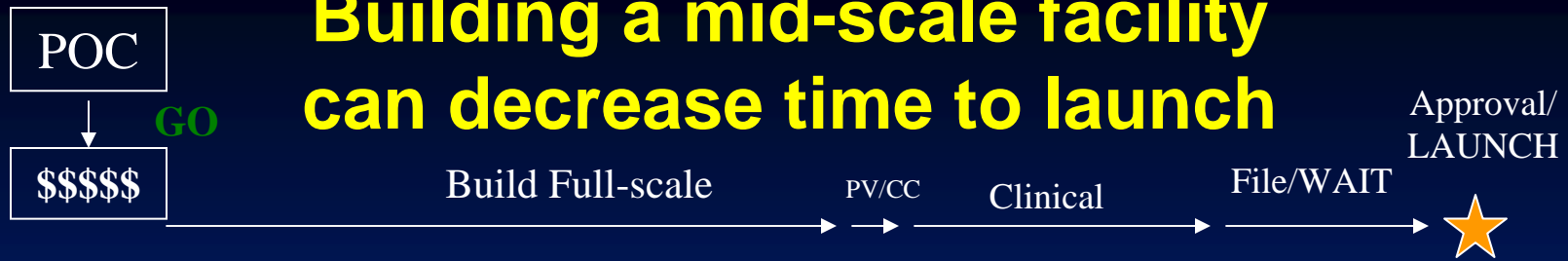
# Manufacturing Strategy

## What are the constraints?

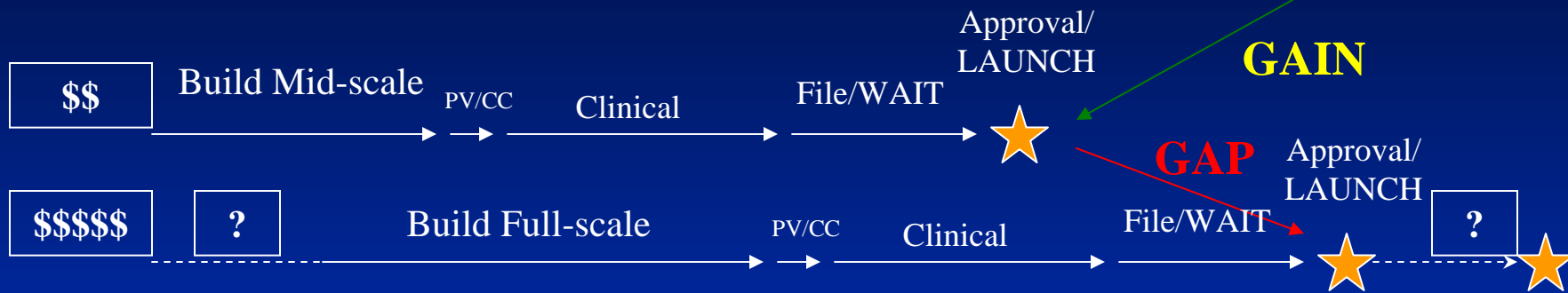
- Clinical studies would take many years
- Proof of concept studies underway
- Early data looks promising
- Need final manufacturing facility for Phase III and manufacturing consistency lots
- Marketing expectations are high
- Properly sized facility years to build
- Proposal to build launch facility (New Products Suite)
- Quicker to build but limited capacity

# Building a mid-scale facility can decrease time to launch

Standard



Alternative



Moderately-scaled facility allows for a **GAIN** in time to filing/launch, but limits supply

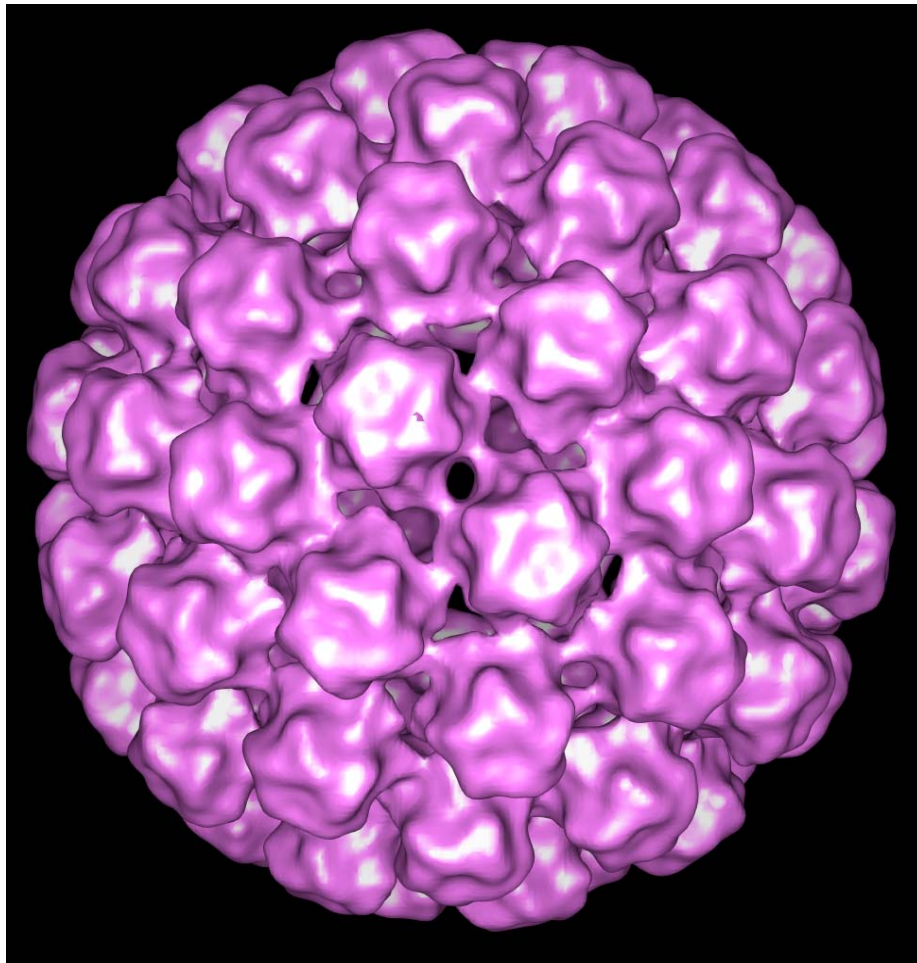
Filling the **GAP** in supply awaits licensure of full-scale facility

# Analytical Comparability

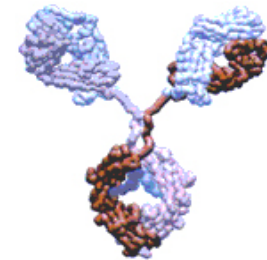
- Used for “specified” or “well-characterized” biologic products such as MABs.
- Facilitate approval of process changes without a clinical trial
- Prospective protocol for documenting process changes
- Can't always state if a change matters.
- Focused testing rather than testing to infinity
- Testing strategy validated with known samples with known differences in performance



# HPV-18 VLP Image Reconstruction (20-Å Resolution *False-color* Image, Cryo-TEM)



IgG Immunoglobulin

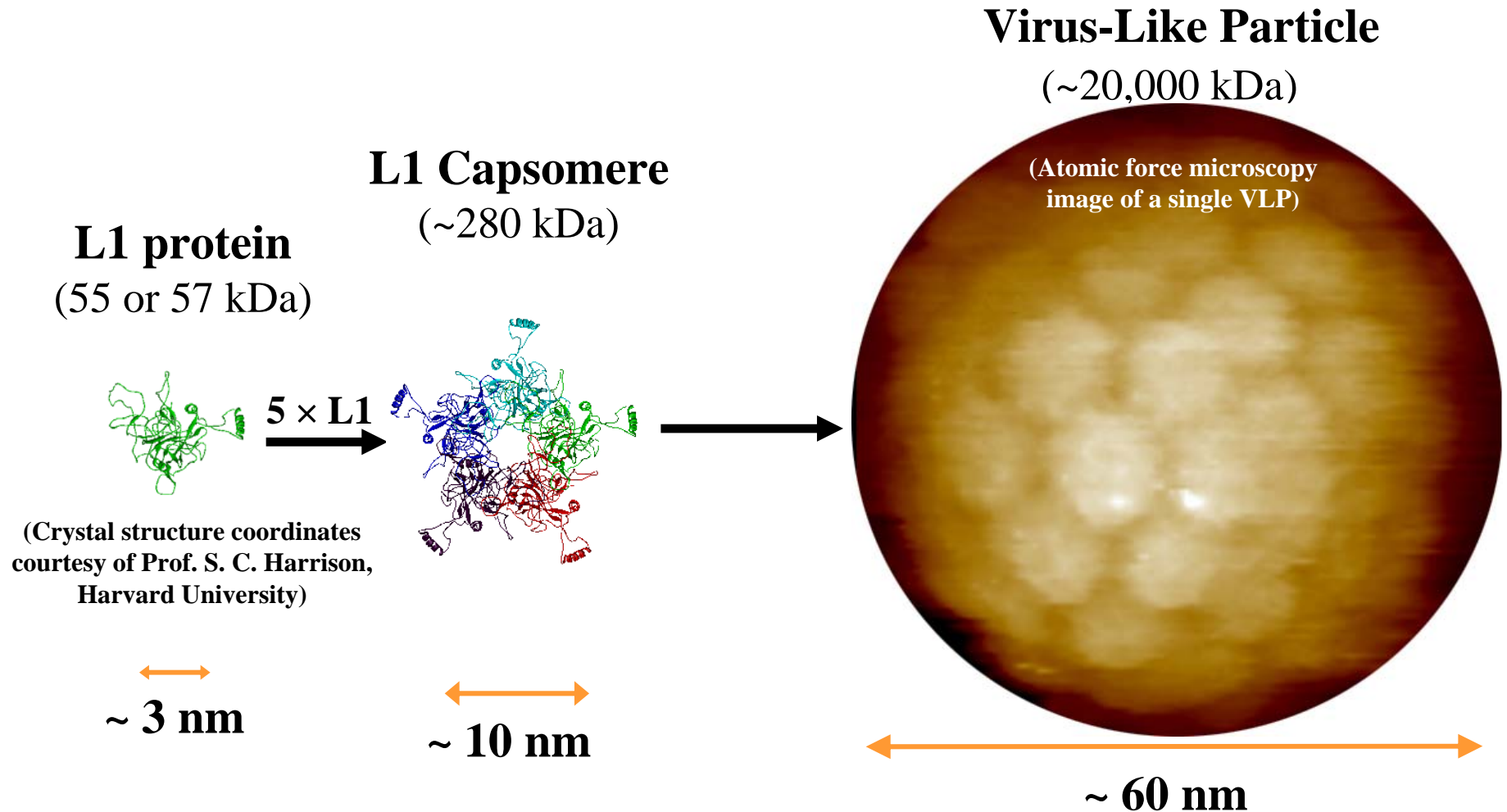


Courtesy of  
NanoImaging Systems

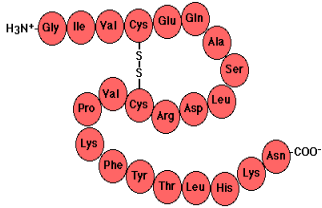
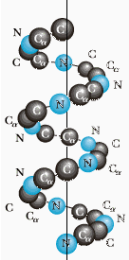
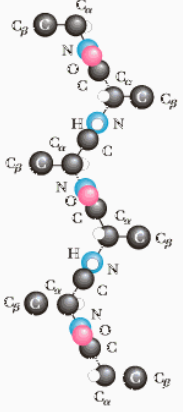
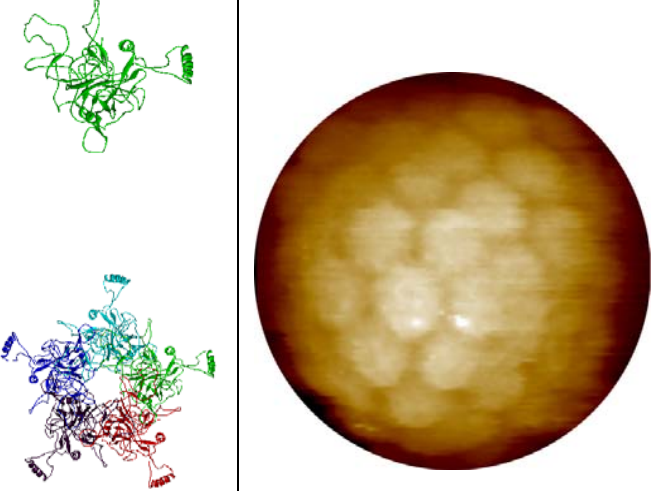
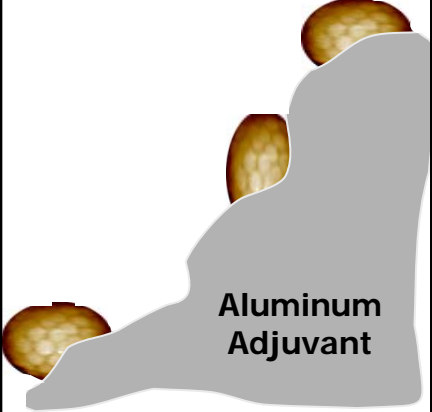
# Comparability Strategy

- Ideal case: Have two samples:
  - Differ in characterization data
  - Differ in process source
  - Differ in “potency” e.g. mouse
  - Differ in clinical performance (!!!!!)
- Will validate that assays are sensitive to significant process changes.

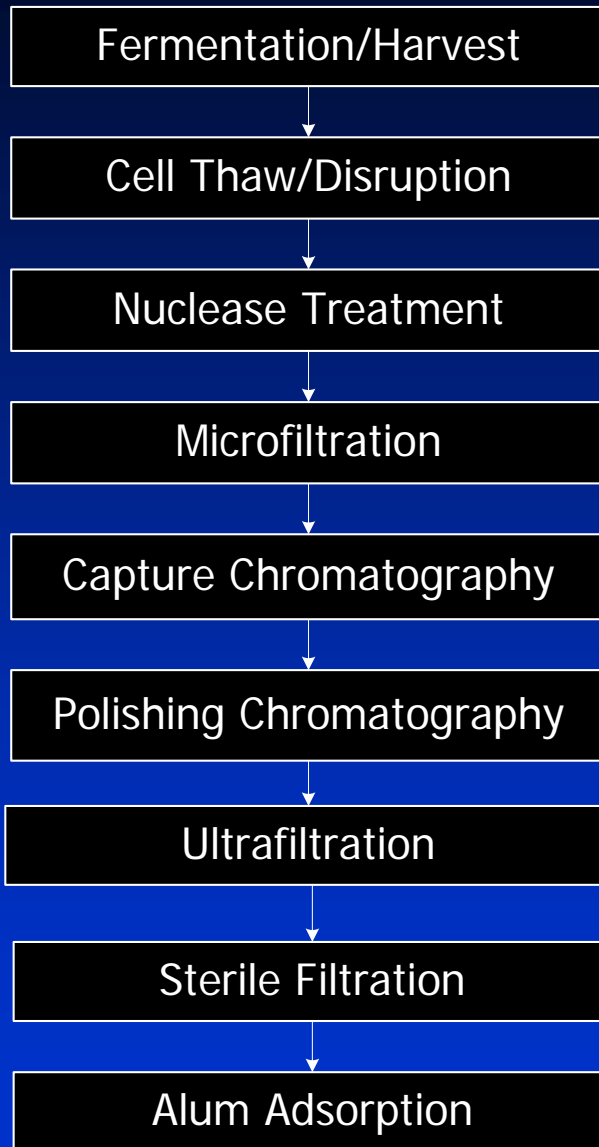
# Structural Model of HPV VLP



# GARDASIL Analytical Characterization

<p><b>Amino Acid Sequence</b></p> 	<p><b><math>\alpha</math>-Helix</b></p>  <p><b><math>\beta</math>-Sheet</b></p> 	<p><b>Assembly</b></p> <p>↔</p> <p><b>Disassembly</b></p> 	<p><b>Adsorption</b></p>  <p><b>Aluminum Adjuvant</b></p>
<p><u>1° Structure</u> Peptide Map, <b>Purity, Integrity, Deamidation</b> &amp; Free Thiols in Denatured Form</p>	<p><u>2° Structure</u> CD &amp; FT-IR</p>	<p><u>3° and 4° Structure</u> <b>DLS, IC<sub>50</sub>, Relative Antigenicity, Free Thiols in Native Form &amp; L1-Oligomer, Cryo-EM</b></p>	<p><u>Adjuvant-Antigen Complex</u> <b>DLS, DSC, IVRP &amp; IC<sub>50</sub></b></p>

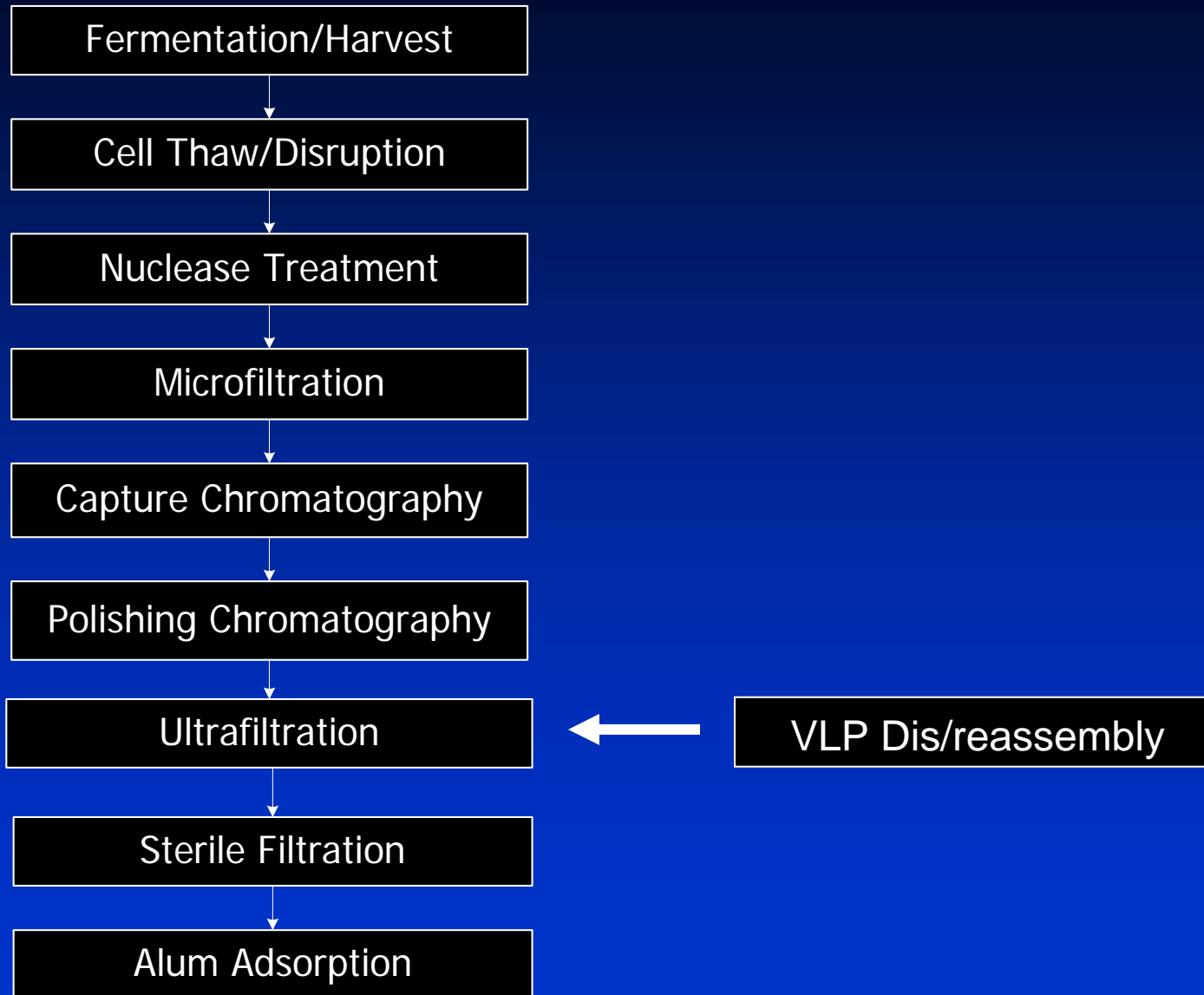
# Manufacturing Process For Early Studies



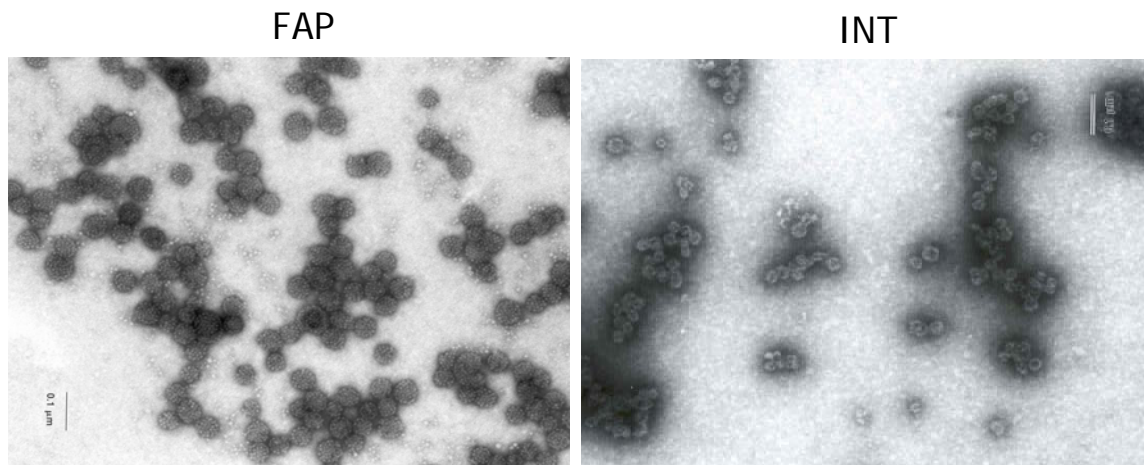
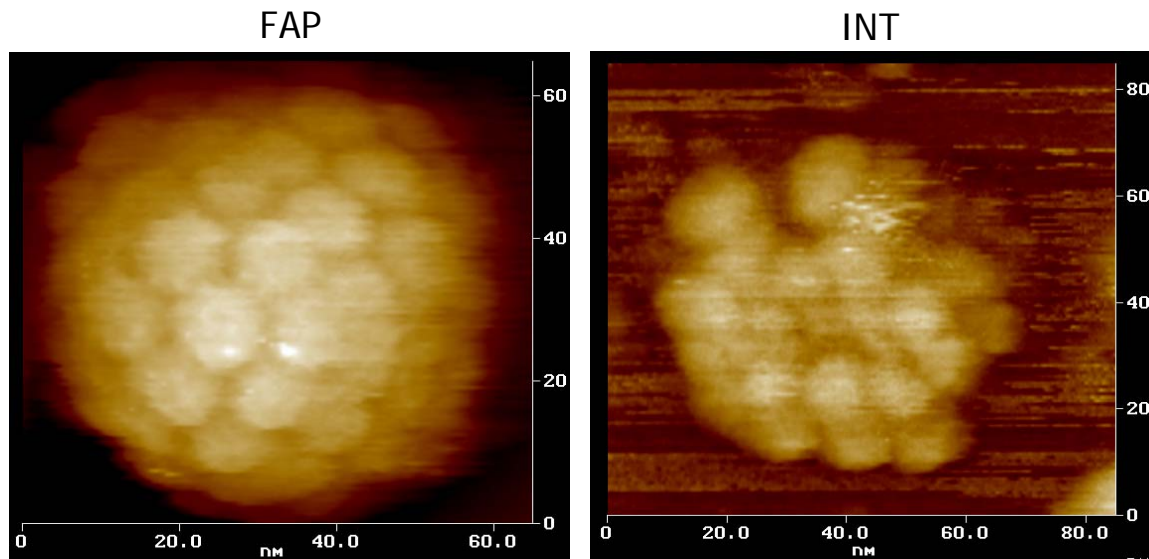
# Prelicensure Process Change

- Introduce disassembly/reassembly before Phase III and Process Validation
- Part of final manufacturing process
- More stable product

# Final Manufacturing Process



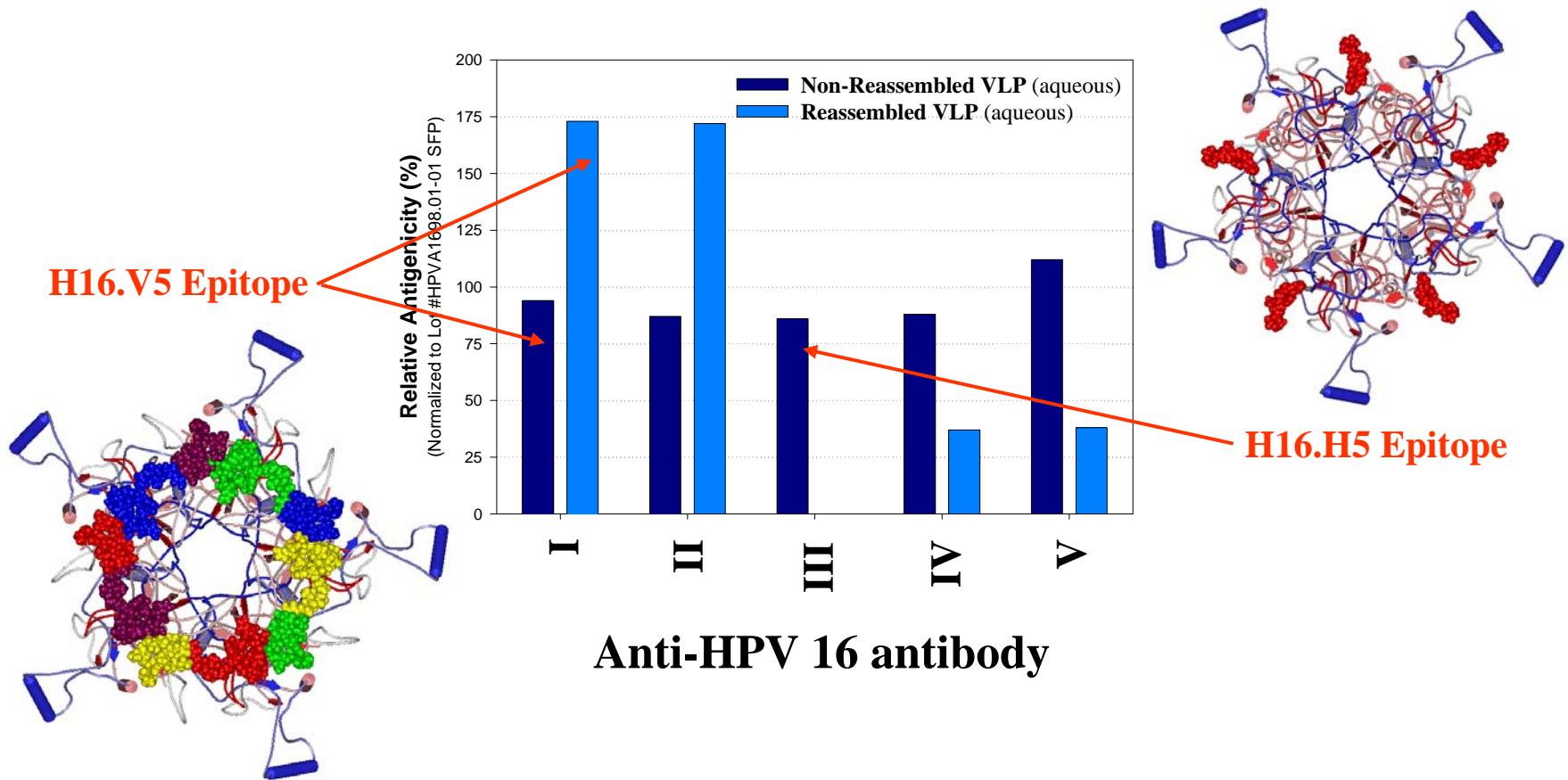
# VLP Characterization by Atomic Force and Transmission Electron Microscopy



TEM Images of HPV-16

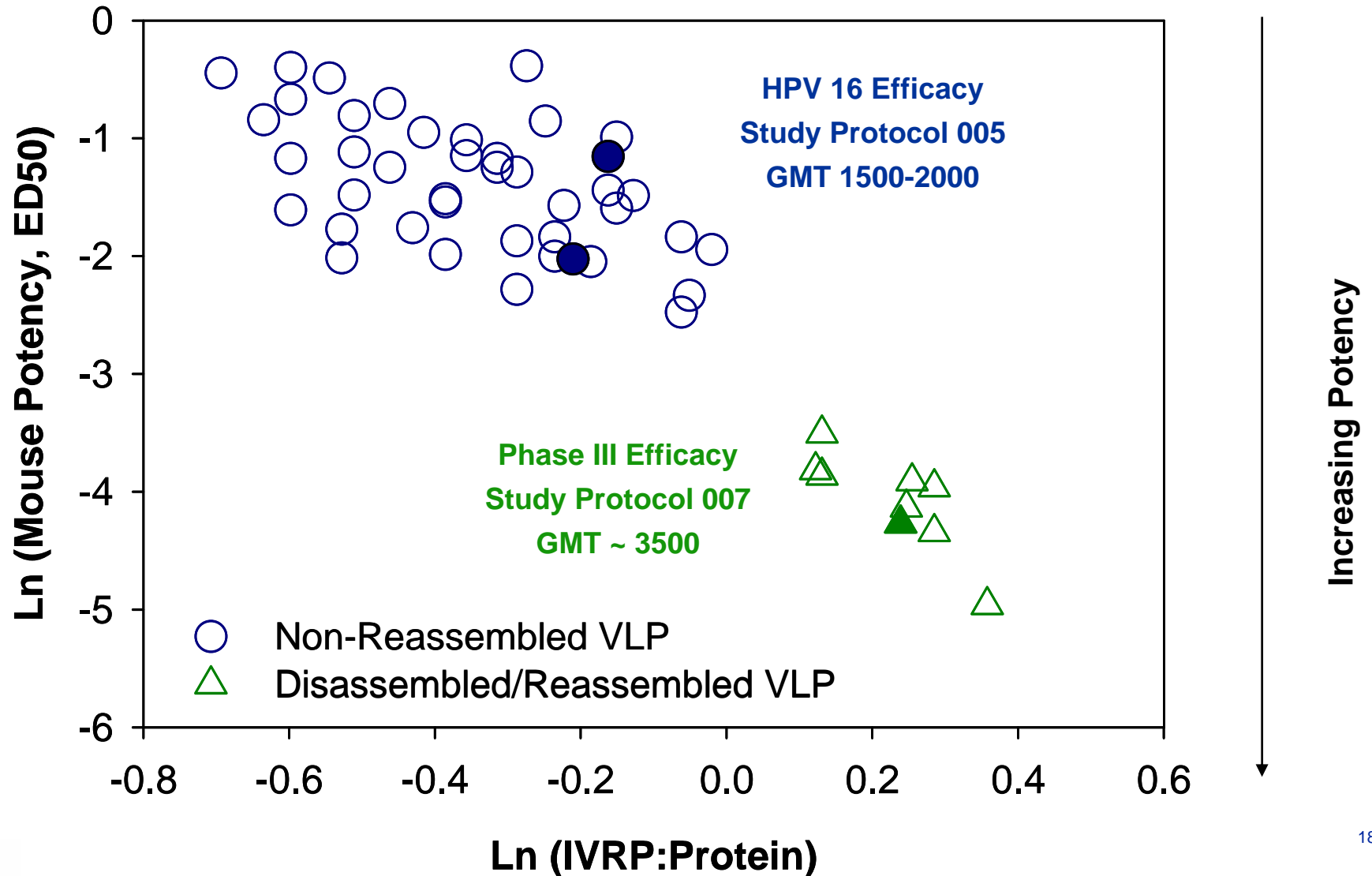


# Relative Antigenicity Comparison between Non-Reassembled and Reassembled HPV16 VLP Samples



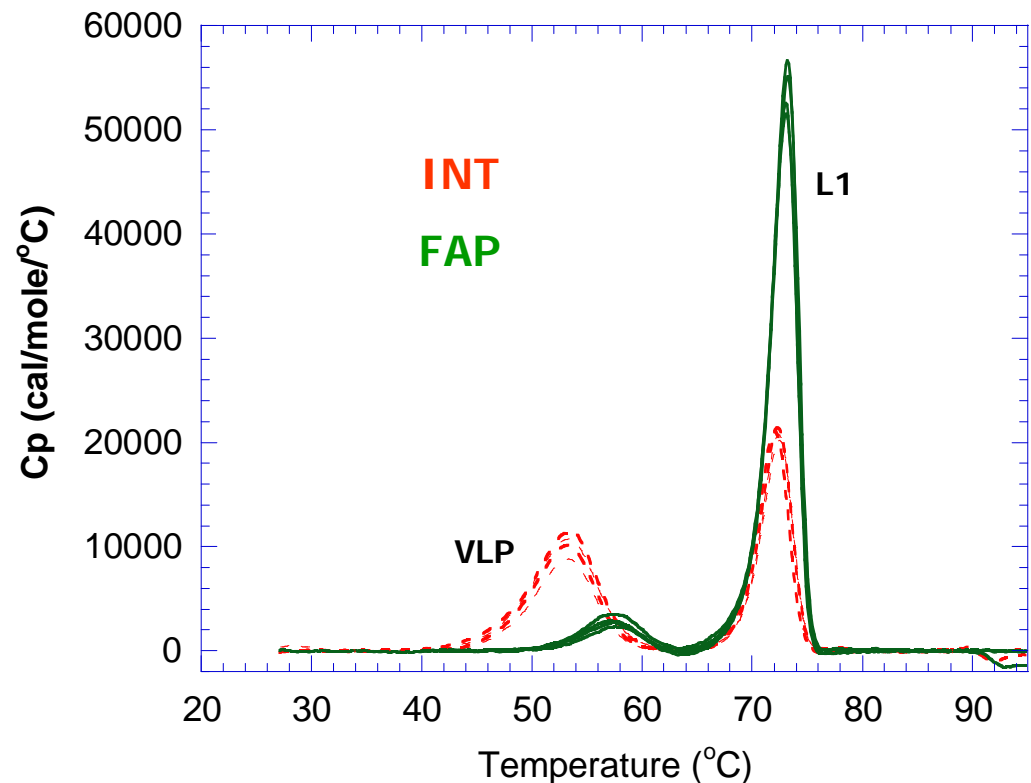
- Antigenicity defined by neutralizing antibody is enhanced.
- Antigenicity defined by antibody against linear epitope is reduced.

# Correlation of IVRP and Immunogenicity Type 16



# Comparability: Differential Scanning Calorimetry

- Measures the change in the heat capacity during thermal unfolding.
- VLPs adsorbed to aluminum adjuvant.
- Distinguishes INT & FAP samples.



# Comparability Strategy

- Ideal case: Have two samples:
  - Differ in characterization data
  - Differ in process source
  - Differ in “potency” e.g. mouse
  - Differ in clinical performance (!!!!!)
- Will validate that assays are sensitive to significant process changes.
- **Criteria met by unassembled/reassembled product pair for Type 16**
- **Concept applied to other types (Type 18 not Reassembled)**

# Manufacturing Strategy

- **New Product Suite constructed**
- **Process validation completed**
- **Phase III and clinical consistency lots manufactured**
- **Facility operated during clinical studies and agency review to build inventory**
- **Extensive characterization testing applied to lots made in New Product Facility**

# Manufacturing Strategy (Ctd)

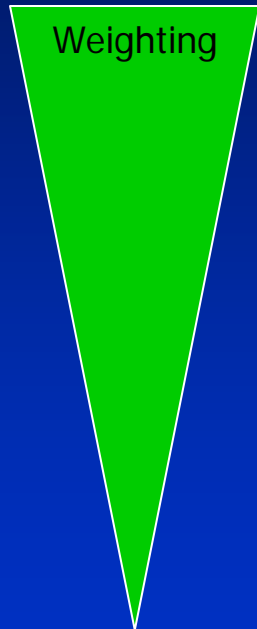
- **Clinical studies completed**
- **BLA filed**
- **New full scale factory completed**
- **PV lots completed in new facility**

# How to Claim Comparability ?

## Two Parts to Comparability

- Demonstrate Process Comparability
- Demonstrate Product Comparability

# Analytical Matrix for Comparability



Method	HPV6			HPV11			HPV16			HPV18		
Release - Potency												
Release – Purity & Integrity												
Mouse Potency												
IC50												
Rel. Antigen.												
DSC												
DLS												
Free Thiols												
Oligomer												
Deamidation												

- Monitor clinically-relevant structural features that are desirable properties of the product.
- Emphasis on release assays & epitope structure (conformation) during manufacture & storage.



# Limits

Limits prospectively established to define potential deviations from comparability

- Provides rigor and credibility

Two types of limits

- Acceptance limits = deviation generally means failure to demonstrate comparability
- Alert limits = deviation results in investigation, but not deemed a failure *a priori*
- Limits must be sufficiently rigorous but not so tight as to cause “nuisance alarms”

# Limits: Product Characterization

## Acceptance and Alert limits

- Release tests
- Process Validation CQAs: impurities

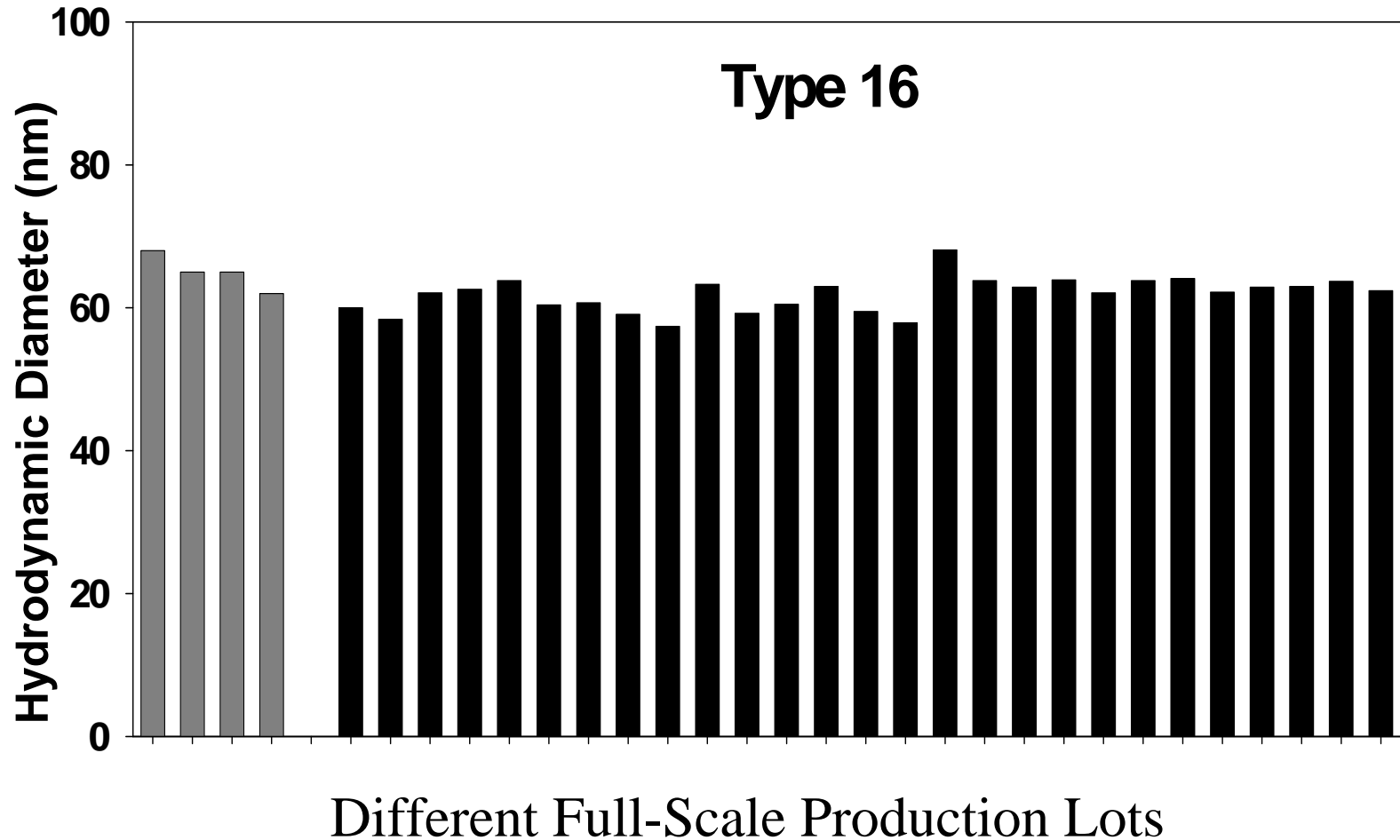
## Alert limits only

- Characterization tests

## Qualitative comparisons

- Some Characterization tests: profiles for intermediate product stability, CD, FTIR

# VLP Size Distribution Characterization by DLS



# Plan Ahead to Manage Deviations

Resources – especially in the lab !

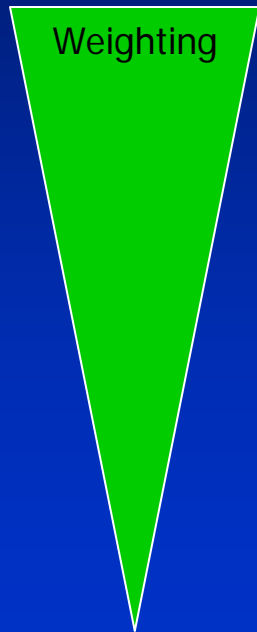
Purification in launch and new facility performed using same inputs to allow direct comparison (“sister lots”)

- Same fermentation cell paste input
- Same lot of chromatography resins

Some analytical tests had very limited history

- Include samples from Phase III lots in the same assay run as the new facility lot

# Results - Analytical Comparability (Drug Substance)



Method	HPV6			HPV11			HPV16			HPV18		
Release - Potency	Green	Green	Yellow	Green	Green	Green	Green	Green	Green	Green	Green	Green
Release – Purity & Integrity	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
Mouse Potency	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
IC50	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
Rel. Antigen.	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
DSC	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
DLS	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
Free Thiols	Green	Green	Green	Green	Green	Green	Green	Green	Yellow	Green	Green	Green
Oligomer	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
Deamidation ➤	<b>All parameters within Acceptance Limits</b>											

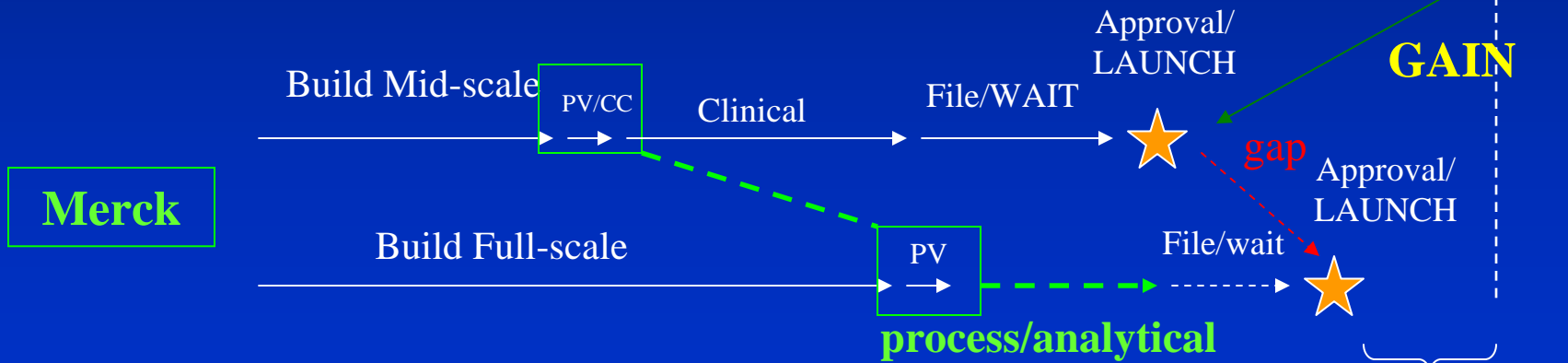
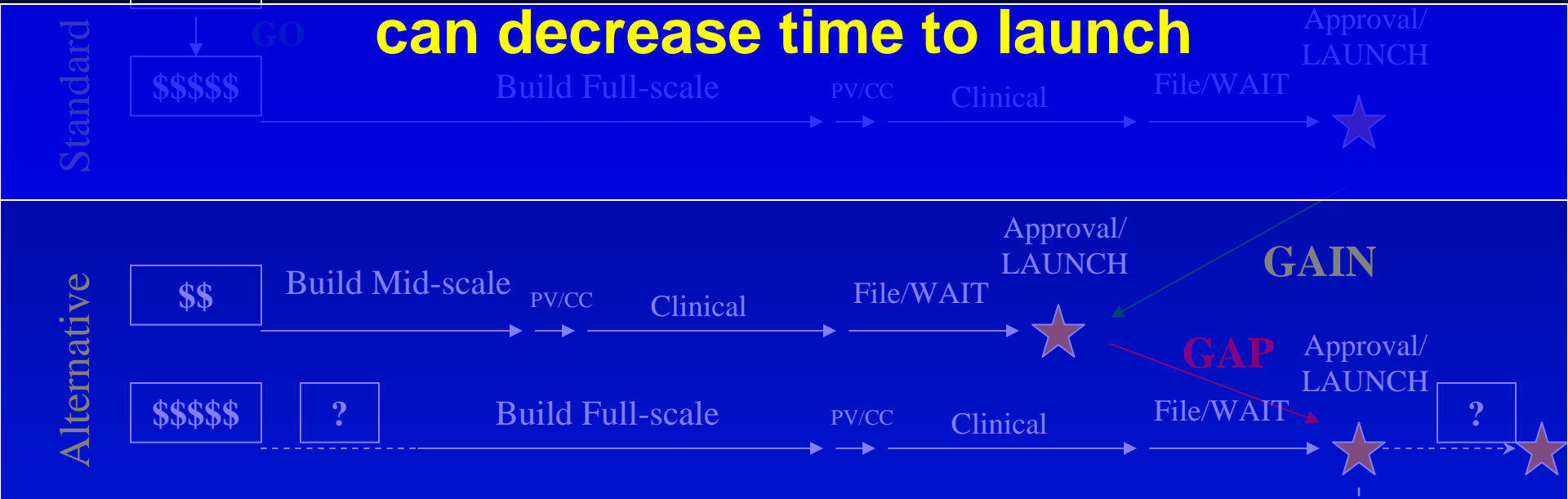
- No Excursions
- Alert Limit Excursion
- Acceptance Limit Excursion

➤ **3 excursions of Alert Limits investigated**

# Results - Analytical Comparability

- All parameters within Acceptance Limits
- 3 excursions of Alert Limits investigated
- New facility approved world wide

# Building a mid-scale facility can decrease time to launch



**GAIN brings a cervical cancer vaccine to market ASAP**

**& provides world-wide supply ASAP**

# Summary

- **Merck leveraged comparability to accelerate licensure of larger-scale facility meeting market demand.**
- A modestly scaled purification facility was used to supply Phase III and launch material
- A larger facility was required to meet expected demand
- Analytical data confirmed comparability of product from both facilities
- A comprehensive analytical characterization package is critical to managing process changes in the development cycle for a vaccine.



# Modernization of Analytical Methods

# Process vs Analytical Changes

- Many vaccines (and Biologics) were licensed years ago with older technology
- Process changes are well accepted in the Biotechnology Industry
- What about changes in Analytical Methods?

# Process Changes

- Numerous Major Process changes have been implemented throughout the years
  - Plasma derived to r-Hepatitis B
  - Whole cell pertussis to acellular
  - Required extensive clinical trials to assure safety and efficacy
- New Facilities, scale up and other process changes are common

# Process Changes

- Process changes are well accepted in the Biotechnology Industry
- Process changes are **forward** looking ie the new lots are distinct from the older process lots
- Release and distribution are unique for new process lots

# Why modernize Analytical Methods?

- Vendors discontinue instrument or reagents
- Improvement in Robustness in existing assay
  - New Format
  - Automation vs manual (different philosophy)
  - More reliable technology
- Agencies encouraging application of modern methods
- Recent FDA Draft Guidance Document on Process Validation – “Continued Process Verification”

# Why modernize Analytical Methods?

- New technology can be more precise and more efficient
- Competitive newer or second generation products bring on newer methods
- New and more precise tools to monitor existing processes and process improvements

# What are the Barriers to implementing New Analytical Methods?

- Will detect new impurities or residuals which were already present
- Concern on looking back
- Difficulty to get concordance data between imprecise and more precise assays.

# Modern “purity” Methods

- New methods like HPLC or CZE have higher resolution and show the presence of new impurities not seen before
- Less of an issue as long as samples of older clinical lots have same components
- **Keep your PV samples!!!**



# Issues on Implementation of Improved Assay Technology

- New methods might have higher precision than older cellular and in vivo based potency methods
- Many potency assays (eg flu, D, T, Pertussis) were originally validated years ago and might have been animal based and quite variable
- How do you correlate a new more precise potency assay to a highly variable assay?
- How do you set specs for a new potency assay?
- Will the new specs applied to older lots?

# Hypothetical Results Old vs New Assay



Old Assay  
Different lots

New Assay

# Issues on Implementation of Improved Assay Technology

- Must equivalency be demonstrated?
- Should the new assay give identical results?
- If the older assay had high variability, difficult to demonstrate equivalence
- Target should be a “superior” assay
  - Higher precision
  - Easier to run
  - Automatable
  - Animal sparing

# Issues on Implementation of Improved Assay Technology

- Concordance vs offset of assay in comparative studies
- Characterize difference
- Pay attention to sample handling and container issues
- Seek agency agreement on statistical approach

# Proposal

- Define principles for dealing with mismatch between highly variable and tighter assay technologies
- Consensus on assay concordance around the industry: new and old assays are not going to be concordant across technologies that are 20-30 years apart in sensitivity and accuracy
- Work through the implementation of new assay methodology thru:
  - Further discussions with agencies on issue
  - Joint Industry – Agency groups
  - PDA?

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