



Reprogramming the Immune System

Validation of the ISS-Based Hepatitis B Vaccine HEPLISAV™ Oligonucleotide Manufacturing Process

Mark C. Guzman
Director, Technical Affairs

Presentation Outline

- Three-Company Collaboration
- Process Definition
- Process Validation
- Outcomes

A Collaborative Effort

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Technology and Manufacturing Solutions
for the Biopharmaceutical Industry



DYNAVAX
DYNAX TECHNOLOGIES

Karen Clark

Ivonne Cruz

Kevin Fettes

Patrick Foster

Paul McCormac

J.P. Rodrique

Christian Zdybowicz

David Fetterolf

Patrick Giljum

Becky McCuen

Jon Demeter

Martin Gohlke

Bob Milley

Rowena Ng

Dao Ton-Nu

Stephen Tuck

Collaboration Structure

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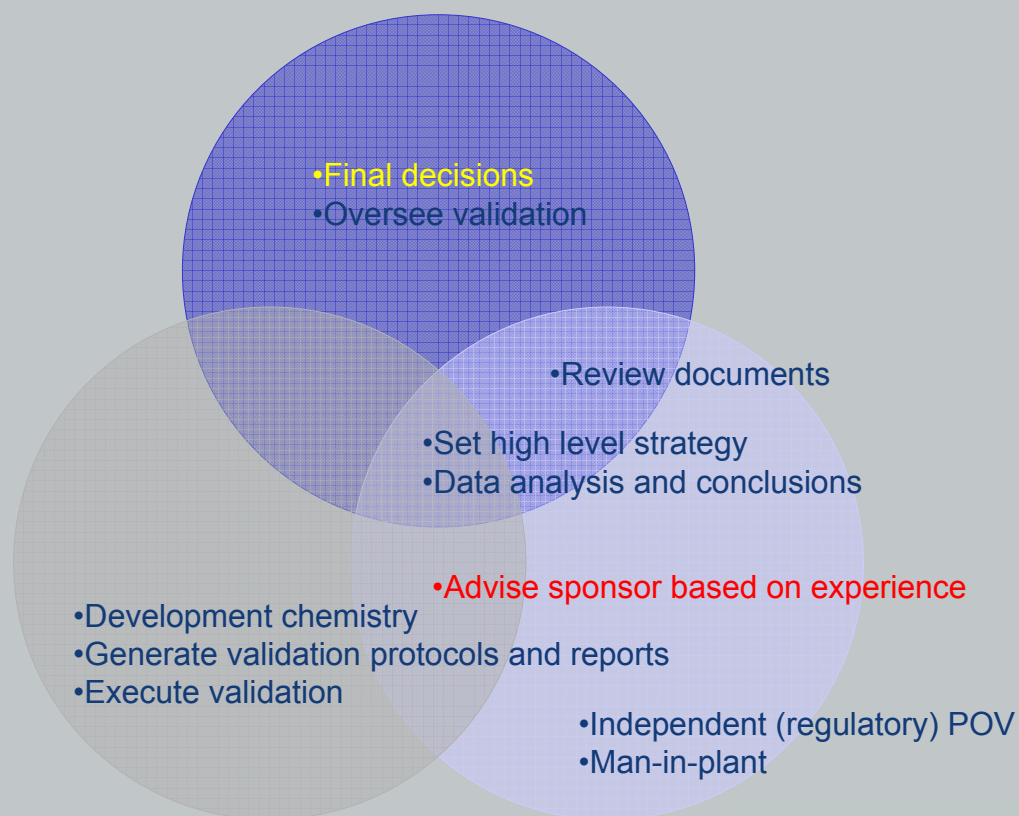


DYNAVAX
DYNAX TECHNOLOGIES

- Management
- Project Management
 - Process Development
 - Manufacturing
 - Validation
 - QC
- QA
- Validation
 - PD
 - Manufacturing
 - QC
 - QA
 - Regulatory
- Management
- Project Leader
 - PD
 - Manufacturing
 - "Validation"
 - QC
- Regulatory
- QA

Definition of the Collaboration - Roles

DYNAVAX
DYNAVAX TECHNOLOGIES

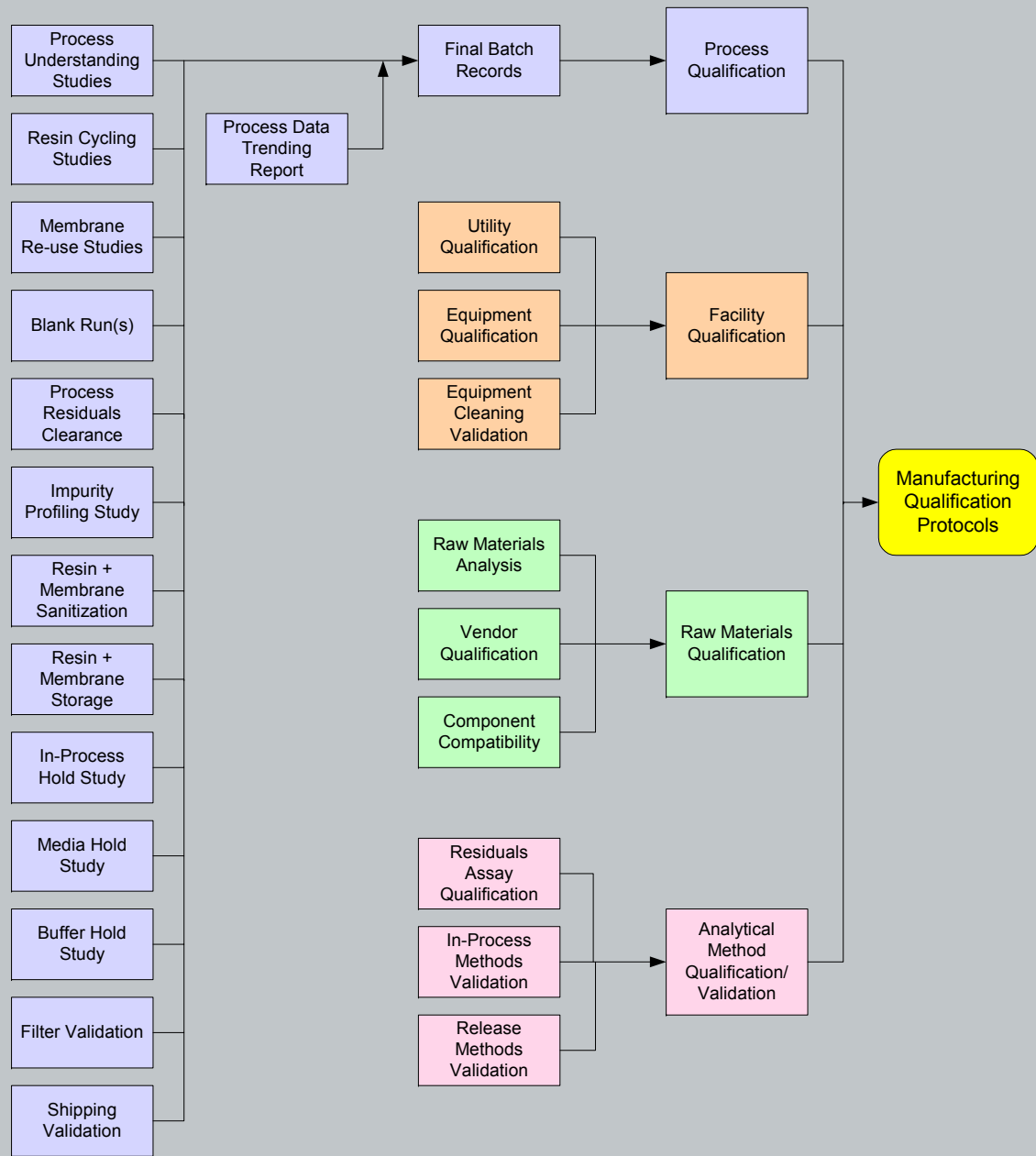


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Pre-Validation Activities – The Ideal



Validation in a Multi-Product Facility

- Requires clear documentation
 - Multi-product equipment
 - Product-specific equipment
 - Product-specific analytical methods
 - Product-specific process methods (e.g., synthesis)
 - Facility versus process validation
- Cleaning multi-product equipment
 - Cleaning verification between products
 - Cleaning validation between batches
 - Maximize use of disposables to lower overall surface area

Process Definition

- Challenges

- Limited early development work
- Limited process history
 - 8 GMP lots total
 - 2 representative of proposed commercial process
 - Setting acceptance criteria
- Completion of analytical method validation before initiation
- Timeline – Engineering Run?

- On the up side

- 1018 ISS is a straightforward oligonucleotide
- Process appeared robust
- Well defined and well controlled starting material supply chain
- LC/MS method available for process characterization

Pre-Validation Activities – The Reality

Summary reports signed off before PV

Process Understanding Studies

Resin Cycling Studies

Not now

Membrane Re-use Studies

Not now

Blank Run(s)

Not now

Process Residuals Clearance

Write separate report post-PV

Impurity Profiling Study

Resin + Membrane Sanitization

Not now

Resin + Membrane Storage

Not now

In-Process Hold Study

Do as part of PV

Media Hold Study

Not now

Buffer Hold Study

In progress

Filter Validation

In progress; to be ready for shipment of material from PV

Shipping Validation

Process Data Trending Report

FMP complete; need 1018-specific IQ/OQ complete; run PQ during PV

Final Batch Records

- Process History Report
- Engineering Run campaign summary
- Retest data from preceding lots

Process Qualification

Utility Qualification

Equipment Qualification

Equipment Cleaning Validation

Facility Qualification

Manufacturing Qualification Protocols

Raw Materials Analysis

Vendor Qualification

Component Compatibility

Raw Materials Qualification

Residuals Assay Qualification

In-Process Methods Validation

Release Methods Validation

Analytical Method Qualification/Validation



A Statistical Approach to Development

- Conduct a risk assessment – identify potential Critical Process Parameters (CPP)
- Develop and qualify a small scale model
- Establish robustness via DOE
- Carry out targeted optimization work
- Assign critical parameters by comparing NOR and PAR
- Implement and evaluate any process changes in an Engineering Run

Analytical Methods

- Completed validation prior to initiation of development work
- Greater confidence in assessment of DOE results
- Validation of in-process test methods made development results on individual steps reliable
- Testing retained samples from all batches by validated analytical methods
 - Facilitated setting of DOE acceptance criteria
 - Showed (lack of negative) impact of historical process changes
 - Indication of process robustness

Risk Assessment – Informal FMEA

- Gathered and reviewed all process controls relevant to validation in current batch record
 - Process Parameters
 - In-Process Controls
 - In-Process Specifications

} Define first!
- Evaluated Process Parameters for potential criticality – targeted for study in DOE development work
- Rationale based on:
 - Previous experience (other projects)
 - Operating experience (earlier batches/development work)
 - Scientific rationale
 - Literature
 - Information from equipment manufacturers

Risk Assessment Outcome

- Synthesis cycle
 - Potential CPP 10-15% of a large parameter list
 - Still, a large DOE
 - Optimization opportunity – solid support protecting group
- Post-Synthesis Wash – small DOE (2 potential CPP)
- Cleavage and Deprotection – time course study deemed sufficient; no DOE
- Purification
 - Potential CPP 15-20% of parameters identified
 - Another large DOE
 - Optimization opportunity – on-column detritylation time
- UF/DF – explore effect of neutralizing agent; no DOE
- Freeze Drying – cycle optimization; no DOE
- **Significantly narrowed scope of development work**

Definitions for DOE Work – 1

➤ Normal Operating Range (NOR)

- The range within which the process works under typical conditions (documented in batch record)
- Defined as combined error associated with unit operations
- Errors are multiplicative and normally distributed

➤ Proven Acceptable Range (PAR)

- The range within which the process works outside of typical conditions; may be approaching edge of failure
- Defined by design space, a multiple of NOR

➤ Critical Process Parameter (CPP)

- $NOR \approx PAR$
- Significant correlation between parameter (a.k.a. inputs) and quality attribute(s) (a.k.a. responses)

Definitions for DOE Work – 2

➤ Robust

- $NOR \ll PAR$
- No statistically significant correlation between parameter ranges studied and the quality attributes

➤ Statistically Significant

- If $Prob > F$ is less than 0.05, then there is a $> 95\%$ confidence that a correlation exists between the input (parameter) and the response (quality attribute)
- $Prob > F$ – the probability that a change in response is about the same as a variation by chance

➤ Center Point

- Conditions in which parameters are set half-way between the parameter ranges being explored
- Replication provides information on inherent error (noise)

Small Scale Model

- Qualified that the results from small scale DOE work would translate to similar results in the plant
- Runs at ~1/1000 plant scale from synthesis through purification
- Synthesis cycle and purification expected to scale linearly – both column-based processes
- Post-Synthesis Wash/Cleavage and Deprotection – current conditions used; evaluated as part of Synthesis
- UF/DF – linear scale down
- Freeze Drying – scale down difficult due to differences in equipment controls; base optimized cycle on physical properties of 1018 ISS

Outcomes of DOE Work – Process

- Overall, the process was found to be robust
 - Correlations existed
 - Most impacted yield, not CQA
- Targeted optimization successful
 - Alternate solid support protecting group demonstrated equivalence; simplified supply chain with no impact on CQA
 - Increased detritylation time increased yield and completely removed DMT-ON impurity
- No effect of UF neutralization agent – no benefit in introduction of a chemical change in process
- Freeze Drying cycle time cut by ~50%

Outcomes of DOE Work – Validation

- Simplified defining path forward (and thereby the working relationships) – based decisions on data
- Straightforward assessment of potential CPP via NOR versus newly-established PAR
- Made up for lack of extensive process history in setting parameter operating ranges and CQA acceptance criteria
- Strong basis for Validation Protocols and MBR
- Confirmed by Engineering Run – **once!**

The Real Deal – Process Validation

- Remaining Challenges – Timeline Driven
 - Simultaneous document generation, review and approval
 - PVMP
 - Development Reports
 - Process Description
 - Validation Protocols
 - Inherent risk – consistency
 - Staged versus Whole Process approach
 - 3 successful consecutive batches, plus:
 - Supporting Validations
 - Hold Time Studies
 - Cleaning Validation
 - Residuals Clearance
 - Equipment and Method Process Qualifications

Process Validation – Staged Approach

- Relatively simple (multiple) batch records, protocols, and reports
- Time efficient
- Representative of commercial, campaign-based process
- Mitigates risk – need to revalidate a stage doesn't lead to the need to revalidate entire process
- Complex execution – running multiple stages simultaneously

Process Validation Schedule

Sun	Mon	Tue	Wed	Thu	Fri	Sat
		Syn Prep 1	PV Syn 1	PV Syn 1	PV C&D 1	
	Crude 1 to QC	Chrom Prep 1 Syn Prep 2	PV Chrom 1 PV Syn 2	Chrom 1 to QC PV Syn 2	PV C&D 2	
	Crude 2 to QC	Chrom Prep 2 Syn Prep 3	PV Chrom 2 PV Syn 3	PV UF 1 Chrom 2 to QC PV Syn 3	PV FD 1 PV C&D 3	
	PV Harvest 1 Crude 3 to QC	Chrom Prep 3	PV Chrom 3	PV UF 2 Chrom 3 to QC	PV FD 2	
	PV Harvest 2			PV UF 3	PV FD 3	
	PV Harvest 3					

Process Validation Outcomes

- “Man-in-Plant” collected/tracked data real time – confirmed successful Process Validation
 - Parameter Ranges
 - In-Process Controls
 - In-Process Specifications
 - Quality attributes
- Discrepancies noted between documents
 - Highlighted need to clearly defined process controls
 - DOE work ensured proper parameter ranges and CQA acceptance criteria – no “fatal flaws”
 - Virtually all Protocol Generation Errors
- Support Validations successful
- Equipment and Method PQ successful

Process Validation Path Forward

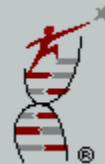
- Complete Validation Reports
 - Report for each process stage
 - Reports for supporting validations
 - Reports for equipment and method qualification
 - Overall Validation Summary Report
- Ongoing ICH Stability Studies
 - PV Batches will be included in studies
 - Will now be assured to have at least 12 months stability data for HEPLISAV BLA filing

Ensuring Successful Validation

- Targeted late-stage process definition work
 - DOE is an excellent approach
 - Makes up for aggressive approach to development
 - Mitigates risk introduced by tight validation timelines
- Pick experienced and talented partners

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