Quality by Design in Human Vaccines

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Outline

- Vaccine Technology and Manufacturing Process
- Biopharma Development Process
- Quality by Design, Why and How?
- Quality Attributes and Risk Assessment
- Process steps and Parameters, The Design Space
- Summary of the Overall Scheme

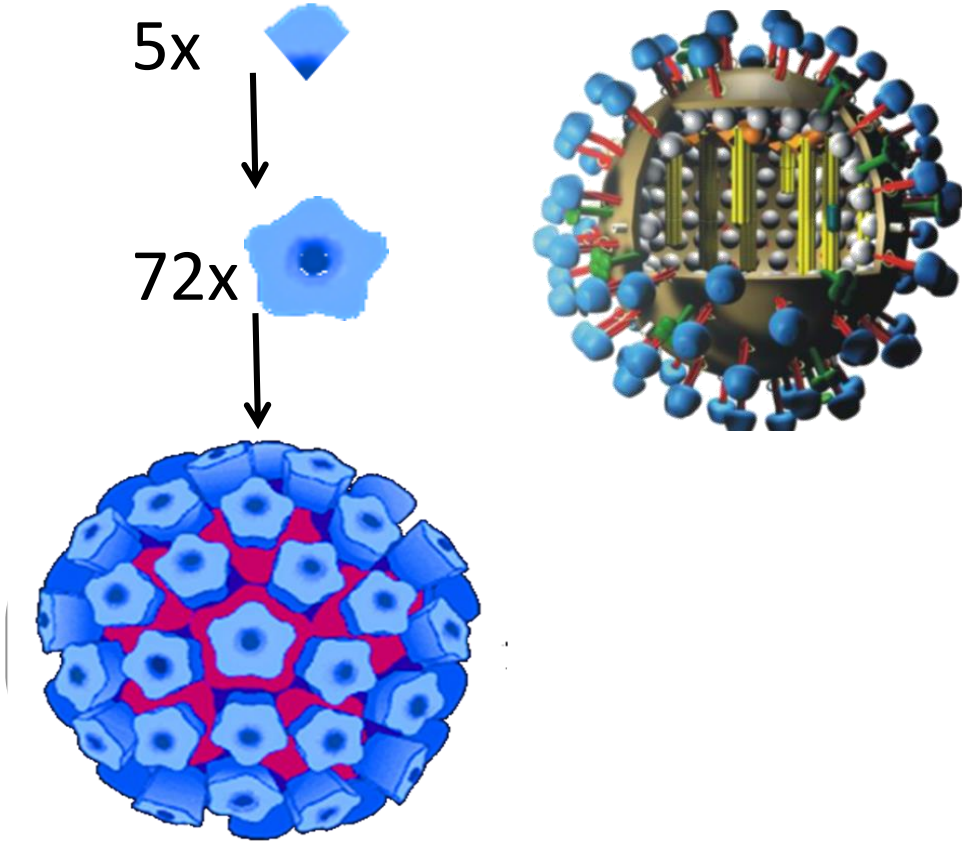
Nivad Pharmed Salamat

Focused on Human Vaccines:

Human papillomavirus Vaccine

Recombinant Influenza Vaccine

- Insect Baculovirus Platform



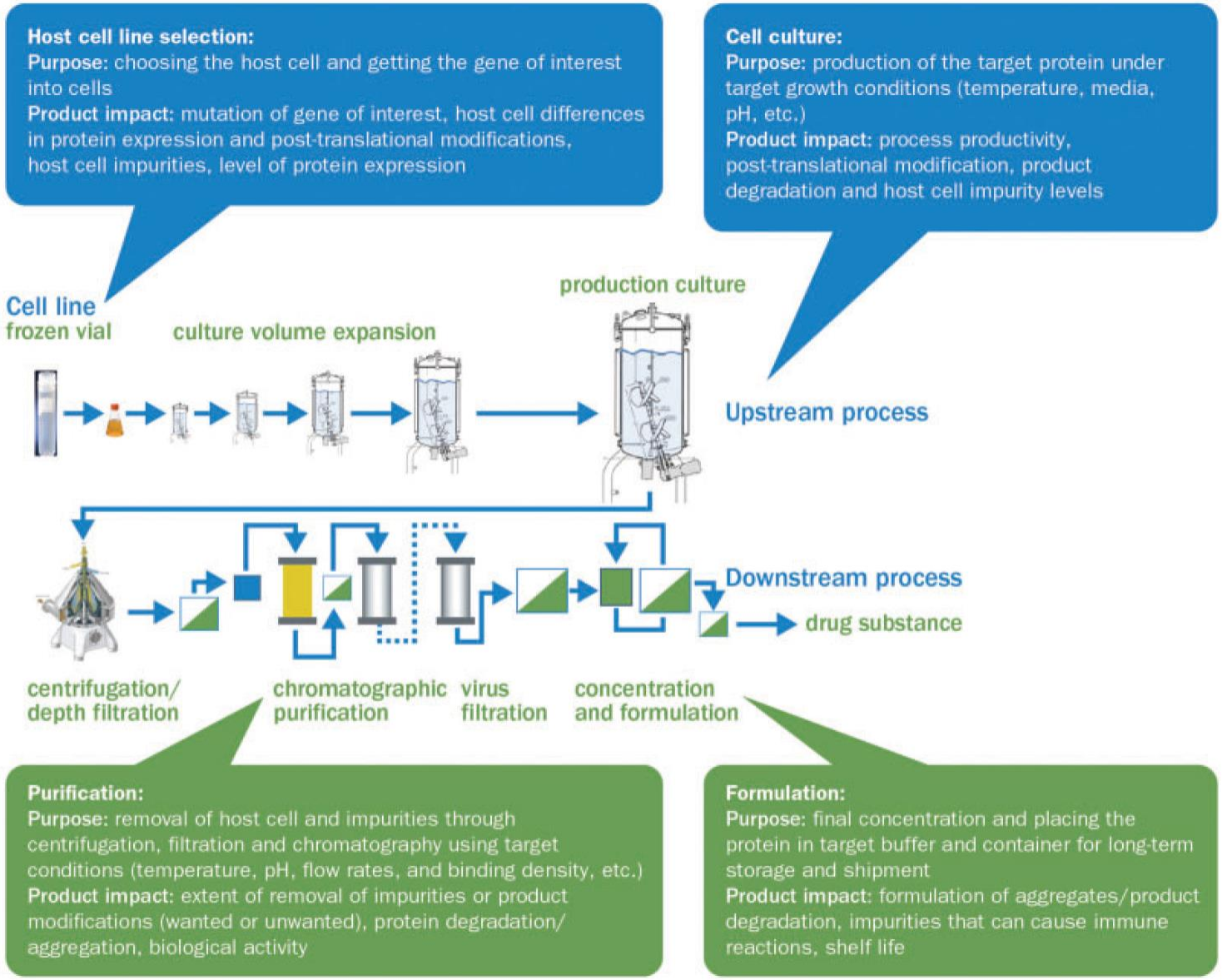
Different types of vaccines

Recombinant Vaccines:

- Human Papillomavirus (Cervarix, Gardasil)
- Hepatitis B Virus (Engerix)
- Influenza Virus (Flublok)
- Varicella Zoster Virus (Shingrix)
- Plasmodium falciparum (Mosquirix)

	Live attenuated	Killed inactivated	Subunit
Viral	Vaccinia Polio (OPV) Yellow fever Measles Mumps Rubella Influenza Rotavirus	Polio (IPV) Rabies Influenza Hepatitis A	Hepatitis B (HepB-surface antigen) Human papilloma virus (HPV)
Bacterial	BCG (tuberculosis) *Salmonella typhi* (oral)	*Bordetella pertussis* (whole cell) Cholera *Bacillus anthracis*	Tetanus (toxoid) Diphtheria (toxoid) *Neisseria meningitidis* (polysaccharide) *Bordetella pertussis* (acellular) *Streptococcus pneumoniae, 23* valent (polysaccharide) *Haemophilus influenzae*, type b (Hib) (polysaccharide) *Neisseria meningitidis* (polysaccharide conjugate) *Streptococcus pneumoniae*, heptavalent (conjugate polysaccharides) *Salmonella typhi* Vi (capsular polysaccharide)

Biopharma Manufacturing Process



Expression System

Different Expression systems for different applications

Table 2. A brief comparison among different systems with respect to their applications in producing recombinant VLPs

Property	*E. coli*	Yeast	Baculovirus-insect cells	Mammalian cells
Production cost	+	++	+++	++++
VLP production levels	++++	+++	++	+
VLP complexity[20]	+	++	++++	++
Post-translational modifications(PTMs)*				
Disulfide bond	Unfavorable redox potential for disulfide bond formation	Yes	Yes	Yes
O-glycosylation	No	Yes	Yes	Yes
N-glycosylation	No	Yes	The inability to synthesize mammalian-type N-glycans	Yes
Phosphorylation	No	Yes	Yes	Yes
Acylation	No	Yes	Yes	Yes
γ-Carboxylation	No	No	No	Yes
Applications**	Simple polypeptides and proteins (Hecolin)	Mammalian-like or secreted proteins (Gardasil-4 and Gardasil-9)	Mammalian-like or secreted proteins (Cervarix)	Mammalian proteins (GenHevac B)

Drugs vs Vaccines

Clinical surrogates: HPV no antibody and immunity

No platform, No good QC

Process is product

Formulation

Monoclonal antibodies	***Vaccines***	***Implications***
Often well-characterized	*Often difficult to characterize*	*Less definitive analytical comparability pathways* *Less ability to monitor product quality in mid-process*
Clear link to mechanism of action (MoA) and/or biomarker surrogate for clinical performance	*Difficult to establish clinical potency surrogates*	*Challenging to improve process post-licensure*
Consistent process and product	*Sometimes more complex, less predictable process/product*	*Variability over product/process life cycle*
Therapeutic patient population	*Prophylactic patient population*	*"Process is product" philosophy to assure quality*
Well-understood process; good detectability for test methods	*Less understood process; difficult to measure attribute changes*	*Empirical process models for linking parameter inputs to quality outputs* *More stringent threshold for reporting manufacturing changes*

Adjuvants

Immune response and immunity

- Th1/Th2
- Antibody response
- Antibody maturity

Protective immune response

Continuous protection

Table 1
Immune responses triggered by vehicles/delivery systems.

Vehicles/Delivery systems	Type of immune response					
	Th1 responses	Th2 responses	Cross priming	B cell responses	Mucosal response	Persistent T and B cell responses
Mineral salts [aluminum salts, calcium phosphate, AS04 (alum + MPL®)]	+	++		+++		+
Emulsions [MF59™ (squalene/water), QS21, AS02 (squalene + MPL® + QS21), IFA, Montanide ISA51, Montanide ISA720]	++			+++	+	
Liposomes [DMPC/Chol, AS01]	+++		+	+	+	+
Virosomes [IRIV], ISCOMs	++	++	++	+++	++	
DC Chol, mineral oil [IFA, Montanide®, squalene,		++		+++		
Mucosal delivery systems: chitosan					++	++
Microspheres	+		++			

Table 2
Immune responses triggered by immunostimulants.

Immunostimulant	Cellular interaction	Type of immune response
TLR ligands		
Bacterial lipopeptide, lipoprotein, and lipoteichoic acid; mycobacterial lipoglycan; yeast zymosan, porin	TLR-2, 2/1, 2/6	Th1, Ab, NK
Viral double-stranded RNA	TLR-3	NK
Lipopolysaccharide, lipid A, monophosphoryl lipid A (MPL®), AGPs, GLA	TLR-4	Strong Th1, Ab
Flagellin	TLR-5	Th1, CTL, Ab
Viral single stranded RNA, imidazoquinolines	TLR-7/8	Strong Th1, CTL
Bacterial DNA, CpG DNA, hemozoin	TLR-9	Strong Th1, CTL, and Ab; NK
Uropathogenic bacteria, protozoan profilin	TLR-11	Th1
Other		
Saponins (Quil-A, QS-21, Tomatine, ISCOM, ISCOMATRIX)	Antigen processing	Strong Th1, CTL, and Ab; long term memory
Cytokines: GM-CSF, IL-2, IFN-γ, Flt-3.	Cytokine receptors	Th1, Ab
Bacterial toxins (CT, LT)	ADP ribosylating factors	Ab

Process Development

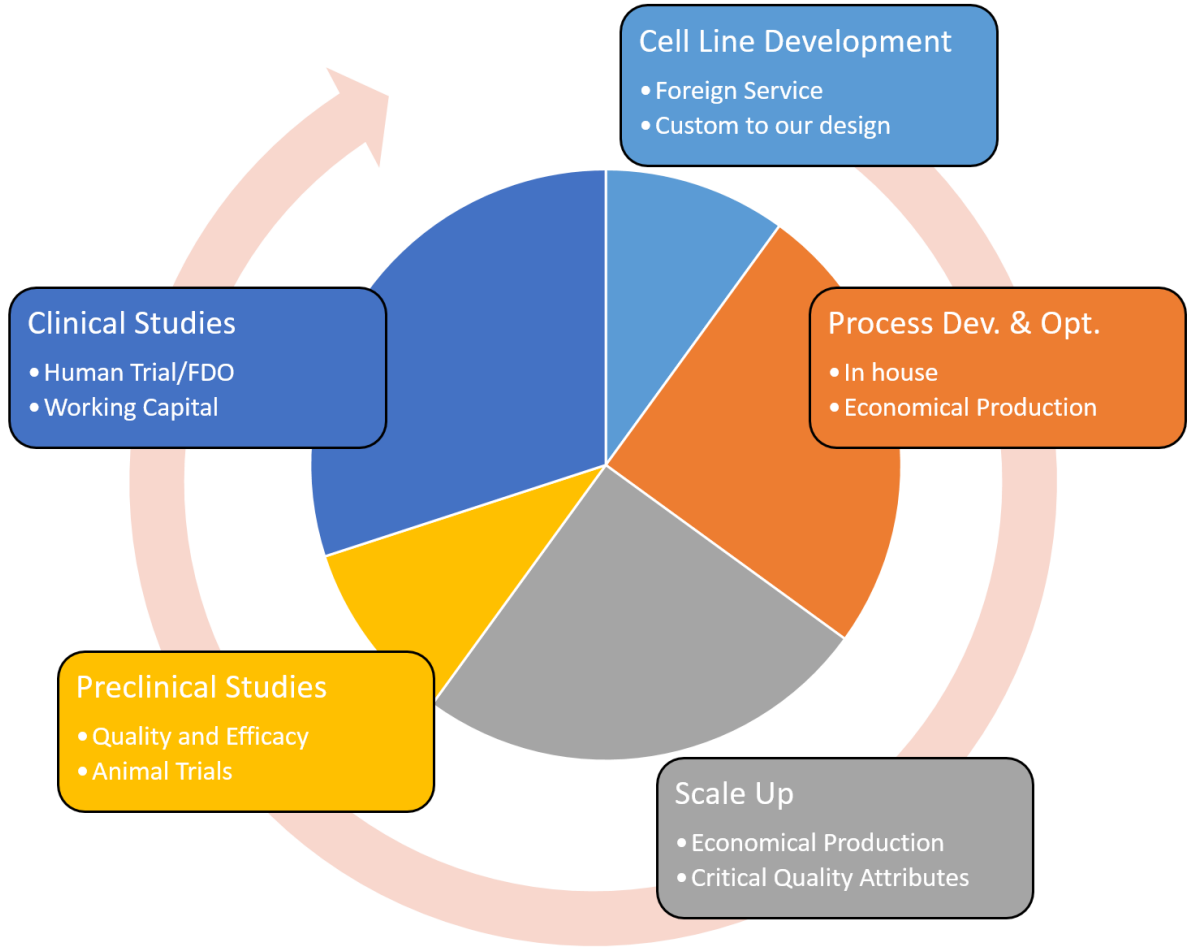
Cell Line Development

Process Development and Optimization
- Development of process in plot scale
- CTD development

Scale up to commercial Scale
- Clinical study batch

Preclinical Studies
- Animal safety and efficacy

Clinical Studies
- Safety and efficacy



Quality By Design (QbD)

Conventional Paradigm:

Quality by Testing of Representative Samples

Flexible Manufacturing Environment with Rigorous Testing

Empirical Development

Manufacturing Process Based on Retrospective Data

Focus on Testing to Document Quality

Product Release based on Batch Data

Regulations Based on Testing Final Product

PharmacopoeialMonographs (USP, EP, JP, etc.)

New Quality Paradigm: Build Quality in the Product

Quality cannot be Tested; should be Built in by Design

Quality by Design of Effective and Efficient Manufacturing Processes

Use of Scientific and **Quality Risk Management** Principles and Quality Control Strategies based on understanding & Knowledge of Product and Process

Identify Critical Starting & Raw Materials and Process Parameters (CPP) Affecting Quality

Evaluate and Determine, if possible, their Relationship with Critical Quality Attributes (CQA)

Design a Process with On-line or At-line Monitoring of CPPs and CQAs

QbD

How?

- Prior knowledge and/or initial development for process definition
- Early stage process risk assessment (e.g., cause and effect (C&E) analysis)
- Identification of high-risk parameters (e.g., screening DOE, one factor at a time)
- Later stage (as well as scale-up) risk assessment (e.g., failure mode and effects analysis)
- DOE for understanding high-risk steps and their associated high-risk parameters (e.g., optimization DOE, design space ranging experiments, modeling simulations for defect rates)
- Scale-up confirmation
- Control strategy, process validation, and continuous improvement implications (i.e., remaining areas of high variability and high risk)

Product Profile

Target Product Profile:

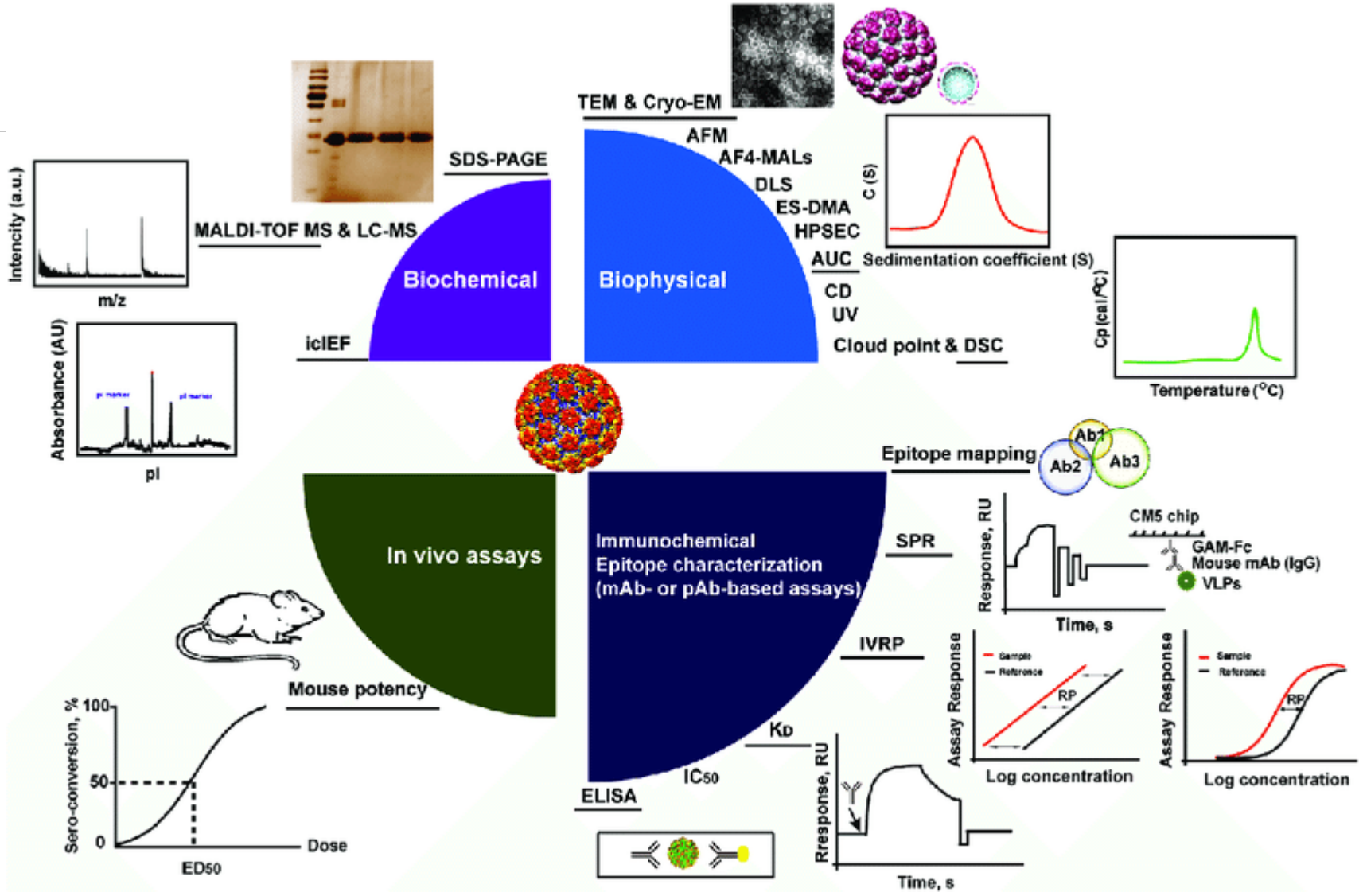
Mechanism of Action	• is a bivalent vaccine containing a non-infectious virus-like particle (VLP) and adjuvanted with an aluminum salt.
	• is expected to provide an enhanced cellular (Th1) and humoral (Th2), antigen-specific, protective immune response
Indication	indicated for the active immunization of 9-25 year old females for prevention of HPV infections.
Primary endpoints	• reduction of rates of HPV contracction within one year after dosing in the target population
	• Safe and tolerable as defined by solicited symptoms, adverse events, and serious adverse events
Key Claim	• Has a favorable risk-benefit profile
	• Universal recommendation
	• Achieves World Health Organization (WHO) stability requirements
Secondary endpoints	• Analysis supportive of primary endpoint in target population
	• Reduction in HPV rates in a 5 year span
	• Reduction in cervical cancer and precancerous lesions in a 15-20 year span
	• Duration of protection >10 years (with/without booster)

Quality Target Product Profile:

Key Claims	• Easy to administer, 0.5-mL intramascular delivery in a healthcare setting using a 1-mL syringe
	• Stability: 6 months at room-temperature storage or 4 years at 2–8 °C
	• No animal- or human-derived products are used in the manufacture
Formulation	• Sterile product
	• 3 doses (containing 20 ug each of VLP; adsorbed to 500 ug aluminum adjuvant) administered at 0, 1, 6
	• Composition: sugar, surfactant, buffer (isotonic pH), and Ps-VLP conjugate
	• Label volume 0.5 mL filled (actual fill volume will be greater than the label volume to account for losses)
	• Single-dose vial (ISO2R vial, clear, Type I glass), latex-free stopper and seal
	• Secondary packaging and shipping: allowed shipping-excursion temperature 2-40 °C for 3 days in a carton

Quality Attributes and Characterization

- **Identity**
- **Purity**
  - Process
  - Product
- **Potency**
  - Bioassay
  - In vitro/in vivo
- **Stability**
  - Shelf life & stressed
- **Quantity**



The Evolution of Quality

Louis Pasteur checking for visible particulates

CQA and Risk assessment

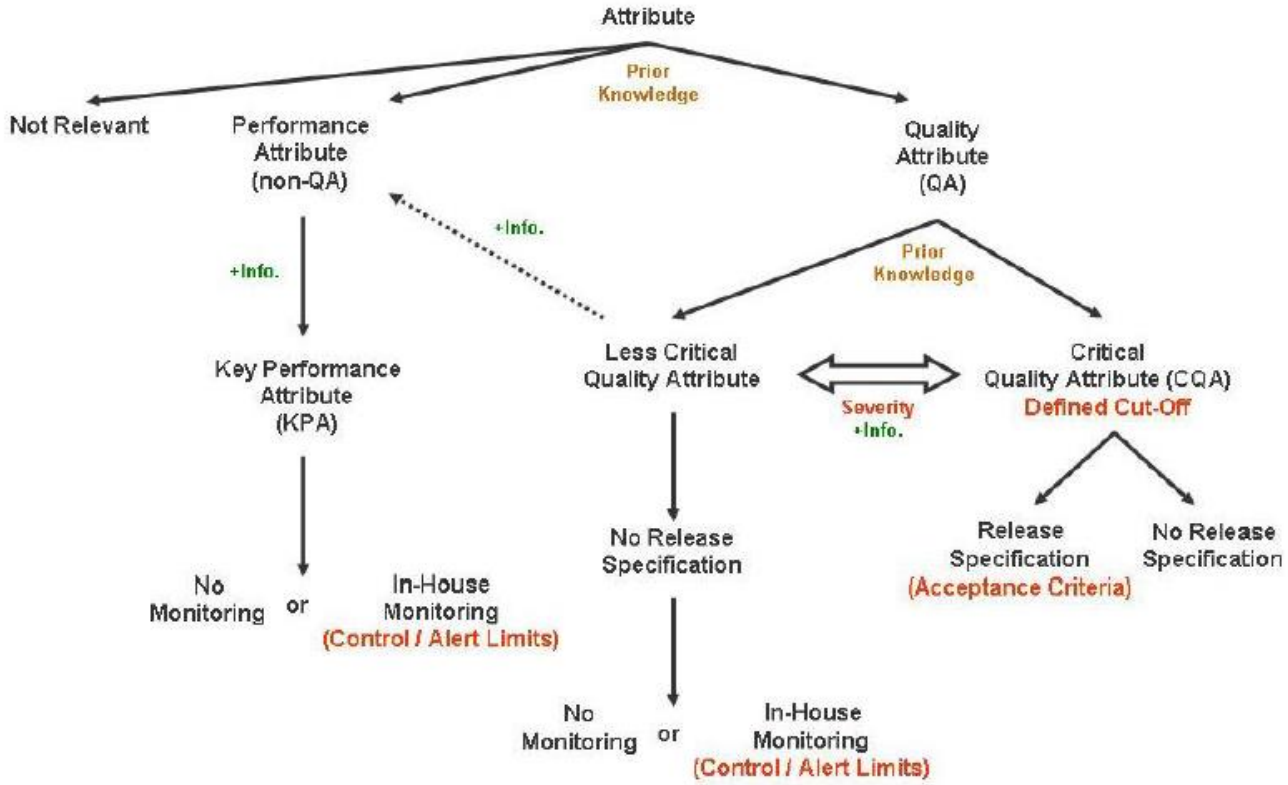
Quality attributes:

- Various effects on Safety, Efficacy
- Level of confidence is important

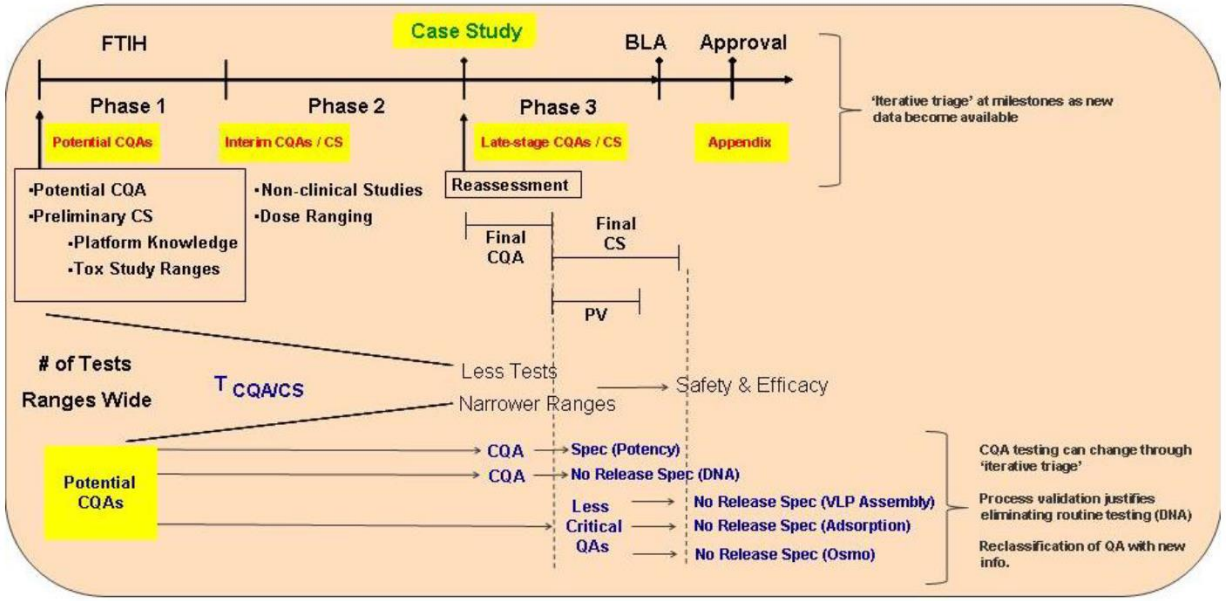
Safety:

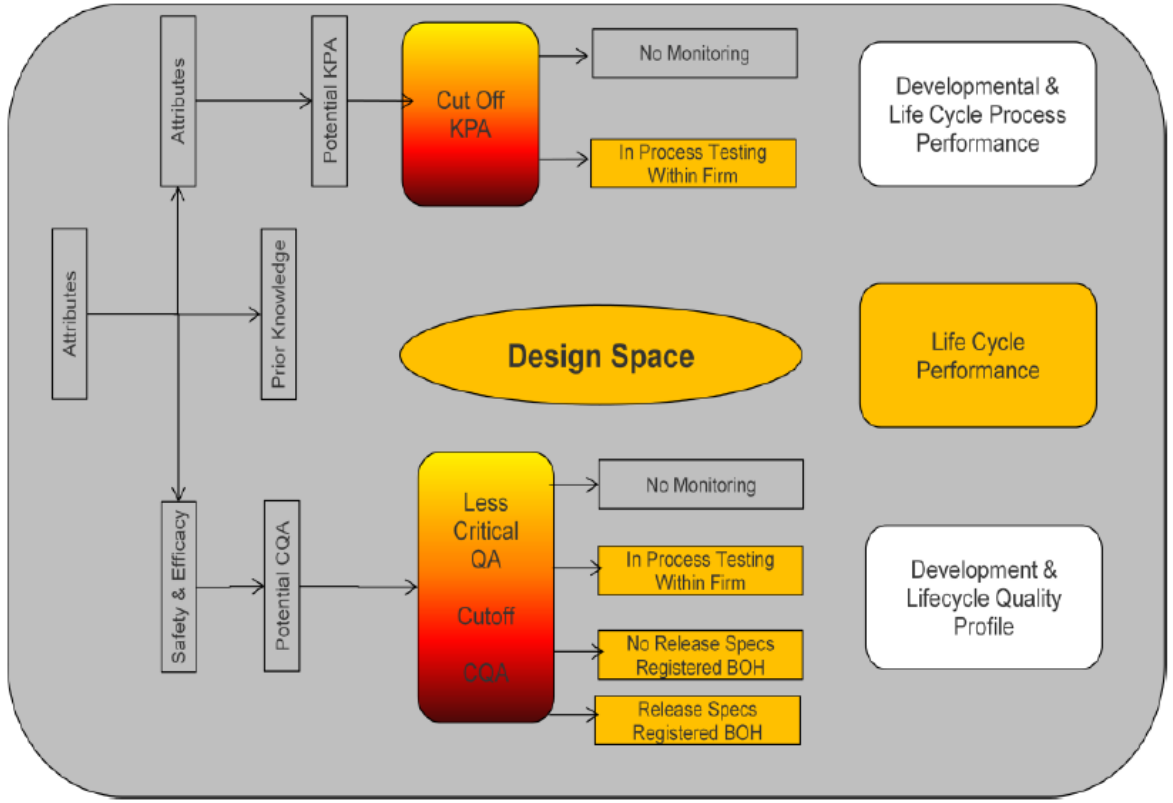
- Number of doses and volume
- Mode of administration
- Type of host, etc….

Score	Uncertainty
Very High 5	No information available
High 4	*External* information available from literature on related vaccine(s)
Moderate 3	Data from *internal* laboratory or nonclinical studies with this antigen:adjuvant complex, or *internal* data extrapolated from related vaccine(s)
Low 2	Supportive data from *clinical studies* with this antigen:adjuvant complex
Minimal 1	Published limits widely accepted by regulatory and scientific community



CQAs: How many? How much?





Control Strategy

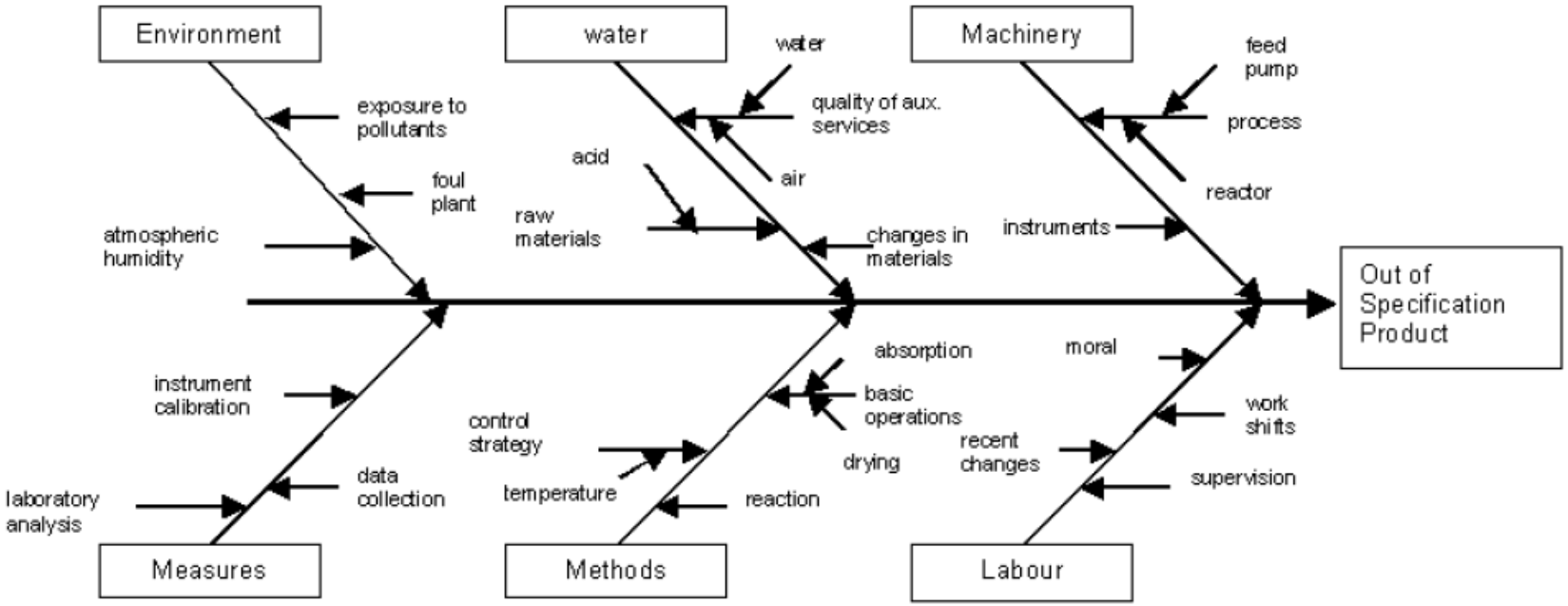
Process Steps

- Some more effective

Process Parameters

Defining Importance?

- Based on risk assessment
- Empirical approach



CPPs: Setting the design space

Detecting contributing effects
- Based on effects on CQA

Effect of CPPs on multiple CQAs

Setting limits
- Difference between regulatory and manufacturer approaches

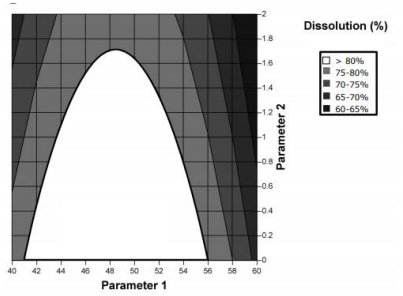


Figure 2a: Contour plot of dissolution as a function of Parameters 1 and 2.

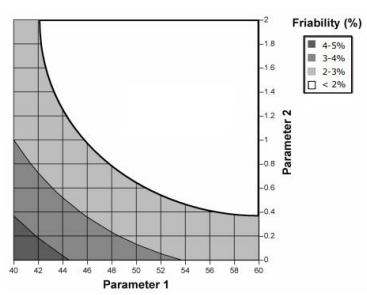


Figure 2b: Contour plot of friability as a function of Parameters 1 and 2.

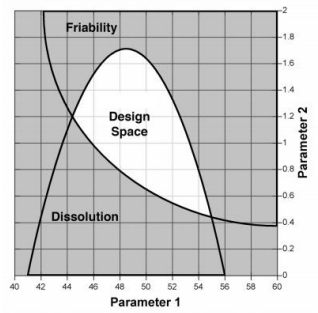


Figure 2c: Proposed design space, comprised of the overlap region of ranges for friability and or dissolution.

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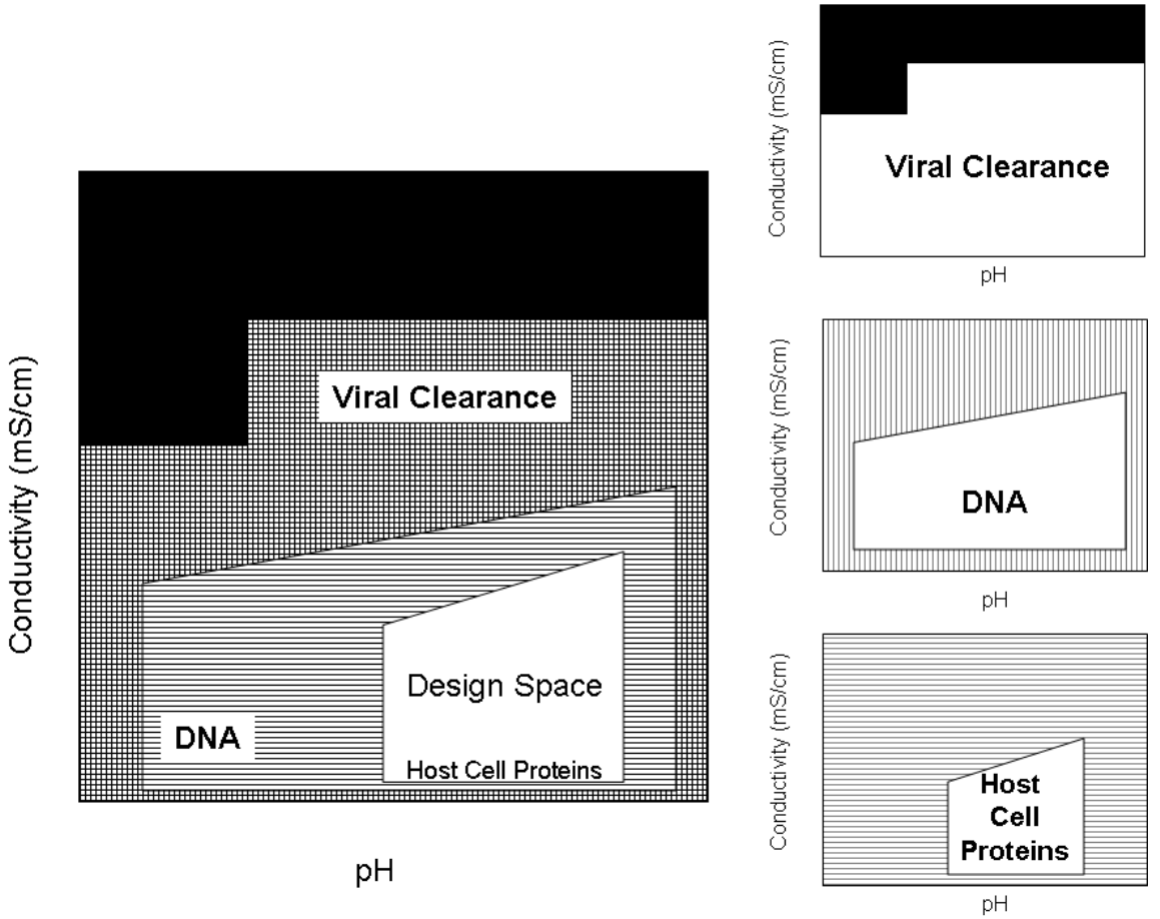

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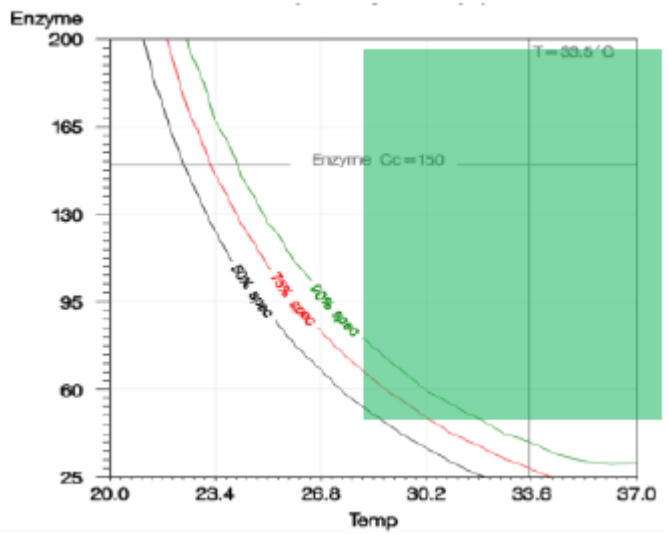

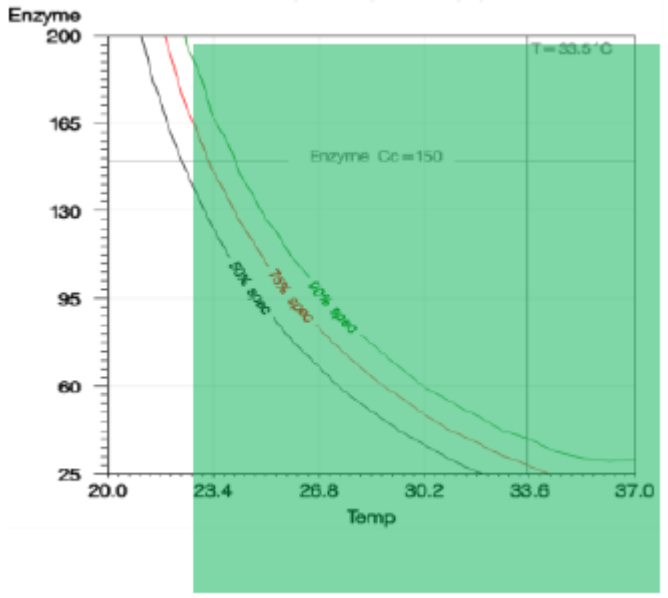

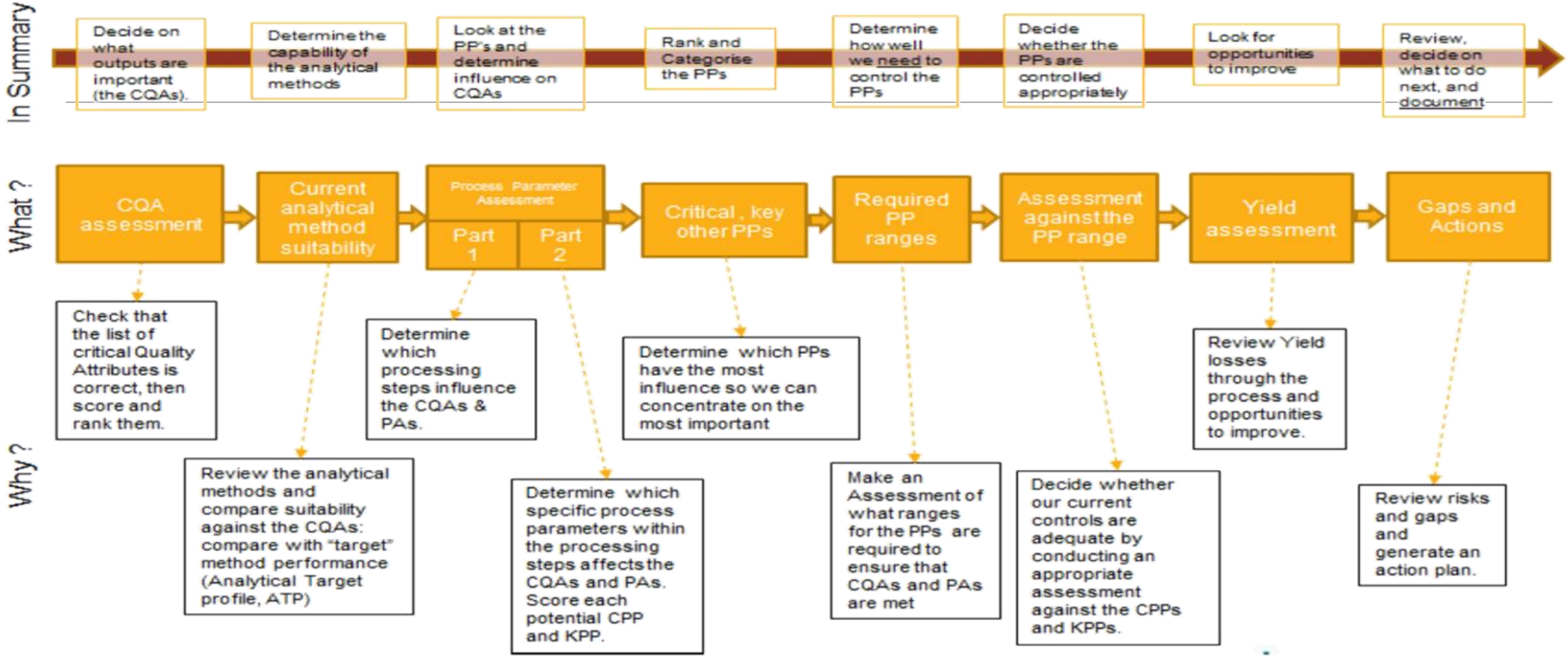
In Summary
Decide on what outputs are important (the CQAs).
Determine the capability of the analytical methods
Look at the PP's and determine influence on CQAs
Rank and Categorise the PPs
Determine how well we need to control the PPs
Decide whether the PPs are controlled appropriately
Look for opportunities to improve
Review, decide on what to do next, and document
What ?
CQA assessment
Current analytical method suitability
Process Parameter Assessment
Part 1
Part 2
Critical , key other PPs
Required PP ranges
Assessment against the PP range
Yield assessment
Gaps and Actions
Why ?
Check that the list of critical Quality Attributes is correct, then score and rank them.
Review the analytical methods and compare suitability against the CQAs: compare with "target" method performance (Analytical Target profile, ATP)
Determine which processing steps influence the CQAs & PAs.
Determine which specific process parameters within the processing steps affects the CQAs and PAs. Score each potential CPP and KPP.
Determine which PPs have the most influence so we can concentrate on the most important
Make an Assessment of what ranges for the PPs are required to ensure that CQAs and PAs are met
Decide whether our current controls are adequate by conducting an appropriate assessment against the CPPs and KPPs.
Review Yield losses through the process and opportunities to improve.
Review risks and gaps and generate an action plan.

Thanks for your attention

Any Questions?