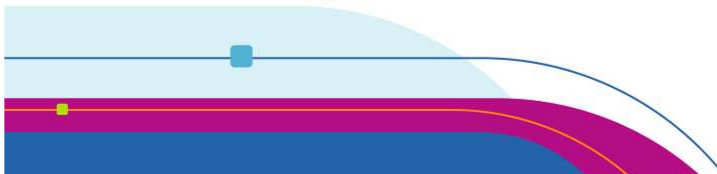





# Bioproduction by Design

13<sup>th</sup> LETI annual review  
June 28 , 2011

Christian valentin , sanofi pasteur  
Bioprocess R&D executive director



- 
- sanofi pasteur
  - Biotechnology and Health
  - Vaccines Bioproduction
  - Challenges and perspectives
  - Bioproduction by Design

## Sanofi Pasteur : the vaccines division of



### ■ World leader in human vaccines :

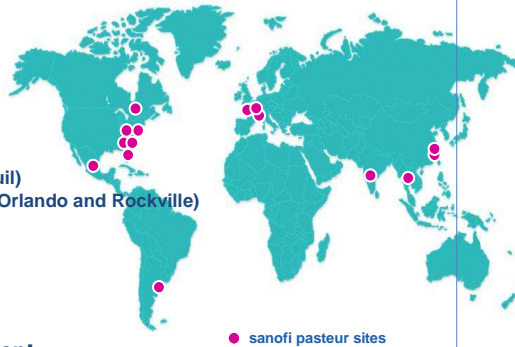
- providing protection against 20 bacterial and viral diseases.
- 1.6 billion doses of vaccine per year,
- More than 500 million people vaccinated/year
- 15 vaccines in development

### ■ Sales 2010: €3,808 million

### ■ Nearly 13,000 employees

### ■ A worldwide presence :

- 12 production / R&D sites
- France (Marcy l'Etoile and Val de Reuil)
- US (Swiftwater, Cambridge, Canton, Orlando and Rockville)
- Canada (Toronto)
- Argentina (Pilar)
- China (Shenzhen)
- India (Hyderabad)
- Thailand (Chachoengsao)
- 3 new facilities under construction:
- Mexico , France (Neuville) China



sanofi pasteur  
La division vaccins du Groupe sanofi-aventis

3

## The Broadest Range of Vaccines Worldwide

### ■ Vaccines against 20 diseases

#### Viral diseases

- Yellow fever
- Mumps
- Poliomyelitis
- Measles
- Rubella
- Influenza
- Hepatitis A
- Hepatitis B
- Rabies
- Japanese encephalitis
- Chickenpox

#### Bacterial diseases

- Pertussis
- Diphtheria
- Haemophilus influenzae* type b infections
- Meningococcal meningitis
- Pneumococcal infections
- Tetanus
- Tuberculosis
- Typhoid fever
- Cholera

and against one eradicated disease

- Smallpox (\*)

(\*) This vaccine is produced in response to the threat of bioterrorism using strains of the smallpox virus.

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis

4

- 
- sanofi pasteur
  - Biotechnology and Health
  - Vaccines Bioproduction
  - Challenges and perspectives
  - Bioproduction by Design

5

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## Biotechnology ....

- **Biotechnology** is a field of applied biology that involves the use of living organisms and bioprocesses in engineering , technology, medicine and other fields requiring bio products.
- Modern use of similar terms includes genetic engineering as well as cell- and tissue culture technologies.
- The concept encompasses a wide range of techniques for modifying living organisms according to human purposes going back to :
  - domestication of animals
  - cultivation , selection of plants
  - France as a strong Biotechnology land : wine , cheese and bread

6

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## Main Biotechnology areas :

### ■ Healthcare / RED Biotechnology

- Medicinal , diagnostic product or a vaccine that consists of, or has been produced in, living organisms and may be manufactured via recombinant technology .

### ■ Agricultural / GREEN Biotechnology

- Plant Biotechnology to grow food , feed , fuel and fibres with less input and impact on the environment .

### ■ Industrial / WHITE biotechnology

- To use yeasts , bacteria and enzymes as « cell factories » to make sustainable energy , detergents , vitamins , chemicals , paper ...

- <http://www.europabio.org/>

**sanofi pasteur**  
La division vaccins du Groupe sanofi-aventis.

7

## Conventional drugs

Made by mixing chemicals

Mostly small, relatively simple molecules and can usually be shaped into a pill oral administration

Around 50 monitoring and quality tests for a traditional (chemical) medicine

Conventional drugs, based on relatively simple molecules, are easy to copy

## Biotech drugs

Far more complex, mimicking large substances produced by the human body (enzymes, insulin, antibodies...)

Biotech drugs are grown in live cells in a bioreactor and then purified. injection administration

Complex molecules : high level of monitoring and quality testing (around 250 in-process tests are conducted for a biological medicine)

Unique starting material and complex manufacturing processes make it more difficult to exactly reproduce /copy a biological molecule : Biosimilars

**sanofi pasteur**  
La division vaccins du Groupe sanofi-aventis.

8

## Vaccines value :

### ■ Vaccines save lives

Millions of cases of disease prevented

- Smallpox has been eradicated
  - Before eradication in 1980, smallpox threatened 60% of the world's population and killed 1 out of 4 people infected
- Polio infections have fallen globally by 99% since 1988
  - An estimated 5 million people have escaped paralysis
- Measles mortality has decreased by 74% worldwide between 2000 and 2007



### ■ Vaccines save money

- Vaccination is undoubtedly one of the most cost-effective public health care investments available :
  - In the United States, cost-benefit analysis indicate that every dollar invested in a vaccine dose saves US \$2 to \$27 in health-care expenses

9

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## But challenges remain...

- Dengue fever threatens at least 2.5 billion people in 100 tropical and subtropical countries
  - Of the estimated 230 million people infected annually, 2 million people, mostly children, develop dengue hemorrhagic fever (DHF), a severe form of the disease
- Seasonal influenza strikes about 600 million people a year leading to 250,000 to 500,000 deaths worldwide
- Hospital-acquired infections, a major concern for public health in many industrialized countries



10

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

- sanofi pasteur
- Biotechnology and Health
- Vaccines Bio production
- Challenges and perspectives
- Bioproduction by Design

11

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## Vaccine Bio - production

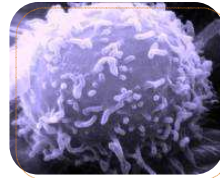
- Vaccination consists of introducing an agent (a bacterium, virus or molecule) into the body
  - deprived of its pathogenicity (its ability to make you ill)
  - but has kept its immunogenicity (its ability to induce an immune response).
  - **Preventive medicine** : In case of contact with the pathogen agent, the body will be ready to defend itself, protecting the vaccinated individual /population against the disease
- Vaccine manufacturing steps :
  - The « cell factory » to produce the product of interest
    - From Recombinant protein to multivalent live attenuated vaccine
    - Upstream Biomass productivity
  - Purification steps : downstream
    - From crude extract : Product Recovery and Purity
  - Formulation
    - Presentation ready for administration : dosage , Stabilisation , combination

12

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## Vaccine Bio production :

- **1796** : vaccine for smallpox developed by Edward Jenner.
  - derived from a weakened version of the disease cowpox
  - eradicated in 1980
  - but vaccine produced in response to the threat of bioterrorism
- **1885** : First vaccine for rabies by Louis Pasteur and Émile Roux
- **1922** First tetanus vaccine
- **1955** First Salk (inactivated) polio vaccine
- **New Era 1953** : Crick and Watson :  
double helix structure of the DNA molecule
- **1987** recombinant Hepatitis B vaccine



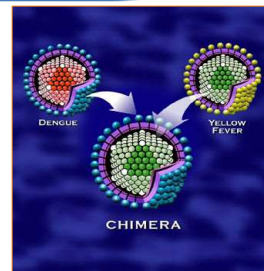
**sanofi pasteur**  
La division vaccins du Groupe sanofi-aventis.

13



## sanofi pasteur's approach to Dengue and other Mosquito-borne Flaviviruses

- **Chimerivax™** vector technology using yellow fever 17D backbone
  - Recombinant viruses developed with envelope genes from Dengue (or other flaviviruses)
  - Production in proprietary and well established Vero cell line in serum-free conditions and at high yields
  - Established genetic stability of 17D backbone
- **Established safety profile**
  - No foreseen environmental risk of 17D backbone and chimeric viruses
- **November 2010** : final stage of clinical development for sanofi pasteur's dengue vaccine which entered its first phase III clinical study in Australia.
  - Our vaccine is the world's most clinically advanced dengue vaccine candidate
- The vaccine is expected to become available as early as 2015



### Dengue fever

**A mosquito-borne disease**  
A potential **threat to almost half of the world's 230 million people** infected annually  
**No effective** drug treatments  
**No effective** prevention

**sanofi pasteur**  
La division vaccins du Groupe sanofi-aventis.

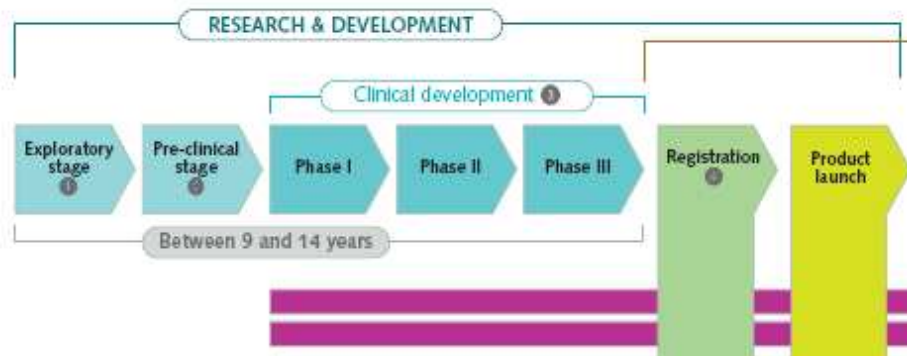
14

- sanofi pasteur
- Biotechnology and Health
- Vaccines Bioproduction
- Challenges and perspectives
- Bioproduction by Design

15

## Vaccine R&D cycle time :

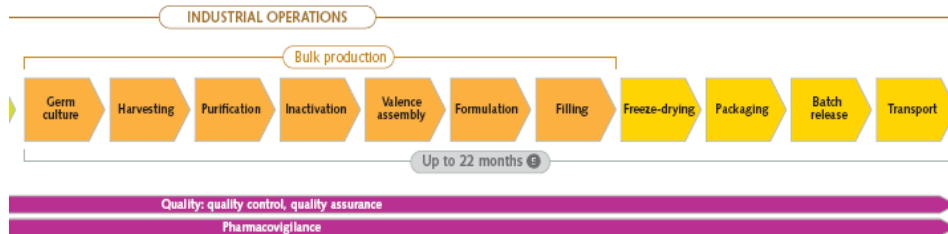
Bio Process R&D :To Develop the manufacturable process and Deliver material for clinical evaluation



Average development time for a vaccine: **12 years**

16

## Vaccine Bio-manufacturing Cycle time



⑤ The infectious germs are cultured, harvested and purified. After formulation and freeze-drying (which stabilizes the more fragile vaccines),

the vaccines are filled, primarily in vials and syringes and then packed. When the manufacturing process is complete, the cold chain must be constantly maintained

during all stages, from distribution to vaccine administration to patients.

70% of a vaccine's production time dedicated to quality control.

17

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## The challenges of vaccines production

- **To respond to global demand**, to meet public health needs with a reliable supply of vaccines. while conforming to very strict quality and regulatory controls .
- **The challenge of anticipation:**
  - The production of vaccines requires the ability to **anticipate**.
  - Vaccine **production cycles are long** and production capacity (setting up a new production facility takes years).
  - to be able to **support public health** by responding to unanticipated needs, outbreaks, epidemics .
- **The challenge of quantity**
  - In 2009, sanofi pasteur produced more than **1.6 billion doses of vaccine**,
  - To meet growing demand, sp reinvest 10% of revenues into capital investments annually ( Neuville site for Dengue vaccine )
  - The company's global presence makes it possible to meet this production challenge
- **The challenge of quality**
  - Sanofi pasteur has a strong quality culture . incorporated into the daily mindset of each employee.
  - To constantly improve customer satisfaction and meet regulatory demands,

18

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## Bio Production Challenges

- To obtain greater process understanding
- To improve quality
- To increase productivity : lower manufacturing costs by increasing yield
- To Reduce manufacturing downtime
- To Decrease amount of rework or rejected batches
  - Right 1<sup>st</sup> Time

19

**sanofi pasteur**  
La division vaccins du Groupe sanofi-aventis.

- sanofi pasteur
- Biotechnology and Health
- Vaccines Bioproduction
- Challenges and perspectives
- Bio production by Design

20

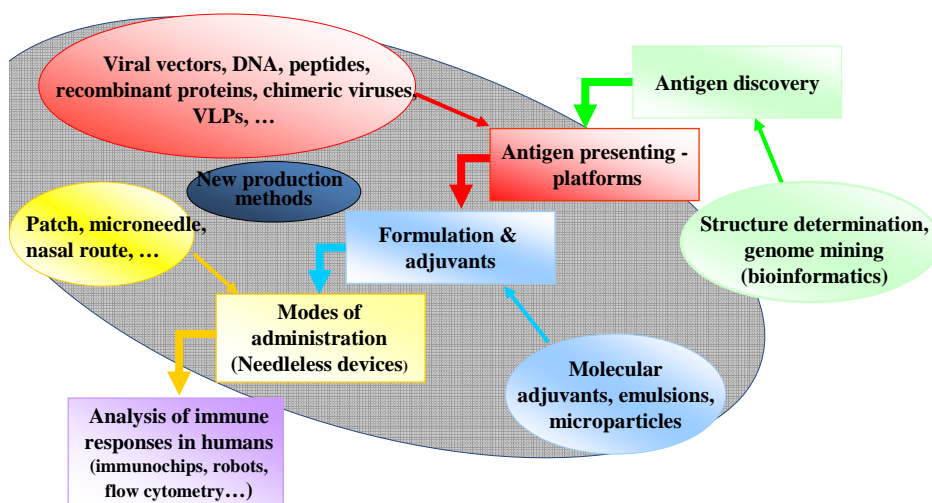
**sanofi pasteur**  
La division vaccins du Groupe sanofi-aventis.

## Bioproduction environment :

- Pharma. Regulatory environment
  - Highly regulated : GMP , FDA , EMA , ICH ....
  - Quality by Control : PASS Specifications
  - Change control for any process improvement
- Bioproduction challenges
  - To Integrate innovation
  - To guarantee Quality
  - To get quick approval from Health authorities
    - Patient need , First to Market

21

## Innovation for vaccines ...



22

## Quality By Design for Health Authorities

*A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.*

FDA representative ( 2005 ) : The Desired State  
A Mutual Goal of Industry, Society, and the Regulators

23

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## What is Quality by Design (QbD)?

- The product is designed to meet **patient needs** and performance requirements
  - Target product profile
- QbD is a scientific, risk-based approach leading to continual improvement :
  - Critical **sources of process variability** are identified and controlled
  - The impact of **starting raw materials** and **process parameters** on product quality is understood
  - The process is designed to **consistently meet** product **critical quality attributes**
- When properly implemented, QbD improves speed to market :
  - The process is evaluated and **updated** to allow for consistent quality over time
  - reduces product variation
  - Improves operating efficiency and reduces costs at all stages of the process.

24

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## FDA's Expectations for QbD

- **The current system is adequate for regulatory submission**
  - Quality is assured by testing and inspection
  - Considerable regulatory oversight
  - Substantial efforts and considerable waste
  
- **However, QbD is the desired approach**
  - QbD principles should result in a higher level of assurance of product quality
  - Additional product and process understanding could lead to regulatory flexibility
  - Implementation of QbD by industry could enhance manufacturing efficiency
  
- **Focus remains on availability of safe, effective and high quality pharmaceuticals**

## Approaches to Pharmaceutical Development

Aspects	Current cGMP	Quality by Design BMP
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, <u>Multivariate experiments</u> , Focus on control strategy and robustness
Manufacturing Process	Fixed	<u>Adjustable within design space</u> , managed by company's quality systems
Process Control	Some in-process testing	<u>PAT utilized</u> , Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on <u>desired product performance</u>
Control Strategy	By testing and inspection	Risk-based control strategy , <u>real-time release</u> possible

## PAT opportunities (FDA's PAT Draft Guidance)

### Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

#### DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to: Dockets Management Branch (HFA-903), Food and Drug Administration, 5630 Fishers Lane, rm. 1091, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Rajendra Uppekar, 301-494-5615, (CVM) Dennis Hanley, 301-827-0956, (CBA) Robert Coleman, 404-215-1200.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Veterinary Medicine (CVM)  
Office of Regulatory Affairs (ORA)

August 2009  
Pharmaceutical CEMPs

CDER/CVM/ORA/CDR/CEMP/09-1163

27

- ✓ Reducing production cycle times
- ✓ Real time release
- ✓ Right first time quality (RFT)
- ✓ Managing variability
- ✓ Facilitating continuous processing
- ✓ Increasing automation to improve operator safety and reduce human errors

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## PAT and Pharmaceutical Quality by Design

- Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing processes based on :
  - an understanding of the scientific and engineering principals involved
  - identification of the variables which affect product quality.
- According to the FDA draft guidance, the desired state of pharmaceutical manufacturing is that:
  - Product quality and performance are ensured through the design of effective and efficient manufacturing processes .
  - Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance.
  - Quality assurance is continuous and real time .
  - Relevant regulatory policies and procedures are tailored to accommodate the most current level of scientific knowledge .
  - Risk-based regulatory approaches recognize both the level of scientific understanding and the capability of process control related to product quality and performance .

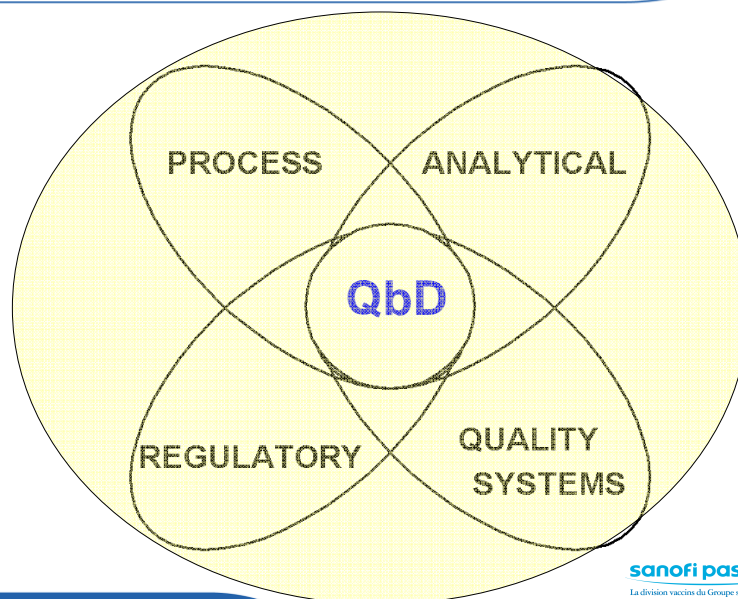
28

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## PAT Goal and objectives :

- The primary goal of PAT is to provide processes which consistently generate products of predetermined quality.
- In so doing, improved quality and efficiency are expected from:
  - reduction of cycle times using on-, in-, or at-line measurements and controls
  - prevention of reject product and waste
  - real time product release
  - increased use of automation
  - facilitation of continuous processing using small-scale equipment ( scale down) , resulting in improved energy and material use and increased capacity

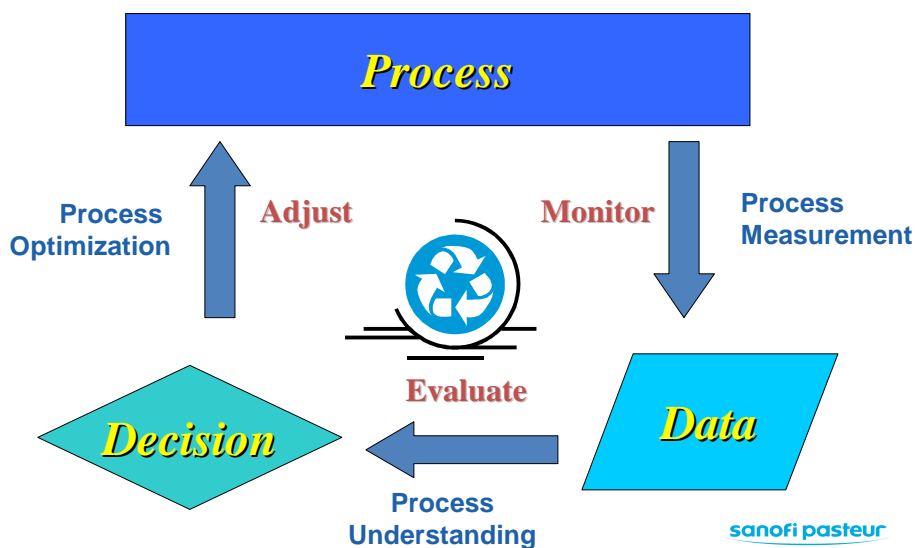
## Efficient Quality by Design / PAT Team



## Bioproduction by Design key players :

- **Process development :**
  - Process monitoring , process understanding , process modeling
- **Analytical development :**
  - From off line to near line analyzers
  - In line , Real time monitoring
- **Quality :**
  - From QbC to QbD
  - From cGMP to BMP
- **Regulatory :**
  - Submitting a design space to get flexibility on process improvement

## PAT for Process development :



## PAT Tools :

- Multivariate tools for design , data acquisition and analysis :
  - DoE , PLS , MVA
- Process analyzers :
  - In line monitoring
- Process control tools :
  - Feed back loops Automation
- Continuous improvement and knowledge management tools.

33

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## PAT as a common language between process development steps :

- Upstream : the cell
  - Input : raw material , expression system
  - Output : DS Productivity
- Downstream : the product of interest
  - Input : Ability to purify
  - Output : DS /API Recovery : DSP as a variability regulator
- Formulation : the product ready to administer :
  - Input : DS /API : DS Processability
  - Output : Drug Product
    - Manage excipient , formulation process , DP stability ...
  - As Final step : cumulate previous variability and its own variability

34

sanofi pasteur  
La division vaccins du Groupe sanofi-aventis.

## PAT Tools : process analyzers

**Near-Infrared Spectroscopy for Rapid, Simultaneous Monitoring of Multiple Components in Mammalian Cell Culture**

**Automated Closed-Loop Solution for Bioreactors and Fermentors**

Redefining Automation in Process Development, Pilot, and Manufacturing Applications

**improving manufacturing performance and developing manufacturing excellence, by using PAT in vaccine manufacturing**



**Proteomics Technology Applied to Upstream and Downstream Process Development of a Protein Vaccine**

Online Analytic as a QbD tool in mAb Process Development and Manufacturing

**sanofi pasteur**  
La division vaccins du Groupe sanofi-aventis.

35

## Interfacing Quality standards :

Current GMP :

- Quality by Control
- Specifications
- Validation
- Change control
- Batch release

21<sup>st</sup> Century GMP :

- Quality by Design
- Process understanding
- Design space
- Continuous improvement
- Real time product release

**sanofi pasteur**  
La division vaccins du Groupe sanofi-aventis.

36

## Bioproduction by design : Take home messages

- From Quality by Control to Quality by design
  - Patient needs : Product quality attributes
  - Manage Critical Process Parameters
  
- Gain in process understanding
  - Process monitoring , understanding , modeling
  - Product characterization
  
- Gain in Quality and Reduce cycle time
  - Real time monitoring reducing « at risk » steps
  - Real time release
  
- Gain in process improvement and flexibility
  - Flexibility to Introduce Innovation
  - From « time based » to optimum process profile