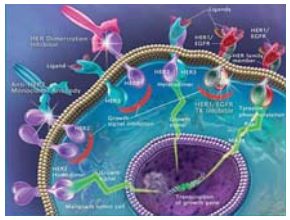

BioProcess Product Management

Building Value in development and Manufacturing

Developing business cases for new products new technologies

Jean-Marc Guillaume Pharm.D; Ph.D
Bioprocessing R&D, Sanofi Pasteur Marcy l'Etoile

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2011

New Products New Technologies
Context of a Business Case

- **New Target**
  - *Focus on vaccines to prevent infectious deseases*
  - *Therapeutic & prophylactic indications*
- **Marketed product**
  - *Line extension, new device, formulation.*
  - *New process*
- **Existing process or capacity**
  - *In-house constraints, flexibility*
  - *Build or Buy*
- **New Regulatory environment**
- **Competitive environment**
  - **Time to implement, Time to market**
  - **Fast to transfer**
  - **Risk of failure**
- **New technologies**
  - *Expression systems*
  - *Delivery*
  - *Single use processes, manufacturing..*

New Products New Technologies

Business case, Identifying what is at stake

Strategy

Issues identified by function

Themes
Competition
Capital intensity
Industrial cycle time
Quality issues
Reactivity to sanitary crises
Access to emerging markets
Innovation and product development
Position of Sanofi Pasteur in the value chain
Guideline evolution
Business risks
…

What is at stake by time horizon

Time horizon	Questions
Short term	▪ Establish POC with clinical trial ▪ Solve a localised technical issue on a specific production equipment ▪ Improve rapidly the cycle time of a saturated line
Mid Term	▪ Enter market ▪ Accelerate the industrialisation of product ▪ Save capital expenditure
Long term	▪ Secure competitive advantage ▪ Fuel sustained product portefolio ▪ Create framework for new products

The single use technology (SUT)
New options for biotech manufacturing

- The SUT allows to replace hard reusable manufacturing equipment (which has until now been prevalent in Sanofi Pasteur factories) by disposable, single-use equipment
  - Disposable equipment does not need to be cleaned and controlled between batches when replaced

Benefits
Lower capex
Higher reactivity / flexibility
Ability to launch new products faster
More security and comfort in quality
More progressive capacity growth
Less centralized manufacturing units
More options to subcontract manufacturing
Need for less cleaning and controlling personnel
Select technologies have the opportunity to reduce cycle times

Concerns
Potentially higher opex
Higher risk of new entrants
Technology not entirely mature, some limitations in potential applications
Full-scale production of large volume with 100% disposable equipment not available
Doubts about supply reliability
Environmental concerns due to the disposal of contaminated plastic components
Implication on low-skilled labor

Different views about the usefulness and business attractiveness

New Products New Technologies

KITE Sanofi pasteur perspective, New Technologies

- **KITE initiative: Knowledge & Innovation for Technology Excellence**

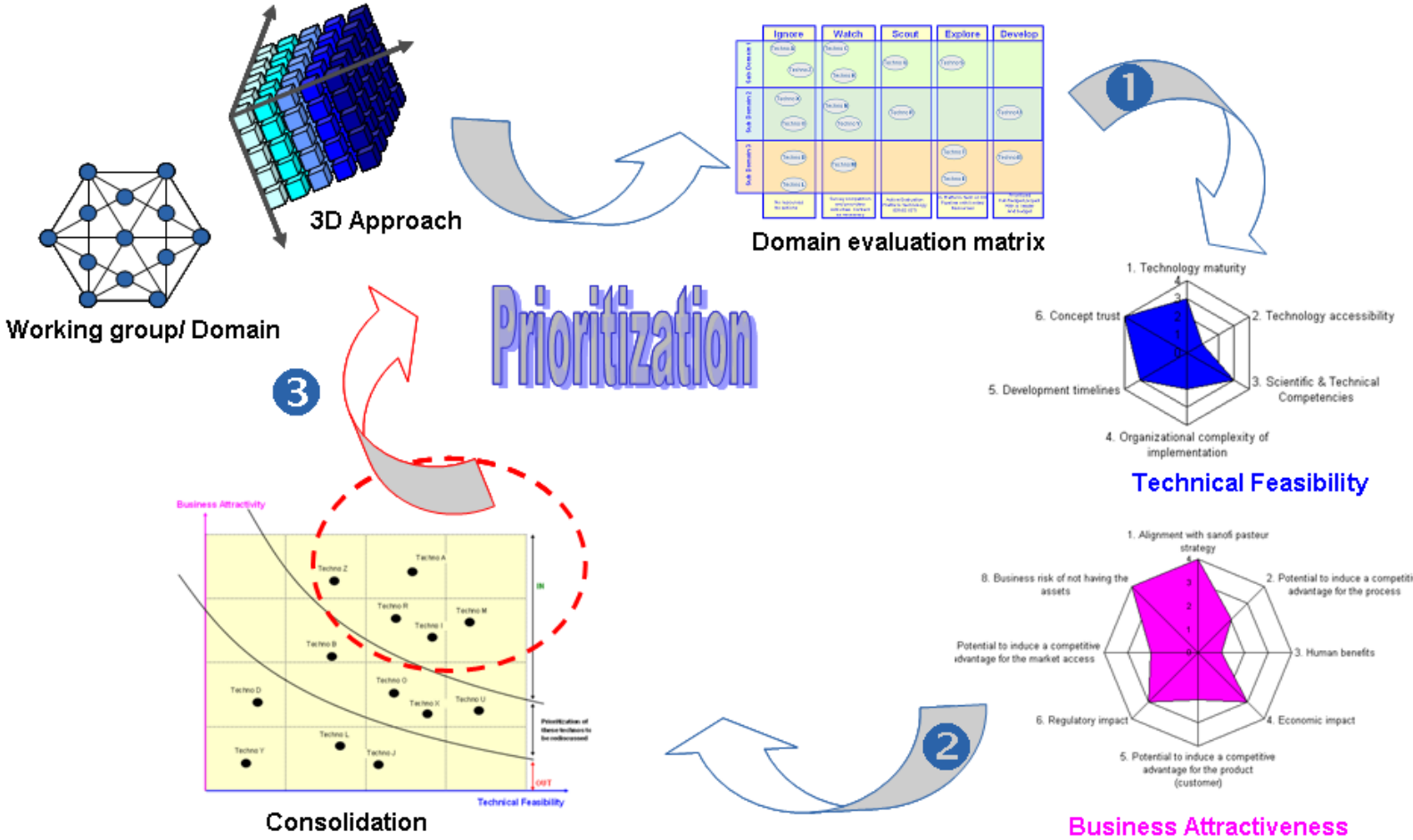
- **Objective is to ensure availability of innovative technologies needed to sustain Sp Industrial performance & products development**
  - Dedicated forum , group of people mixing operators, experts, R&D and industrial functions
  - Sponsorship shared between R&Dand IO management
  - Scan , evaluate, recommend, ensure implementation
  - Stimulate innovation, share knowledge, develop synergies
  - Established governance
  - Three year rolling forecast budget , yearly review and technology assessment
  - Internal awards program

- **Selected panel domain focus**
  - One axis for development considers single use technology
  - Provide clear understanding on advantages/drawbacks
  - Product and constraints limits
  - Impact on CAPEX, COgs, process facility design

Editing a Roadmap in the SUT diversity

***KITE** Sanofi pasteur perspective*

Single Use Technology Review- Prioritization process



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New Products, New Technologies

Building up business case on SUT

- **Single use technologies (SUT) offer numerous advantages, drivers consider saving in time and cost, however questions remains to be addressed when deciding for implementation:**
- **Standardization**
  - Procurement, alternative supplier qualification
  - Operator training
  - Compatibility with existing process / equipment
  - Development capability
- **Economic assessment**
  - Until time of ‘’’total SUT facility’’ cost saving (water, steam, classified area, equipment, facility..) is complex. Clear advantage in capital investment, to be valued against operating costs
- **Quality**
  - Perform leachable and extractable studies. Stress tests for specific applications
- **Industrialization**
  - Process scale-up
  - Process modelization
  - Process transfer / plant peak throughput/capacity

Upstream SUT Score Card

Selecting the right equipment for your need

Stirred-tank bioreactor system

Bioreactors features

	P.Guerin /ATMI	Sartorius / Stedim	ThermoFischer / Hyclon	Xcellerex
Supplier				
Product Name	Nucleo	Biostat Cultibag STR	S.U.B	XDR
Scale (working)	20-50-200-500-1000L	50-200L	50-100-250-1000L	50-200-1000-2000L
Stirring	Top driven paddle impeller, mechanic coupling, cubical geometry	Top driven marine impeller or rushton, magnetic coupling, cylinder geometry	Top driven tilted pinched blade impeller, mechanic coupling, cylinder geometry	Bottom driven marine impeller, magnetic coupling, cylinder geometry
Aeration	Overlay or sparging (sparger attached to paddle)	Overlay or sparging (ring or micro-sparger)	Sparger / Membrane aeration	Sparger
Sensor	pH,DO, standard probes KPC insertion, disposable sensor option	pH, DO disposable optical patch	pH,DO, standard probes KPC insertion, disposable sensor option (finess optical)	Disposable pH, DO
T° regulation	Double jacket	Heating blanket	Double jacket or heating blanket	Double jacket
Automation capability and level of process control	**Pierre Guerin** control unit supplied, running on LabWindows. SAS automation base on PLC (Siemens/ Allen Bradley) or Delta V or SCADA	Sartorius control unit, SCADA, BioPAT & MFCS	Process control unit **not supplied** with the system. (excl. mixing, heating). 3rd party systems required for new installations	**Delta V or PLC** adaptable. High level of process control via e-factory GAMP compliant software interface
Vendor maturity/ Knowledge-base	Pierre Guerin is established supplier in the fermentation equipment market and control systems. ATMI is established supplier of single use technologies	Sartorius is established supplier in the fermentation equipment market and control systems. Stedim is established supplier of single use technoloies	Hyclone is an established supplier in the cell-culture media market. New to the fermenter/ bioreactor equipment market	Xcellerex is a relatively new company and both a service provider (contract manufacturing) and single-use equipment provider. (est. 2003)
Product maturity/ installed base	Nucleo systems on the market since Q1 2008	Biostat systems on the market since Q1 2010	S.U.B systems products on the market since Q2 2006	XDR systems are new products in development and market since Q1 2006

- **Disposable systems can provide advantages in terms of:**
  - **Rapid facility installation and lower CapEx allow control of risk & costs**
  - **Viable cost-structure even at small capacities**
  - **Flexible production configurations can provide for surge capacity needs**
- **Bioreactor's URS**
  - **Technical assessment**
  - **Suppliers procurement review**
    - ***Manufacturing controls &quality systems***
    - ***Product development capability***
    - ***Supply chain security***
    - ***Available sensor technologies***
    - ***GMP operations and product qualification***
    - ***Manufacturing methods, capacity***
  - **Fit with existing/to be developped process**

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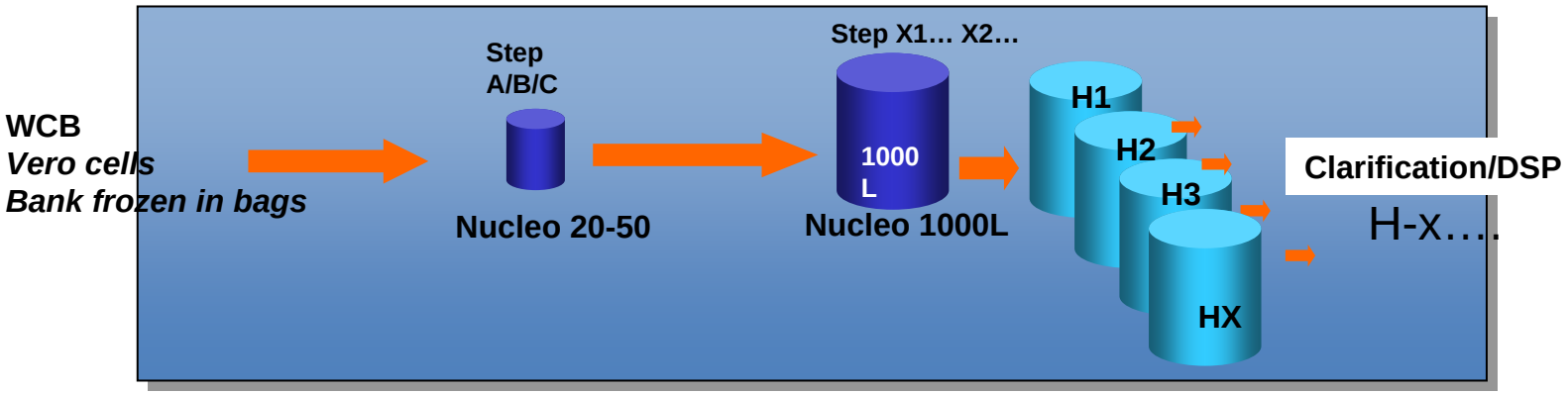
Implementation of Single Use Technology

Vaccine Manufacturing Case Study

- **Process Development**
  - Vero cell culture expanded in serum free media and increasing stainless steel bioreactors scale, pilot established at 180L scale.
  - Multiple harvest from production bioreactor

- **Full disposable cell culture process line:**
  - Including seeds



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Vaccine Disposables Process Cost evaluation

- **Process Cost model with BioSolve ® considering:**
  - Upstream & Downstream Process
  - Capital Investment
  - Utilities requirements
  - Labor time
  - Raw material and consumables
  - Others (waste management, maintenance, metrology….)

Scenario	Bioreactors line	Intermediary product hold + media prep (<200L)	Intermediary product hold + media prep (>200L)
1	Stainless steel	Stainless steel	Stainless steel (line transfer)
2	Disposable	Disposable	Disposable
3	Disposable	Disposable	Stainless steel (line transfer)

- **Modelling with Biosolve® software, Biopharm services**

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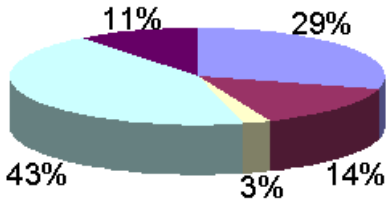
Vaccine Disposables process cost evaluation

- **Relative Cost Spread**

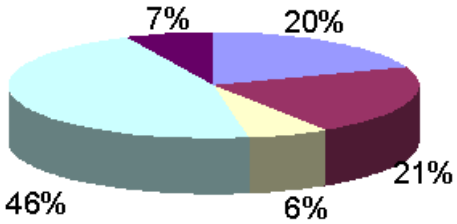
Scenario 1

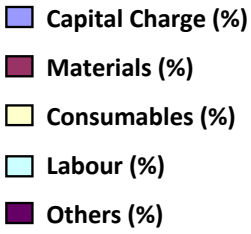
All stainless steel



Scenario 2

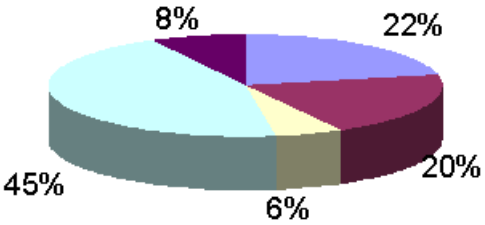
All disposable



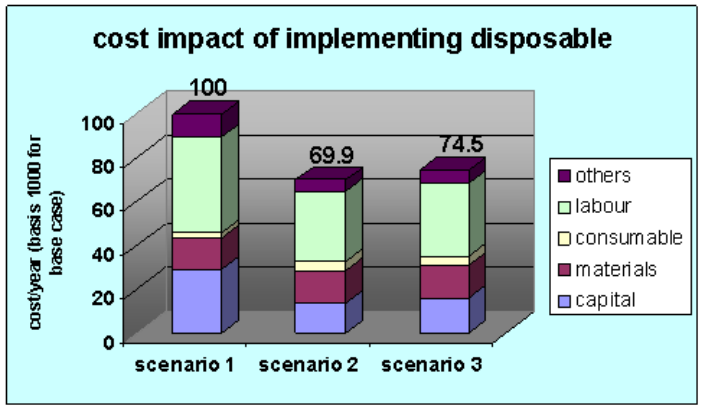


Scenario 3

All disposable, transfer lines



- **Implementing disposables decreases significantly the rate dedicated to capital charge ~< 30%**
- **impact on dose cost up to 40%**



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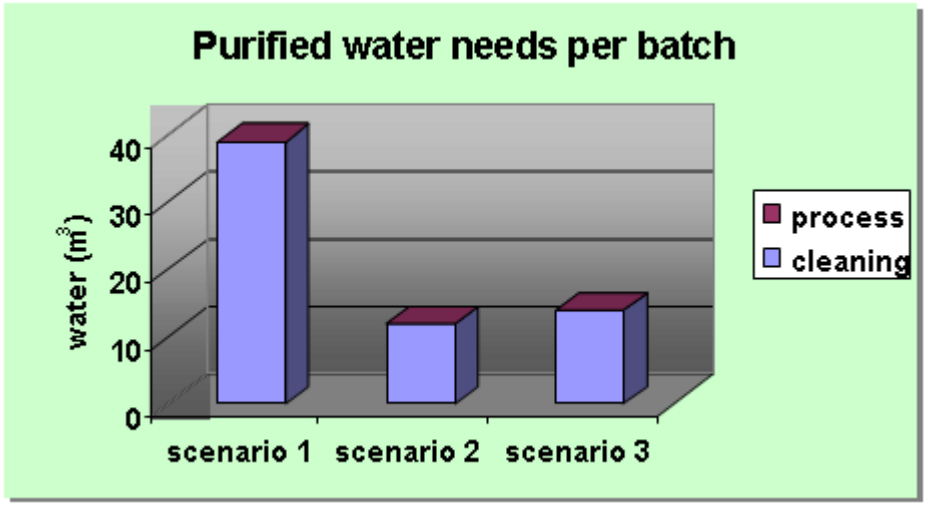
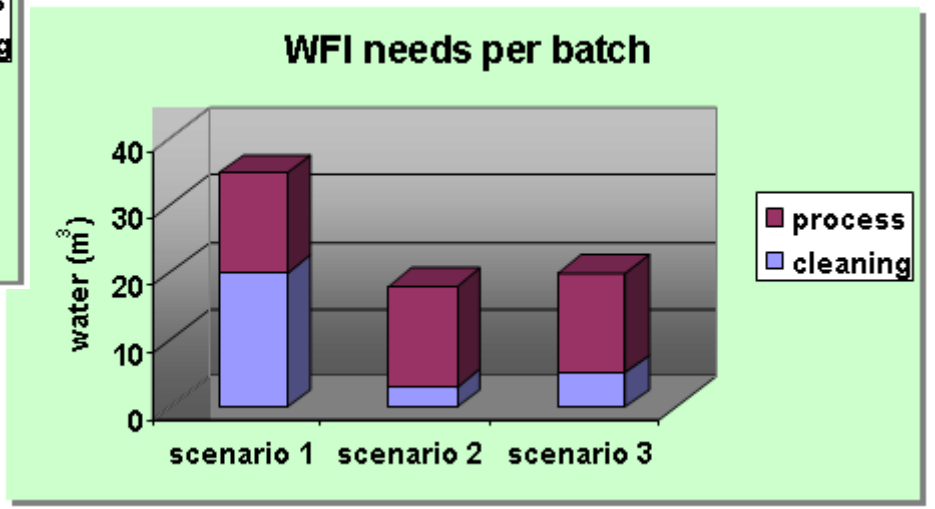
Disposable process, utilities requirements, Water

- Implementation of disposables at each step allows a decrease of 90% and 50% of PW and WFI needs





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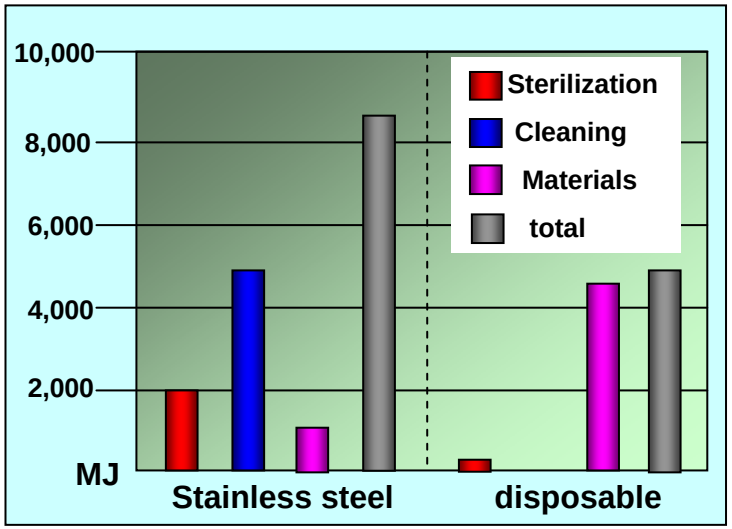
Facility Engineering & Design Consideration

Environmental impact

Energy assessment

- **Disposable process (gamma irradiation sterilization, manufacturing of tubing…) decreases from 40 to 60% needs of Energy comparing with traditional process**
  - SIP/CIP 1T CO2/ batch
  - SUT 0.4 T CO2 / batch
- **However to be balanced with other environmental impacts**
  - Employees driving to work 2T/CO2/ batch
  - Global energy consumption (HVAC..) 20T CO2 / batch



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Disposable waste

- **Recycling : implies waste select, minimal quantity, sometimes specific treatment (ex: disposable sensors)**
- **Energy production : 1L plastic = 1L fuel but high investment**
- **Incineration without energy recovering : better than landfill, modern incinerator allows CO2 capture**
- **Landfill : low cost and applicable to most of solid waste. High impact on environment (noise, odor, visual aspect)**

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SUT-Metrology/Maintenance impact

Example

Maintenance/metrology burden at 500L scale

		stainless steel bioreactor	*bioreactor w/o CIP/SIP*	*SUB*
Sensors	**Temperature**	14	3	3
	Flowmeter	4	4	4
	Pressure sensor	2	2	1
	vessel weight	3	3	3
	pH, PO2, PCO2	5	5	5
	top opening	1	1	0
	Stirring speed	1	1	1
	total sensors	**30**	**19**	**17**
Valves	**CIP/SIP valves**	45	0	0
	process valves	4	4	4
	gaskets	297	122	0
	steam trap	12	0	0
	total regular maintenance	**358**	**126**	**4**
Validation / Qualification	Cleaning	1	1	0
	sterilizating	1	1	0
	decontamination	1	1	0
	total validation	**3**	**3**	**0**

High decrease of metrology, regular maintenance and annual validation when getting a manual single-use bioreactor

- Potentially decreasing shut down period (two weeks less)
- Simplifies trouble shooting/ focus on process
- Spare parts / maintenance logistic decreases

Classified area SUT allocation

- **SUT leverage on decreased area classification**
  - Since floor space decreases, classified area decreases
  - Lower room classification may be accepted , mainly by using aseptic connectors
  - Modular concept, where each unit operation is self contained in its own controlled environment
- **However major floor space reduction take place in unclassified area's**

		Facility		
Room	Classification	Single-Use	Hybrid	Stainless Steel
CIP	NC	-100%	=	=
Washing	NC	-80%	-	=
Material Preparation	C	= (?)	=	=
Media/buffer Preparation	C	=	=	=
Media Holding	C	= (??)	=	=
Process	C	=	=	=
Utilities Steam	NC	-20%	=	=
Over-heated Water	NC	-20%	=	=
HPW	NC	-20%	= (-)	=
WFI	NC	-20%	= (-)	=
HVAC		=	=	=
Decontamination	NC	= (-)	=	=

Capex and COGs

Vaccine case study Summary

Capex cost could be decreased by over 40%.

- However current processes do not meet existing SUT technologies at all steps
- To be balanced by SUT costs increases

Other impacts

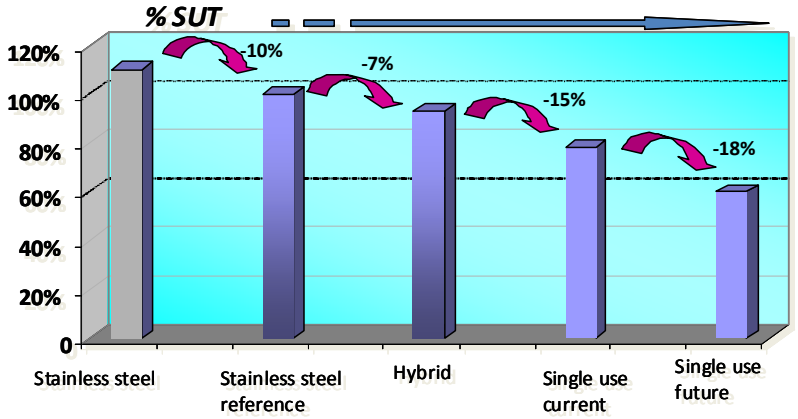
- (water, utilities, energy, headcount, etc…) assessed on several examples : benefits but are less significant.
- Reduced maintenance, metrology, shut down

SUT can significantly speed up project execution

- 70% automation, less piping
- Less long lead time equipment
- Less commissioning & qualification effort
- Modular concept, lower room classification may be accepted through aseptic connections

Preliminary engineering studies are key

- Technology choices requires long term binding commitment with SUT suppliers



Topic	Stainless steel	Single Use
Conception -specifications - manufacturing - FAT - documentation	14	4
Installation - Installation - SAT - User Training	1,5	0,5
Validation/qualification - QI/QO - QP non-product dependant - Qp product dependant (CIP)	5	2,5
Total Months	20,5	7

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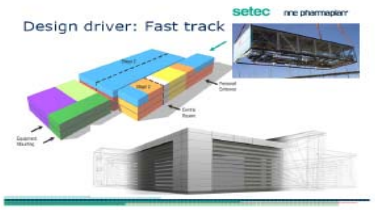

SUT impact on facility design

Trending towards modular design

- **Strategic approach :**
  - Multidisciplinary task force and survey
  - Case studies on actual and prospective projects
  - Large benchmark
- **Main conclusions**
  - Innovative approach of global facility design based on SUT can bring clear advantages
    - Drastic reduction in project cycle time
    - Significant opportunity to decrease capex (over 40%)
  - But many technologies are not yet mature and there are scale limitations
    - Hybrid solutions more likely in the short term
  - Cost wise, there is a clear tradeoff CAPEX vs SUT consumables
    - Consumables costs needs to be monitored not to offset the benefits (example: over 20 batches / year)
    - Other cost benefits (ex labor) claimed are less significant and project dependent
  - Single use plants (SDU) is the clear target for some projects:
    - Multiproduct, scale < 1000 L, limited number of batches / year
    - Fully applicable to launching units
    - Fast track projects.
  - To secure, SUT bring additional supply chain risks (especially from rank 2 suppliers)

MAb Model Case Study

- Question on process definitions, where does the money go?
  - Investigate single use bioreactor vs stainless steel
  - How much product titer increase makes sense
  - Improve facility utilization, process intensification
  - What is cost allocations?
  - What are the leverage for process cost efficiency?
  - How far full single use process is cost effective?

Scenario's

Process assumption -Variables		
Bioreactor	1M3 Stainless	1M3 single Use
Working volume	750L	750L
I seed train	Shaker, 20L wave, 50L wave, 100L SS bioreactor	Shaker, 20L wave, 50L wave, 200L wave
Batch/year	10	20
Production time days	14	14
Product titer g/l	0,8 - 1,0 - 1,2 - 2 - 4	
Overall yield %	70%	
Resin life cycle	50	
Columns	Standart	Ready to process
Columns diameter	30	45

Monoclonal antibody single use opportunity

Case Study, Generic process scheme

Upstream

Equipment scenario

Thawing & cell expansion

Up to 25L, 25-30days

Bioreactor expansion

100L bioreactor, 3-4 days
14days

Media prep

Bioreactor production

1m3 bioreactor, 750L wv
14days

Bioreactor Harvest

Cell settling, three steps
Depth filtration cartridges,
Includes 0.22µm polishing
Harvest titer ~1g/l, yield ~90%

Downstream

Affinity Chromatography

BPG300, 14-28mg/ml capacity
Low pH hold, viral inactivation
0.22µm, 95 % yield

Cat IEC

BPG300, 20-40mg/ml capacity
0.22µm, 90% yield

An IEC

BPG300, 20-50mg/ml capacity
0.22µm, 95% yield

Viral clearance

Planova 20N , load < 150g/m2
0.22µm, 95% yield

UF/DF formulation

30kd , 5.5m2, 95% yield

0.22µ filtration

5mg/ml sollution,
Stored frozen in 1L bottles

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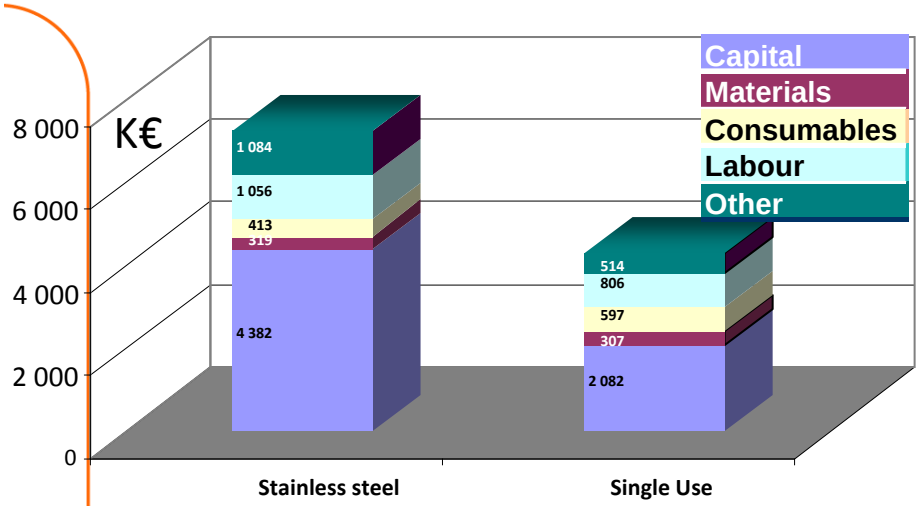
Monoclonal Antibody Case Study

Base Case

- 1 x 1000L Stainless Steel Bioreactor
- 750L working volume
- 14 days Fed-Batch process
- 10 batch per year
- 1g/l
- 3 steps chromatograpy
- 30 cm column chromatography
- 73 % DPS yield

Cost Comparison

Relative cost spread-Stainless vs SUT



Annual Cost of Goods

Capacity output: 5.5kg / year

SUT~788€/g

SS ~1327/g

~ 40% COG reduction SS vs SUT

~22% without CAPEX, under-utilized facility

- **Cost of Goods (CoG)** is lower for single-use
- **Total capital** is also less for single-use option

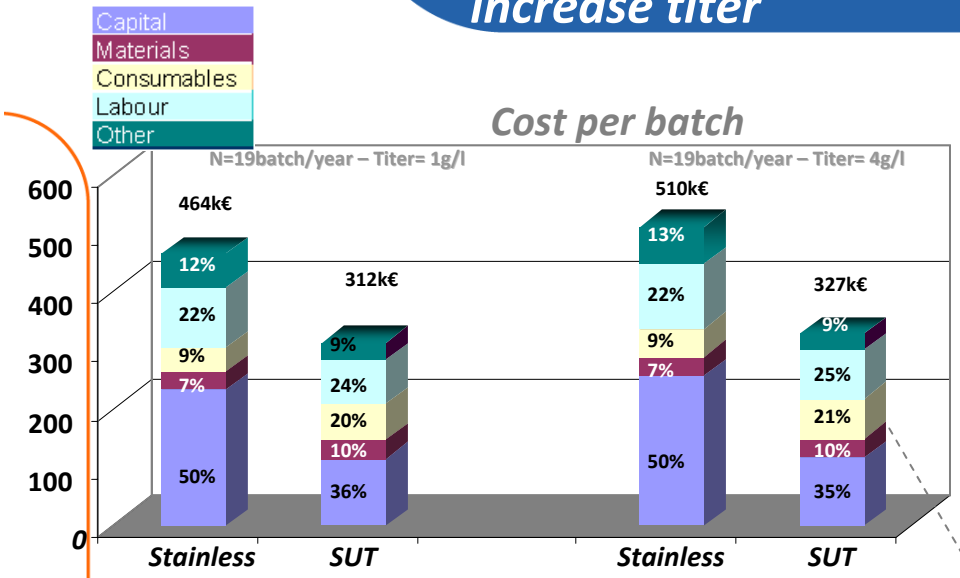
- **Traditional: 21 M€**
- **Single-use: 10 M€**
- **Capital drivers:**

Equipments, utilities, automation,piping

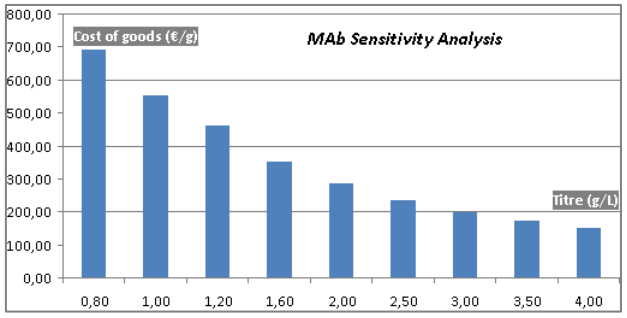
Comparison	Stainless steel	Single-Use	% Change
Annual CoG (EU€)	7 256 550	4 308 654	-41%
Capital	4 382 338	2 082 578	-52%
Materials	319 008	307 380	-4%
Consumables	413 984	597 084	44%
Labour	1 056 529	806 918	-24%
Other	1 084 691	514 694	-53%

Cost Comparison

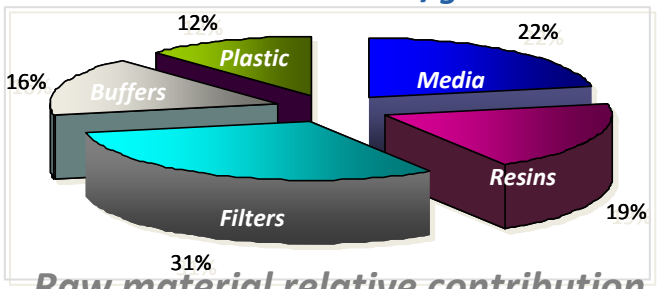
Cost spread-Stainless vs SUT, increased capacity utilization, increase titer



Comparison	Traditional	Single-Use	% Change
Annual CoG (EU€)	9 700 183	6 226 074	-36%
Capital	4 843 828	2 200 157	-55%
Materials	630 531	605 950	-4%
Consumables	904 055	1 306 547	45%
Labour	2 102 022	1 565 622	-26%
Other	1 219 746	547 798	-55%



- **Stainless vs Single-use**
- **19 batches per year (calculated for max schedule.)**
  - *Facility utilization moved from 40 to 90%*
- **Titer 1 to 4g/l**
- **More efficient use of capital**
  - *Respectively 28% & 36 % in COGs reduction for SS vs SUB*
- **Process intensification**
  - *Beyond capital, Increased titer, Cogs offset by DSP, fixed resin capacity, filter capacity*
  - *Additional savings through cycle time, scheduling*
  - *Bottom line COG's ~ 100€/g*



Raw material relative contribution

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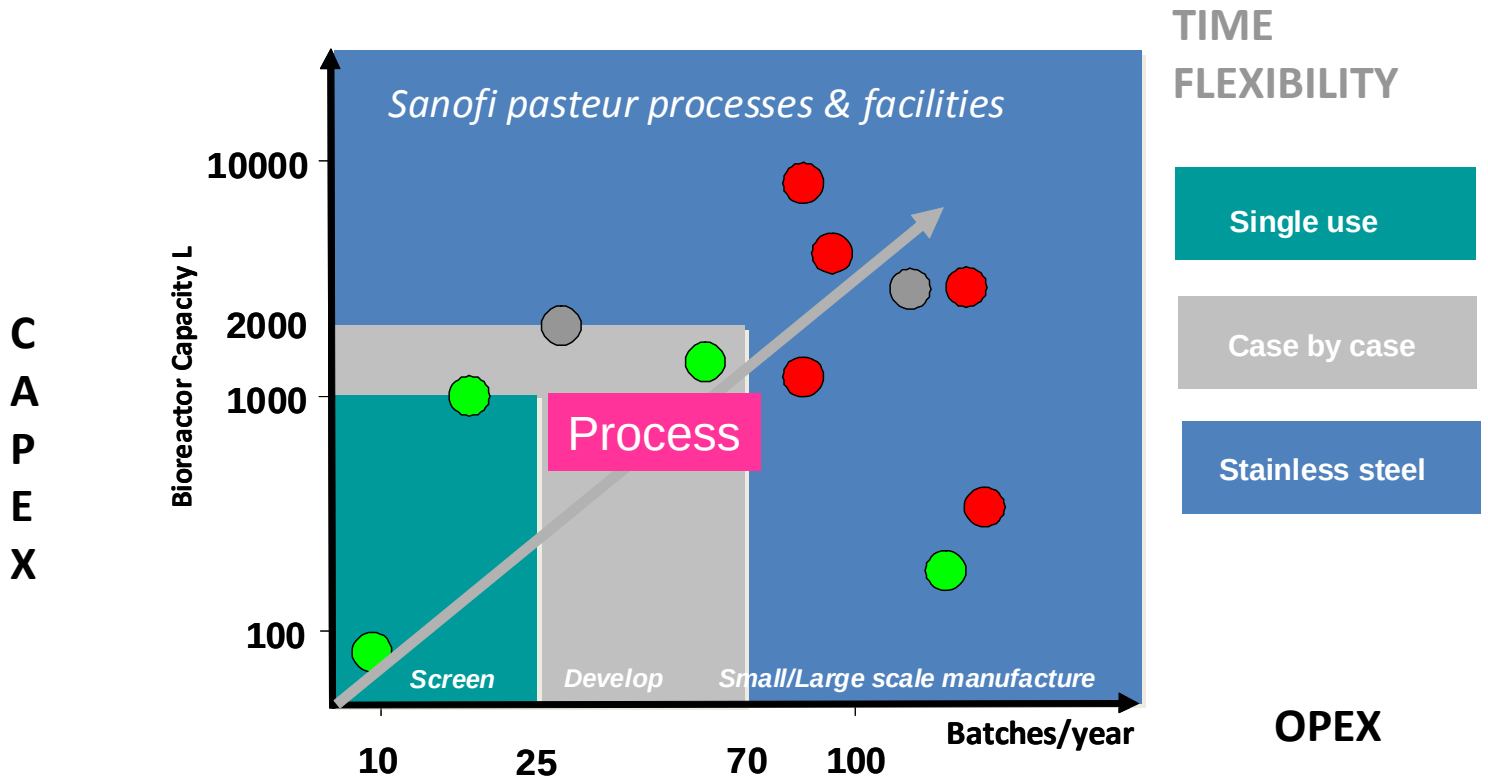
When do SUT make sense for upstream operation ?

Scale and capacity needs, the big picture



- Combination of SUT and high titer antigen expression have impact of economic benefit
  - Potential for significant interim capacity at manufacturing scale adapted to SUT
  - High titers drives for flexible operations allowing more candidates into clinic
  - Flexibility allows for multiproduct facility desing, according to scale needed
  - Open up for easier to manage process/manufacturing transfer when standardized

Summary cost's differences
SUT vs. Stainless steel equipment

Cost	Changes due to use of Single Use Technology
Capital Charge	▢Capital costs for Single Use Technology bioreactors, mixers, hold vessels is lower than for Stainless Steel equipments ▢No cleaning of Single Use equipment therefore lower water usage requiring less utilities ▢Large savings on pipework, control systems and validation ▢No CIP or SIP systems needed
Materials	▢Savings in cleaning materials in the single use scenario ▢Media costs and QC product testing are the same for both scenario's
Consumables	▢Low consumables for the stainless steel scenario (mostly filters) ▢Higher consumables costs for Single use scenario, 17% of total costs
Labour	▢No cleaning of single use equipment therefore ▪Large operator time savings ▪QA, QC time saving due to elimination of post-clean sampling inspection.
Other	▢More solid waste (plastic) for disposal, but much less liquid waste due to avoidance of cleaning ▢Less capital equipment giving lower costs of insurance and maintenance ▢Lower utility costs linked to the lower capital costs

Business case for new product new technology

Conclusions

- Process economic modelling is important to support targeted cost effective disposable process applications
- Economic impact of disposables depends on the scale & type of process
- Economic modelling can be used as a tool at early process development stage to predict and help decision for development solutions
  - Get the big picture
  - What are economic drivers in process definition, evaluate alternatives
  - Build or buy/Contract out
- Still to be modelled is how much you earn being first, or loose if not…

Acknowledgement

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Michéle Garnier
Hervé Pinton

Emmanuelle Trannoy
René Labatut

sanofi pasteur
La division vaccins du Groupe sanofi-aventis.