Using Disposables in an Antibody Production Process
A Cost-Effectiveness Study of Technology Transfer Between Two Production Sites

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Table of Content

Introduction

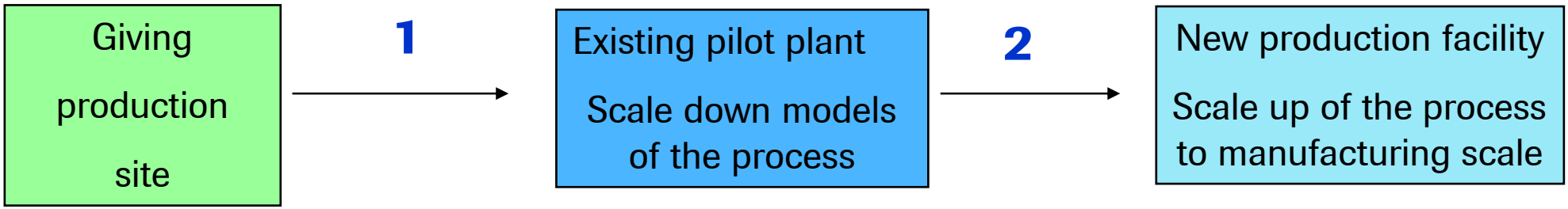
Process transfer

In 2004, the decision was taken to transfer a FDA approved antibody production process from an US production site to F. Hoffmann La Roche's new biologics production site in Basel, Switzerland.

Introduction

Two-step process transfer

- The process transfer was performed in **parallel** to the construction of the manufacturing facility
- The **transfer** was performed in **two steps**:



- **Advantages of this strategy**:
  - Save time
  - Gather experience with the process
  - Training of the new staff

Introduction

Current state of the existing pilot plant

- In Roche Basel a **25-year old** bacterial fermentation **pilot plant** was available:
  - used for the GMP-production (bacterial process)
  - 10-L , 100-L and 1000-L bioreactors
  - a purification suite
- Equipment was initially designed for **bacterial fermentation**
- **Purification** suite could be **simply adapted** to antibody purification
- **Fermentation** could **not** be **easily adapted** to mammalian cell culture:
  - limited space available for transformations of the existing facility layout
  - No delay of the process transfer acceptable to allow adaptation or transformation of existing facility

Introduction

Project constraints

- **Lead time** before project start: **6 months**

- Facility in use during lead time: **no shut down possible**

- **Modifications** of the existing pilot plant facility had to be:
  - within a short and defined time period
  - without disturbing ongoing activities
  - with available personnel resources
  - without major investments in hardware

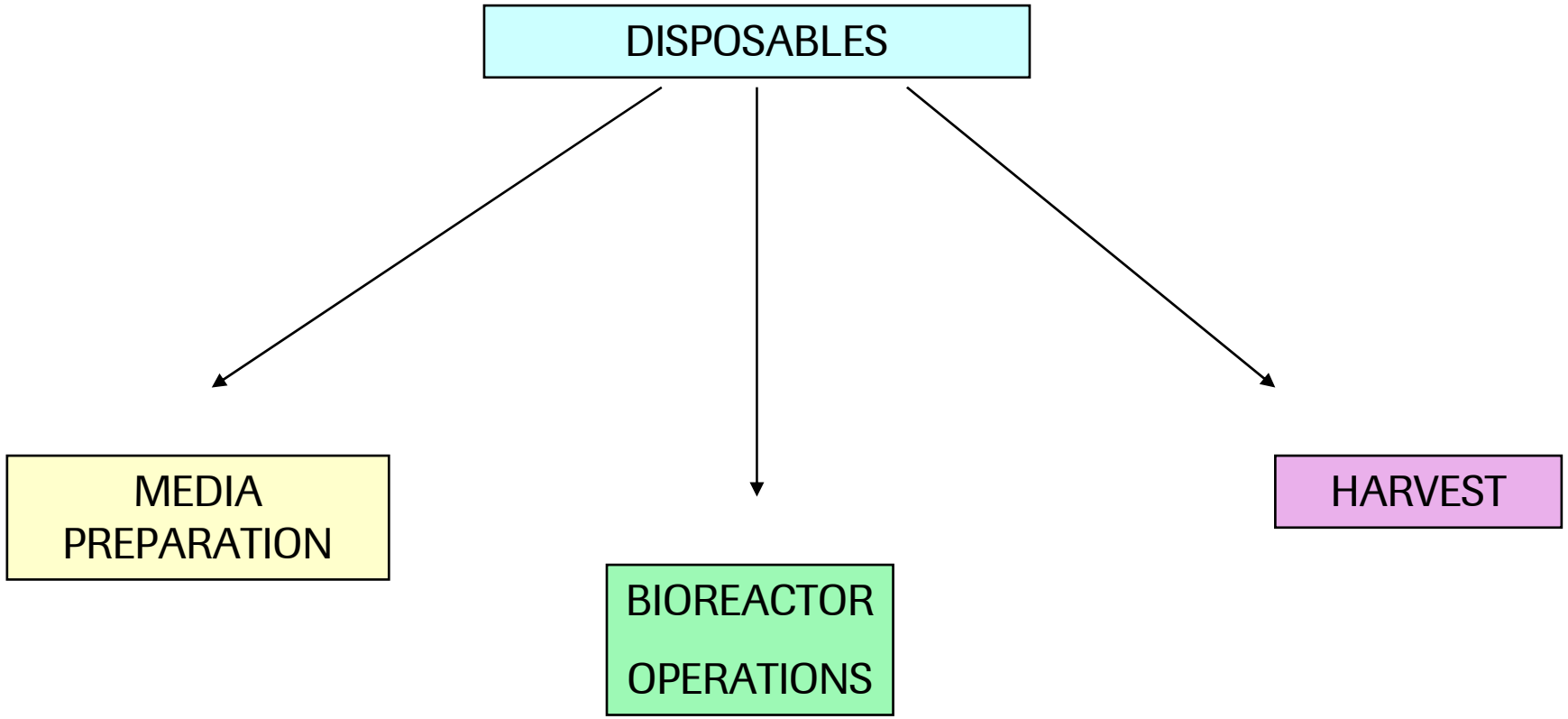
Traditionnal stainless steel VS Disposables

- **Major advantages of the disposables**
  - Significant reduction in lead time for project setup
  - Flexibility: implementation and use
    - customized solutions
  - Significant cost and time savings due to reduction in cleaning and sterilization times (utilities and personnel)
  - Significant reduction of bacterial contamination and cross contamination

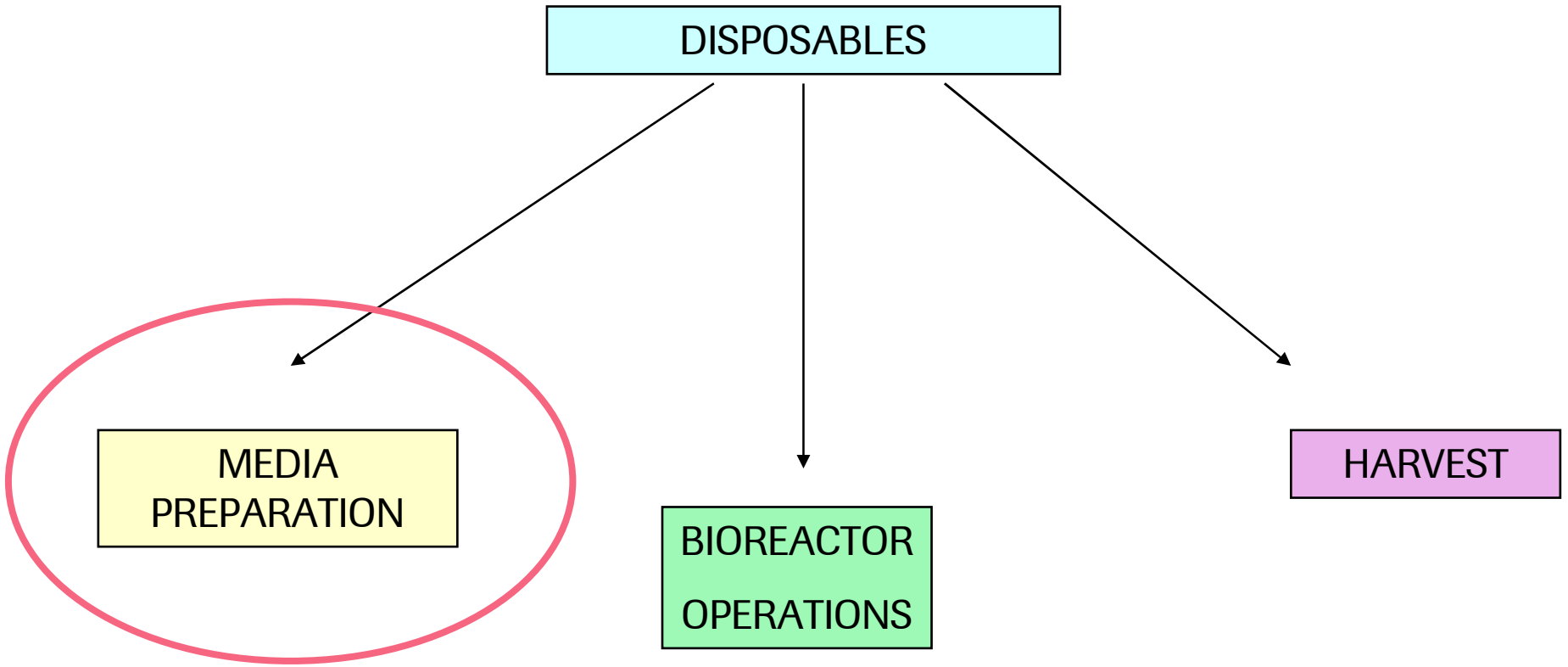
- **Major disadvantages of disposables**
  - Leachables / extractables
  - Extra time for training of personnel needed

=> Solution: implementation of disposables integrated into a traditional stainless steel facility to allow a fast transfer of a culture process

Implementation of disposables in the pilot plant



Implementation of disposables in the pilot plant



Media preparation

Goals

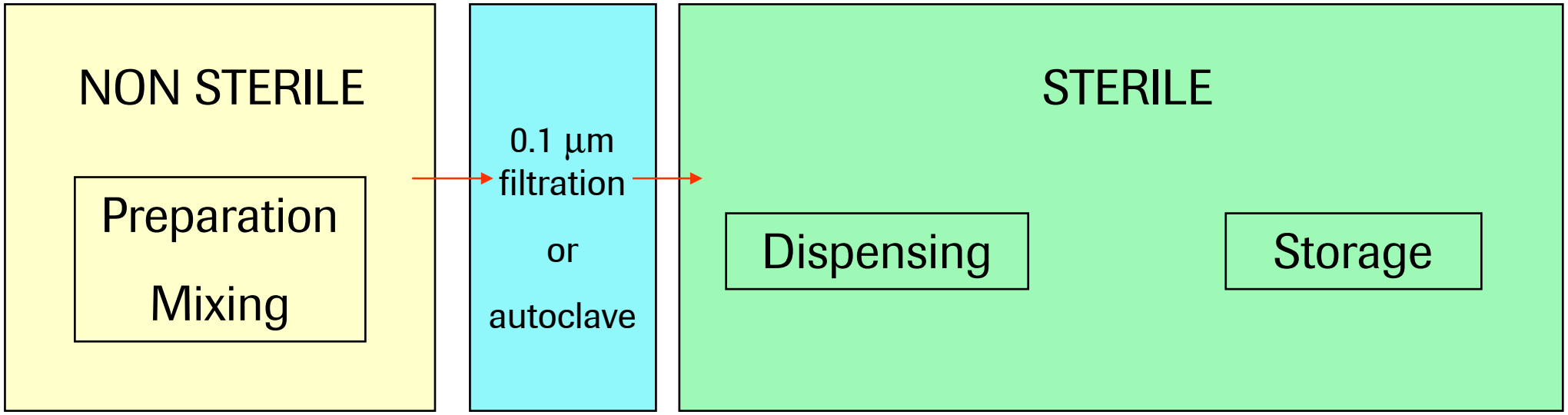
- Avoid major modifications to:
  - the electricity and water supplies
  - the facility
- Equipment used to prepare, dispense and store media and solutions:
  - can be easily moved around

=> All media and solutions used in cell culture are prepared in a **full disposable fashion**

Media preparation

What was implemented?

Media and solutions are prepared under non-sterile conditions. Afterwards, they are sterilized and dispensed in sterile containers.

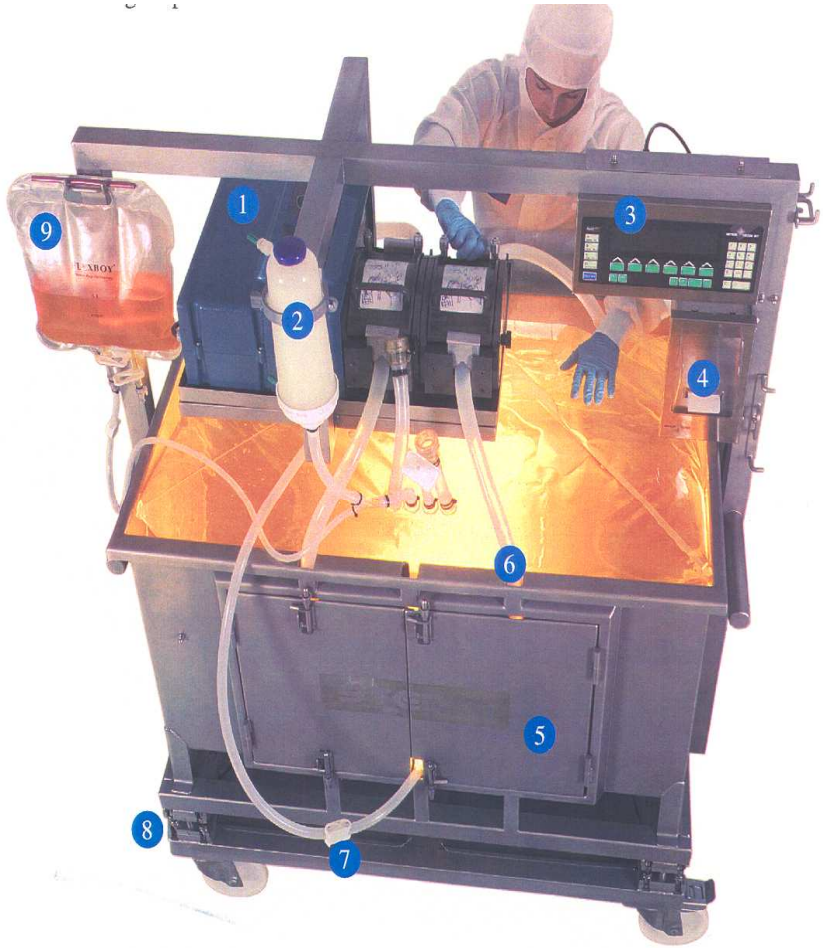


Media preparation: what was implemented?

Mixing

Medium volume to prepare	**Media preparation procedure**
3L to 100 L	Mixing with top agitator, dedicated plastic containers
100L to 200L	Mixing through recirculation, 200L 3D-bag in jacketed Palletank (possibility to heat the media)
200L to 500L	Mixing through recirculation, 500L 3D-bag in jacketed Palletank (possibility to heat the media)

Jacketed Palletank for mixing and heating



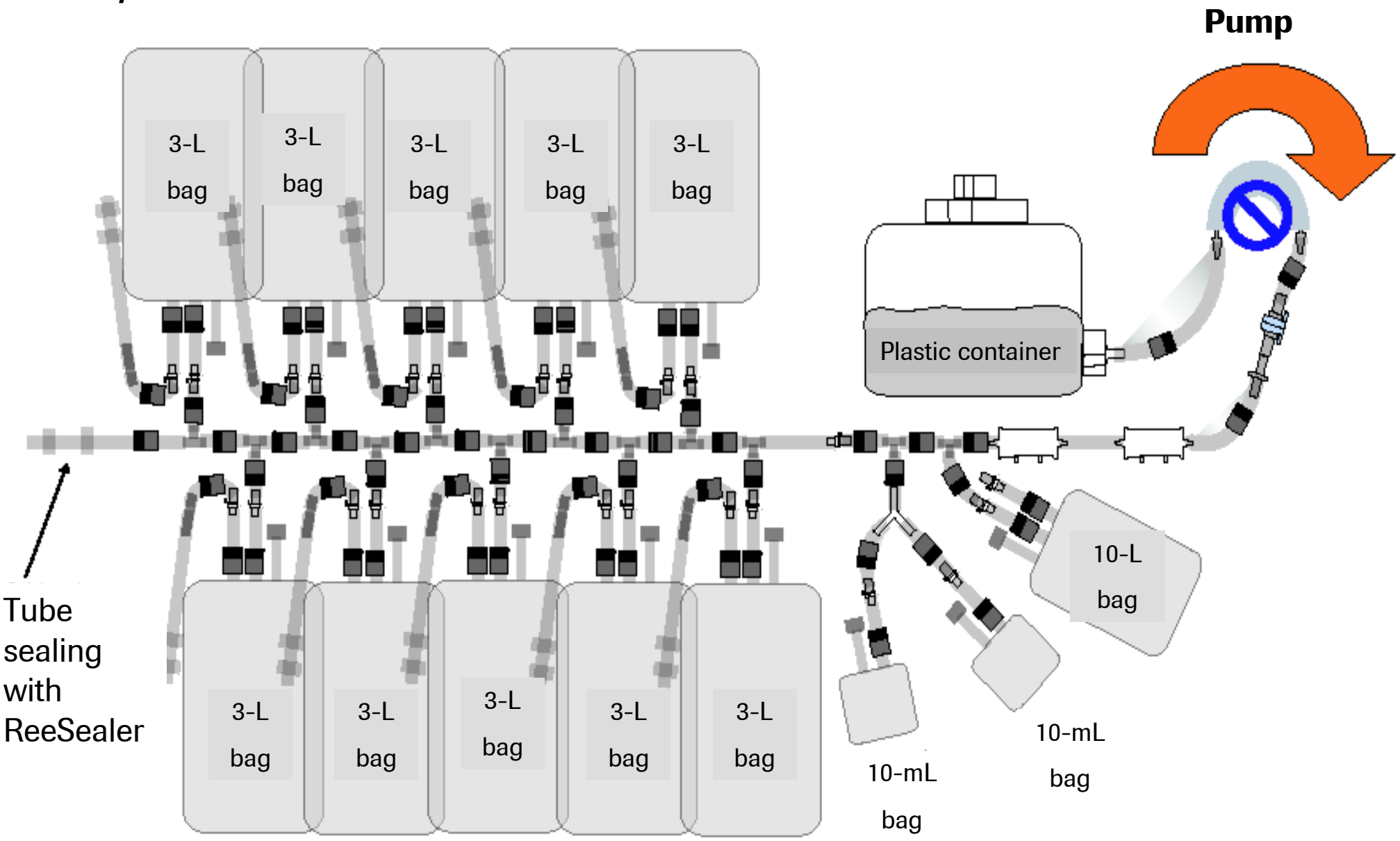
Media preparation: what was implemented?

Dispensing

Cell culture scale	Media dispensed into
Spinners	Plastic bottles
2L Bioreactors	2D-Bags, 3L
10L Bioreactors	2D-Bags, 20L
30L Bioreactors	2D-Bags, 50L
100L /250L Bioreactors	3D-Bags, 200L-500L

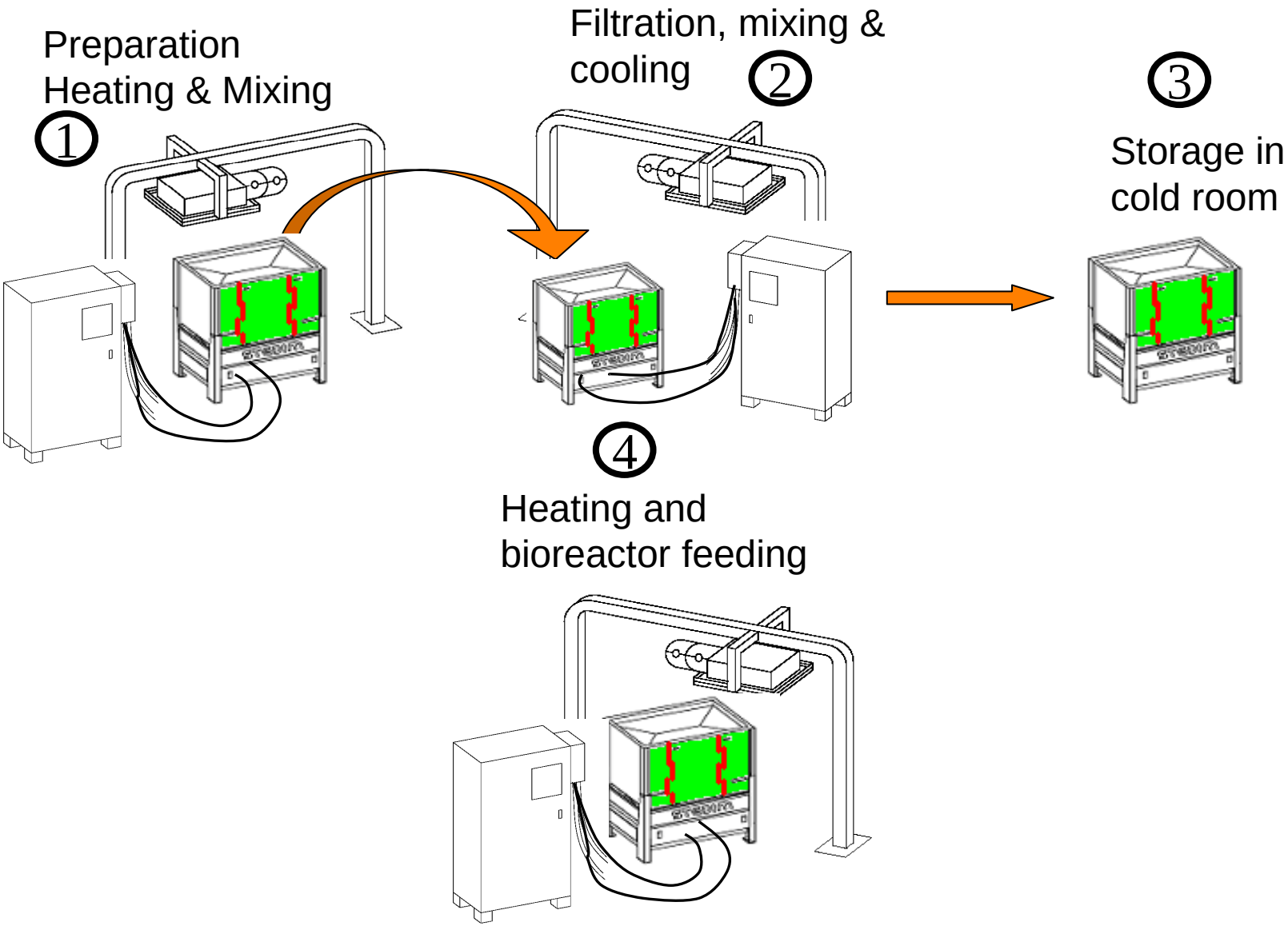
Media preparation example

Preparation of volumes from 3 to 100L

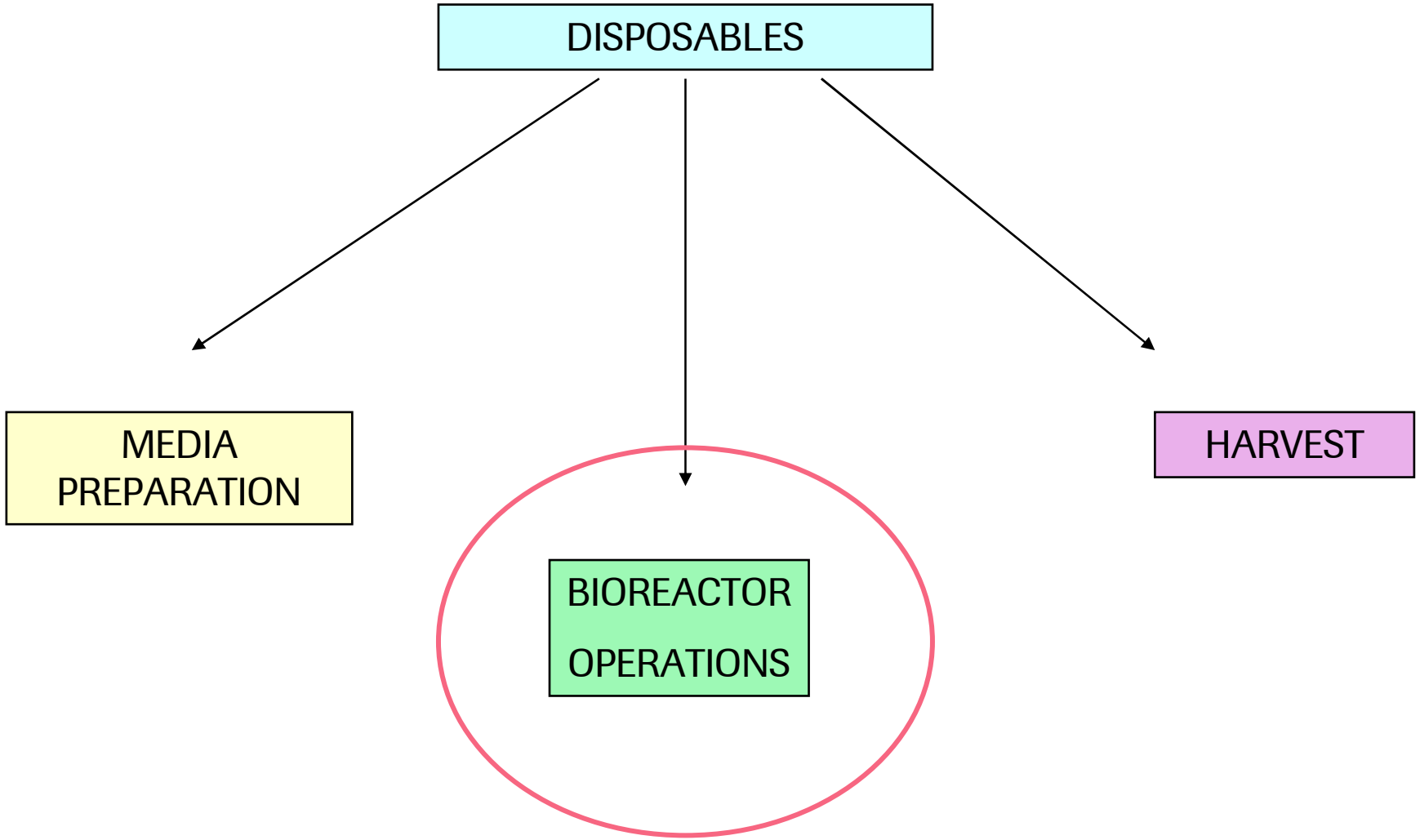


Media preparation example

Preparation of volumes between 100L and 500L



Implementation of disposables in the pilot plant



Bioreactor operations

Goals

- **All media and solutions** used in cell culture should be **connected** to a bioreactor in a fully **disposable** fashion

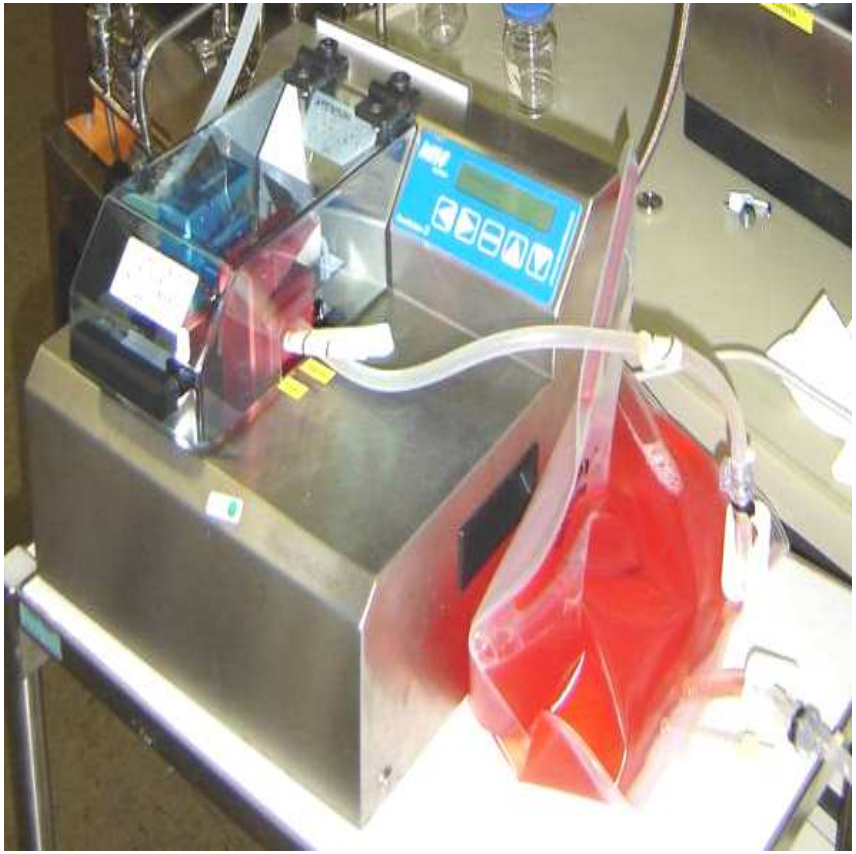
- **Connections** to bioreactors needed for addition (or removal) of cells media, solutions should be made through:
  - welding and sealing
  - steam through connections

- **Sampling** of bioreactors is performed in a fully **disposable** fashion

Bioreactor operations

Connection of media or solution

Steam through connection



Connection through welding

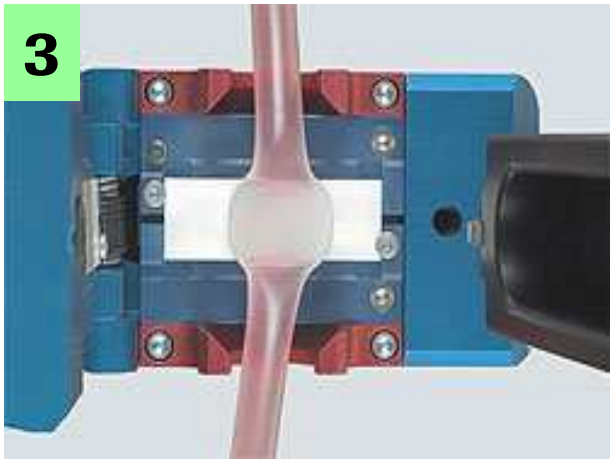
Bioreactor operations

Disconnection of bags through sealing

1

2

3



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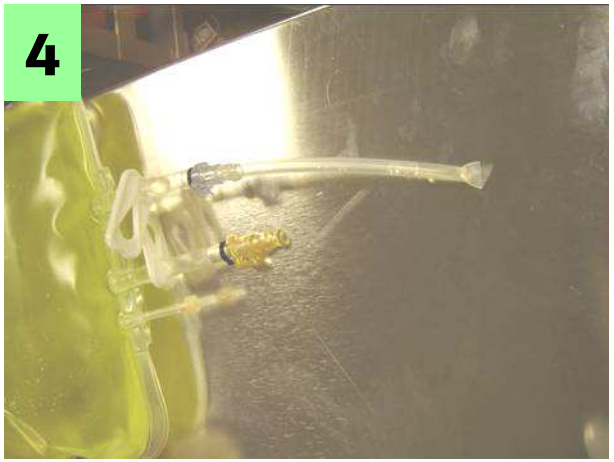
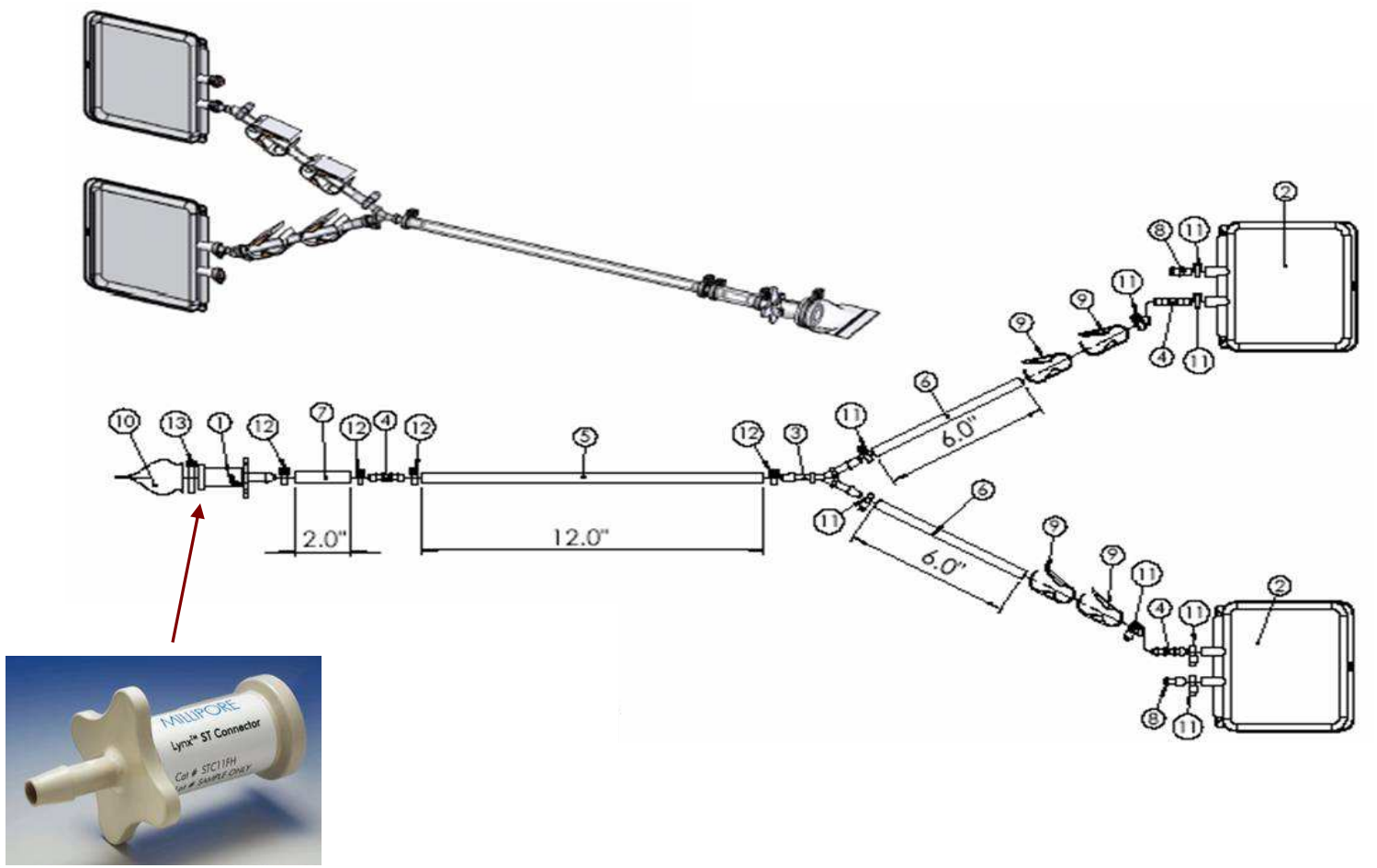


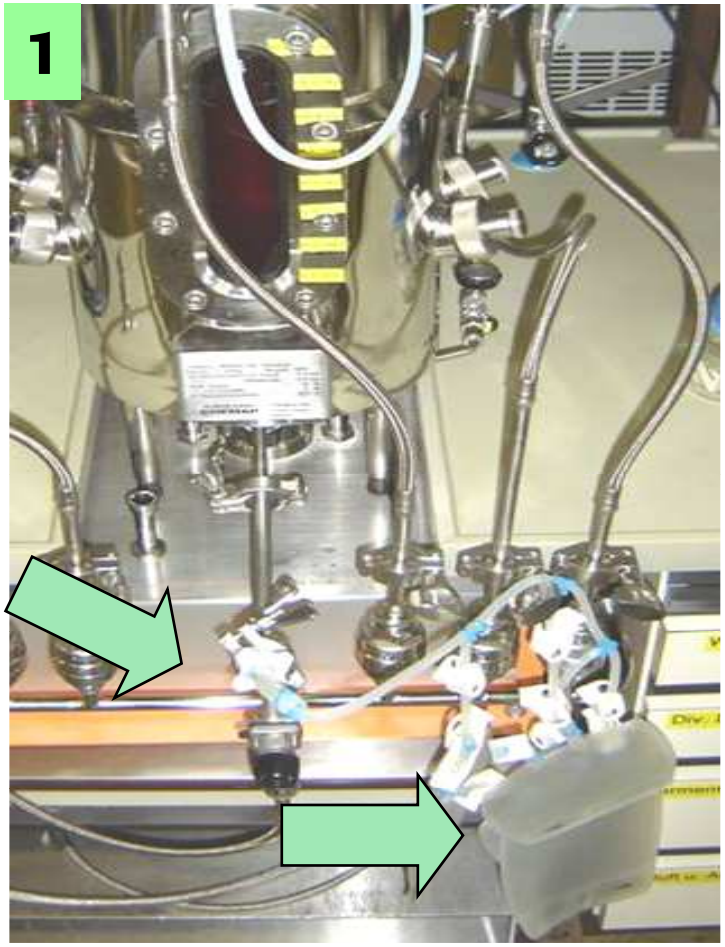
Bioreactor operation

Bioreactor sampling setup



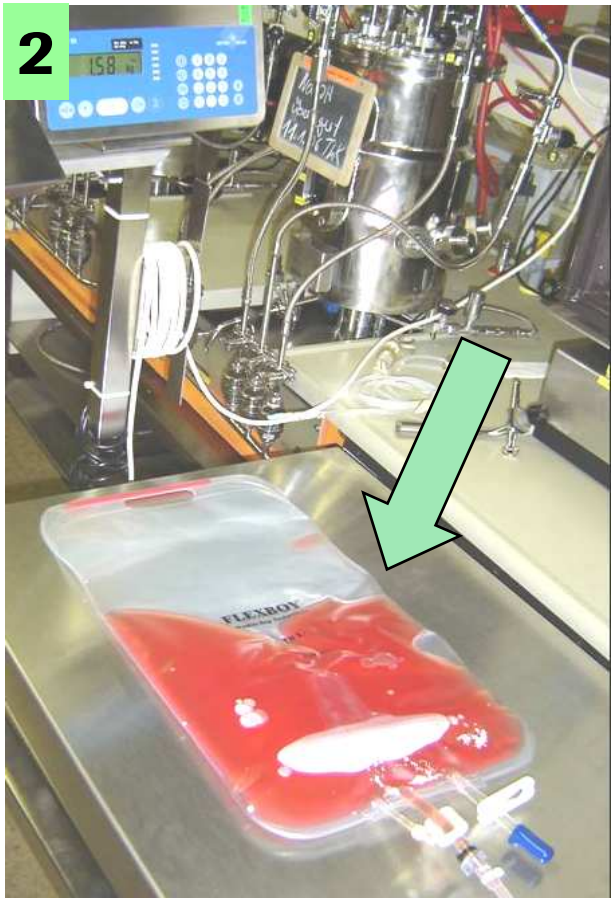
Bioreactor operation

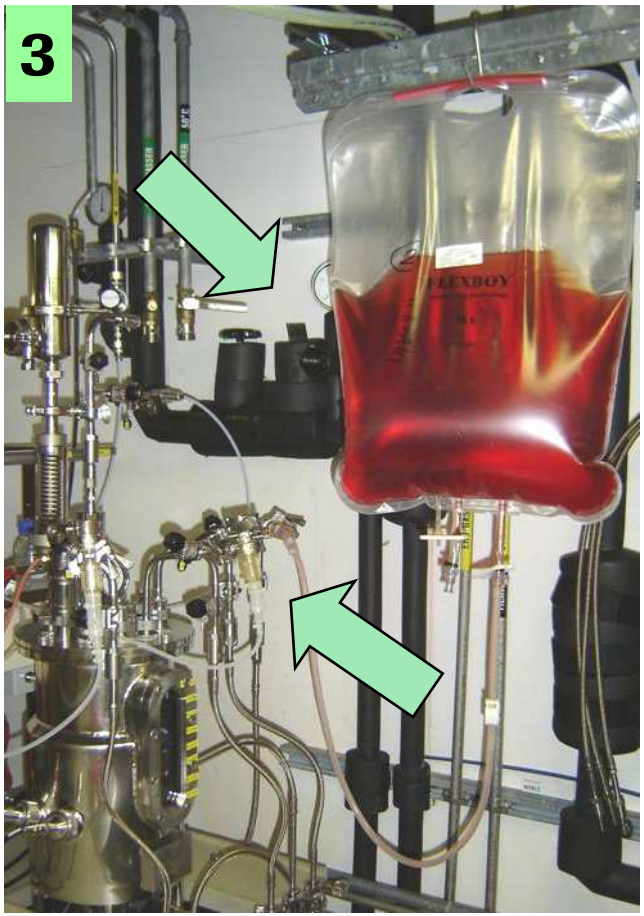
Sampling procedure



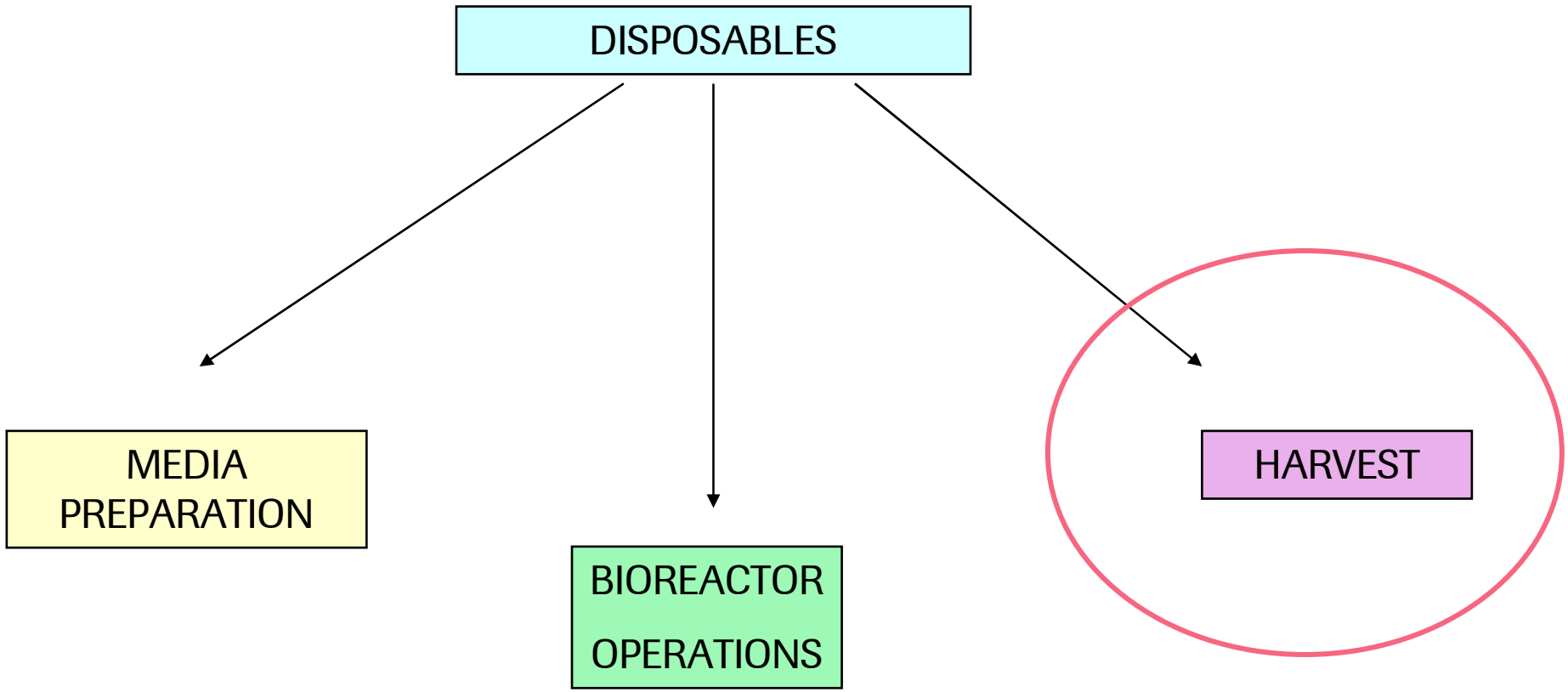
Bioreactor operation

Performing a passage operation in a bioreactor





Implementation of disposables in a pilot plant



Harvest in the pilot plant

Stainless-steel	**Step 1** Centrifugation
Disposable	**Step 2** Filtration •cascade of different filters •Scale down model of the manufacturing filtration cascade **Step 3** Dispensing into 100-L units (Stedim 3D Flexel bags)

Cost effectiveness study

- **Successful implementation of disposables:**
  - All solutions developed and implemented within 6 months while the pilot plant was still operating
  - Process successfully transferred
- **Economical evaluation supporting the benefit of the use of disposables over stainless steel and multi-use solutions was performed**

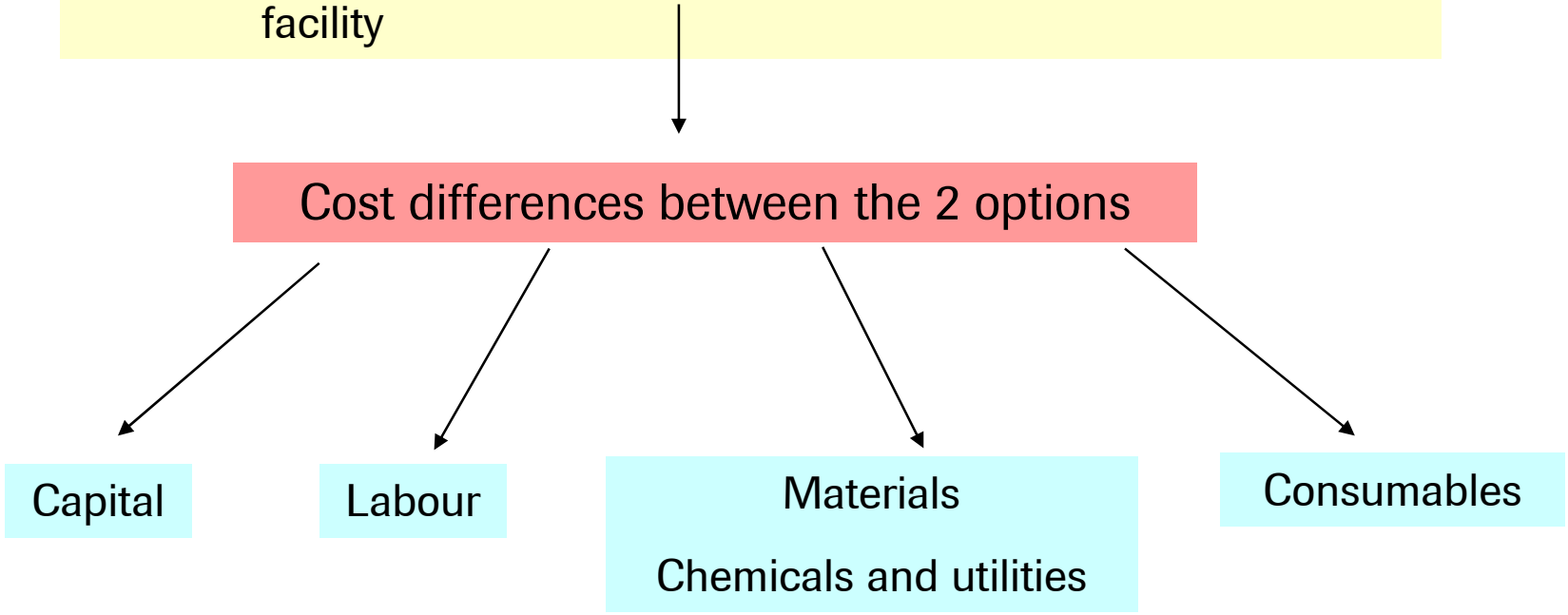
- **Cost analysis model: Biopharm Services, Sartorius Stedim, F. Hoffmann la Roche**
  - Disposable versus traditional
  - Information from Roche and Stedim Biosystems

Cost analysis model

Traditional versus Disposable

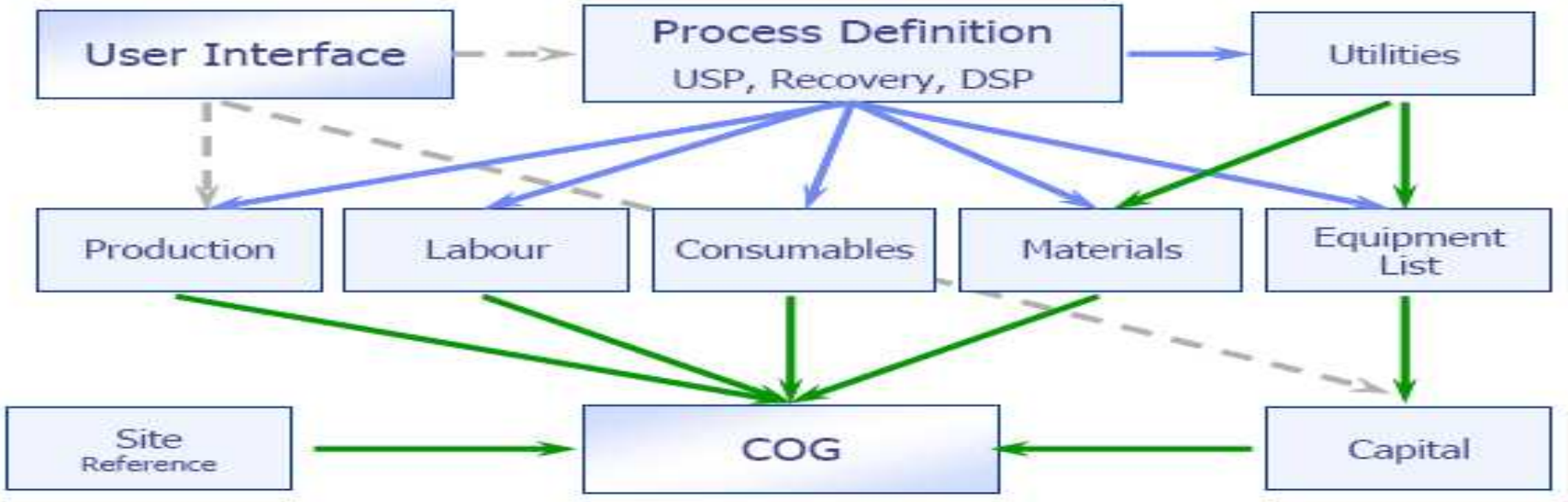
Focus on media preparation, seed train, bioreactors

- Seed operations (from thaw until production step)
- Installed single-use infrastructure systems
- Consumables and running costs
- Cost of the shut down for the refurbishment of the facility
- Size and costs of the media preparation and bioreactor facility



Cost analysis model

- **Spreadsheet-based approach**
- **Cost model**: modules using the worksheets in an Excel workbook.
- **Each module** = a user-defined entry worksheet, a calculation worksheet or a combination of both.
- Process information => captured in the cost model => **operating costs**
- Link between the modules :



Cost Analysis model

Model Inputs

Production	Seed Train for 100L Scale		1x30L
	Product Titre	g/L	
	Penalty for Shutdown		No
Currency	Symbol		€
Capital	Cost of Capital	%	12%
	Future Value	%	10%
	Period	yrs	8
	Include capital		Yes
Operation	Weeks per year	wks/yr	48
	Operator hours per week	hrs	40
Utility Specification	Specify PW Cost		Yes
	Cost of PW	€/L	0.01

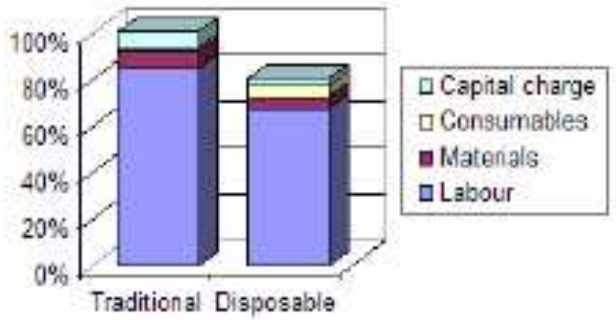
VARIABLES

Key to formatting

black text	Input parameter
blue text	Total calculated value (formula in cell)
blue text	Calculated value (formula in cell)
blue text	Validated cell entry
black text	Static text
Company:	**Roche**
Project title:	**Cost of Goods Model**
Description:	**Traditional vs Disposable Media Preparation**
Version:	**V00**
Date:	**06/07/2007**

Model Outputs

PRODUCTION			Traditional	Disposable
Throughput	No. of 10L Batches	#/yr	23.0	23.0
	No. of 30L Batches	#/yr	6.0	6.0
	No. of 100L Batches	#/yr	9.0	9.0
	Total	#/yr	38.0	38.0
Water Usage	Purified water (PW)	L/g	747	19
		€/g	7	0
		€/L	0.30	0.30



BREAKDOWN OF COST SAVINGS

Cost Savings	Capital charge
	Consumables
	Materials
	Labour
Total Cost Savings	

NOTE: Cost Savings are for the values of the Disposable option below that of the Traditional option
Negative values occur where the disposable option is more expensive.

Savings for the start-up phase over the course of the first year

Model Inputs

Production	Seed Train for 100L Scale		1x30L
	Product Titre	g/L	
	Penalty for Shutdown		Yes
	Shutdown Duration	months	4
Currency	Symbol		€
Capital	Cost of Capital	%	12%
	Future Value	%	10%
	Period	yrs	8
	Include capital		Yes
Operation	Weeks per year	wks/yr	48
	Operator hours per week	hrs	40
Utility Specification	Specify PW Cost		Yes
	Cost of PW	€/L	0.01

Model Outputs

PRODUCTION			Traditional	Disposable
Throughput	No. of 10L Batches	#/y	15.0	23.0
	No. of 30L Batches	#/y	4.0	6.0
	No. of 100L Batches	#/y	6.0	9.0
	Total	#/yr	25.0	38.0
Water Usage	Purified water (PW)	L/g	747	19
		€/g	7	0
		€/L	0.30	0.30

Penalty

for

shutdown

=

Start up phase

Savings for the start-up phase over the course of the first year

Model Inputs

Production	Seed Train for 100L Scale		1x30L
	Product Titre	g/L	
	Penalty for Shutdown		Yes
	Shutdown Duration	months	4
Currency	Symbol		€
Capital	Cost of Capital	%	12%
	Future Value	%	10%
	Period	yrs	8
	Include capital		Yes
Operation	Weeks per year	wks/yr	48
	Operator hours per week	hrs	40
Utility Specification	Specify PW Cost		Yes
	Cost of PW	€/L	0.01

Model Outputs

PRODUCTION			Traditional	Disposable
Throughput	No. of 10L Batches	#/y	15.0	23.0
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	No. of 100L Batches	#/y	6.0	9.0
	Total	#/yr	25.0	38.0
Water Usage	Purified water (PW)	L/g	747	19
		€/g	7	0
		€/L	0.30	0.30

When

- the cost of capital
- a penalty for shutdown (4 months)
- 1x30 L bioreactor to inoculate 1x 100L bioreactor

are included, the highest savings are observed.

Savings for the start-up phase : 59 %
over the course of the first year

Relative reduction in costs

Category	Description	Cost Savings (€/g)			Total Savings (€/g)	Total Savings (%)
		10L	30L	100L		
Capital charge	Facilities	41	41	41	124	3%
Consumables	Sterility sample, integrity, QC bags	0	0	-1	-1	0%
	Filters	0	0	0	0	0%
	Media preparation bags	-14	-5	-5	-24	-1%
	Media hold bags	-10	-4	-5	-19	-1%
	Product hold bags	-2	-1	-1	-4	0%
	Waste hold bags	-7	-3	-4	-13	0%
	Subtotal	**-32**	**-12**	**-17**	**-61**	**-2%**
Materials	Process media	0	0	0	0	0%
	Cleaning chemicals	31	11	5	47	1%
	PW	5	2	1	7	0%
	Subtotal	**36**	**12**	**6**	**54**	**1%**
Labour	Direct production labour	108	36	14	159	4%
	Quality	102	34	10	147	4%
	Shutdown penalty	574	574	574	1,721	48%
	Subtotal	**784**	**644**	**598**	**2,027**	**56%**
Total		829	685	629	2,143	59%

Cost savings = disposables-traditional when disposable > traditional : the result is negative

Savings for the start-up phase : 59 % over the course of the first year

Highest savings observed when are included :

- The cost of capital
- A penalty for shutdown (4 months)
- 1x30 L bioreactor to inoculate 1x 100L bioreactor

•Highest savings due to:

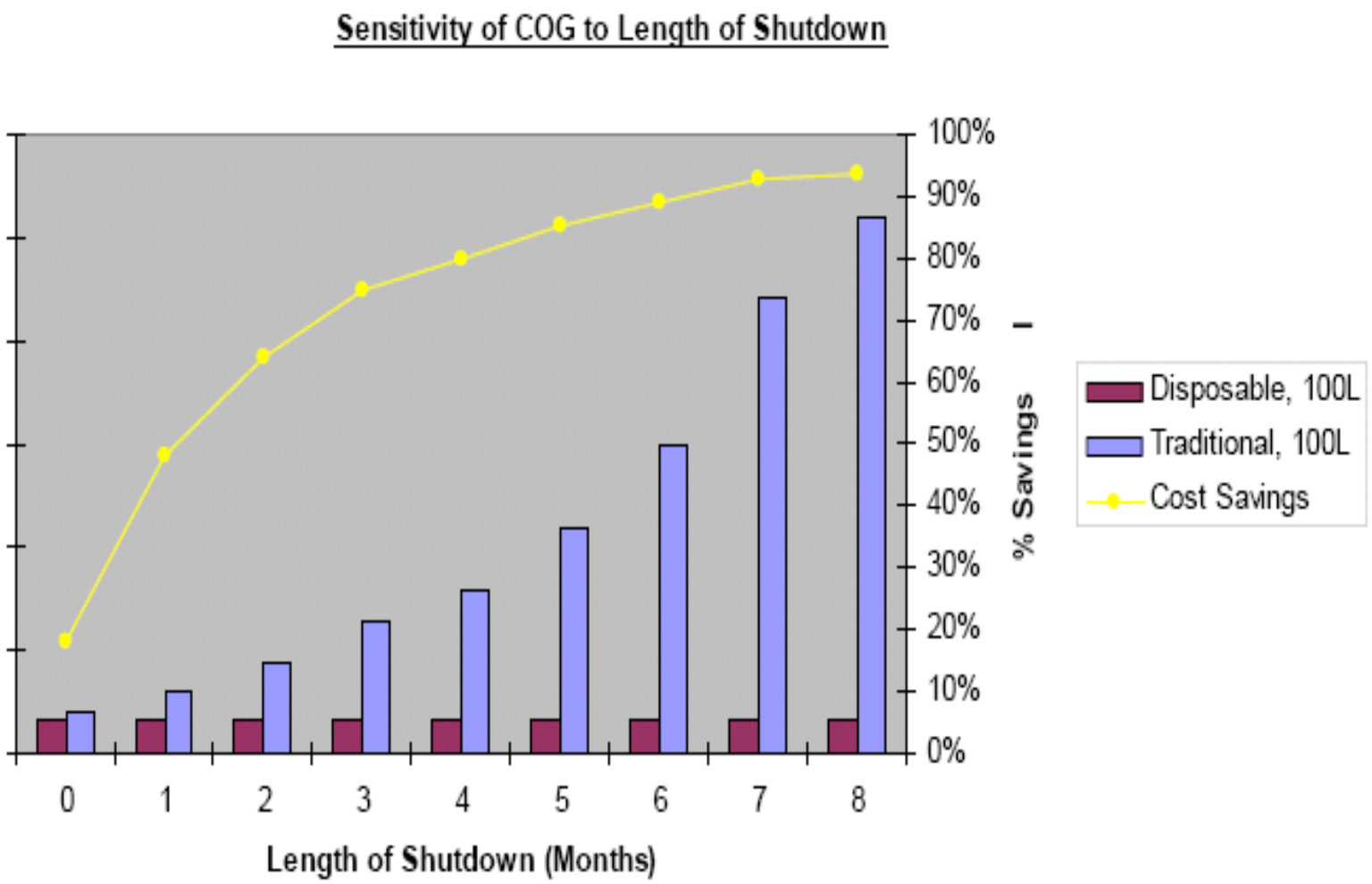
•Cost of the shut down

(=redundant labour)

•Reduced number of batches

(No production during the fit out of the facility)

Start-up phase : sensitivity of the cost of goods to the length of the shutdown



Regular production

Model Inputs

Production	Seed Train for 100L Scale		1x30L
	Product Titre	g/L	
	Penalty for Shutdown		No
Currency	Symbol		€
Capital	Cost of Capital	%	12%
	Future Value	%	10%
	Period	yrs	8
	Include capital		Yes
Operation	Weeks per year	wks/yr	48
	Operator hours per week	hrs	40
Utility Specification	Specify PW Cost		Yes
	Cost of PW	€/L	0.01

Model Outputs

PRODUCTION			Traditional	Disposable
Throughput	No. of 10L Batches	#/yr	23.0	23.0
	No. of 30L Batches	#/yr	6.0	6.0
	No. of 100L Batches	#/yr	9.0	9.0
	Total	#/yr	38.0	38.0
Water Usage				
		€/g	7	0
		€/L	0.30	0.30

No penalty

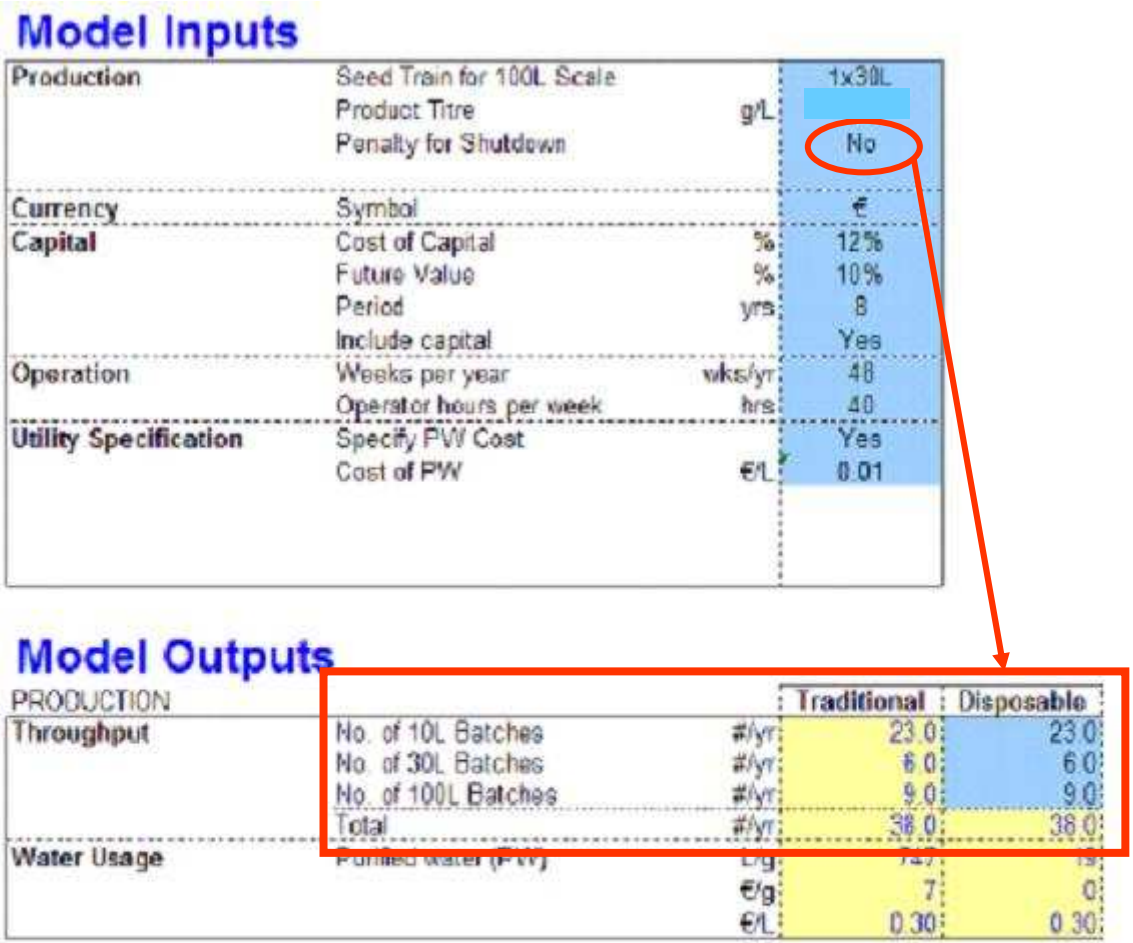
for shutdown

=

Regular production

at full capacity

Regular production



Model Inputs

Production	Seed Train for 100L Scale		1x30L
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Model Outputs

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	No. of 100L Batches	#/yr	9.0	9.0
	Total	#/yr	38.0	38.0
Water Usage	[illegible]	L/g	7	0
		€/g	7	0
		€/L	0.30	0.30

When

- NO penalty for shutdown
- The cost of capital
- 1x30 L bioreactor to inoculate 1x 100L bioreactor

are included, the highest savings observed.

Savings for the regular production : 20 %
(no penalty for shutdown)

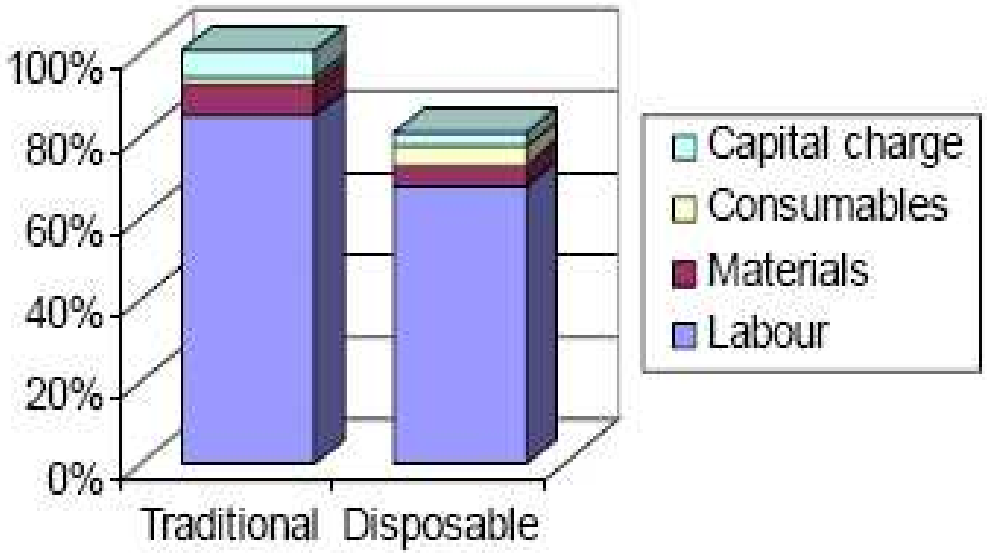
Category	Description	Cost Savings (€/g)			Total Savings (€/g)	Total Savings (%)
		10L	30L	100L		
Capital charge	Facilities	21	21	21	63	3%
Consumables	Sterility sample, integrity, QC bags	0	0	-1	-1	0%
	Filters	0	0	0	0	0%
	Media preparation bags	-14	-5	-5	-24	-1%
	Media hold bags	-10	-4	-5	-19	-1%
	Product hold bags	-2	-1	-1	-4	0%
	Waste hold bags	-7	-3	-4	-13	-1%
	Subtotal	-32	-12	-17	-61	-3%
Materials	Process media	0	0	0	0	0%
	Cleaning chemicals	31	11	5	47	3%
	PW	5	2	1	7	0%
	Subtotal	36	12	6	54	3%
Labour	Direct production labour	108	36	14	159	9%
	Quality	102	34	10	147	8%
	Shutdown penalty	0	0	0	0	0%
	Subtotal	210	70	25	305	17%
Total		235	91	35	361	20%

17% : due to reduction in cleaning, set up, maintenance activities

Savings for the regular production : 20 %
(no penalty for shutdown)

Savings observed when are included:

- NO penalty for shutdown
- The cost of capital
- 1x30 L bioreactor to inoculate 1x 100L bioreactor



Savings mainly due to:

Reduction in manufacturing labour (reduction in cleaning, set up, maintenance activities…)

Conclusion

- **Successful implementation of disposables**:
  - All solutions developed and implemented within 6 months while the pilot plant was running
  - Process successfully transferred
- The **operating cost was reduced** by implementing disposable technology as opposed to using traditional stainless steel vessels.
- The most significant **cost reductions** are:
  - The cost of shutdown that was eliminated by using disposable technology
  - The reduction in labour
  - The reduction in capital expenditure
- The highest savings for the start-up phase were estimated at **59%**

  (over the first year with a 4-month shutdown)
- The overall manufacturing cost has been reduced by up to **20%** by using disposable technology (no penalty for shutdown).

Aknowledgements

- **Biopharm Services** : Mark Proctor, Janice Lim, Miriam Monge
- **Stedim Biosystems** : Jean-Charles Pélanchon
- **F. Hoffmann La Roche Ltd** :
  - Pilot plant fermentation team
  - Media preparation team
  - Frank Trach
  - Christelle Laroche
  - Stefan Rütschlin
  - Anne-Catherine Meyer
- Alain Pralong

Reference

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A Cost-Effectiveness Study of Technology Transfer Between Two Production Sites
Aurélie Foulon, Frank Trach, Alain Pralong, Mark Proctor, and Janice Lim

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