2023 Daiichi Sankyo Seminar

Antibody manufacturing process supporting DS next-generation antibody drug

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September 6, 2023

Today’s Topics

① Antibody manufacturing process

Biopharmaceuticals - especially antibody drug conjugates

How are antibodies manufactured?

virtual tour

Establishment of manufacturing platform process

② CHO cells/CHO cells gene expression system

Daiichi Sankyo's proprietary manufacturing process

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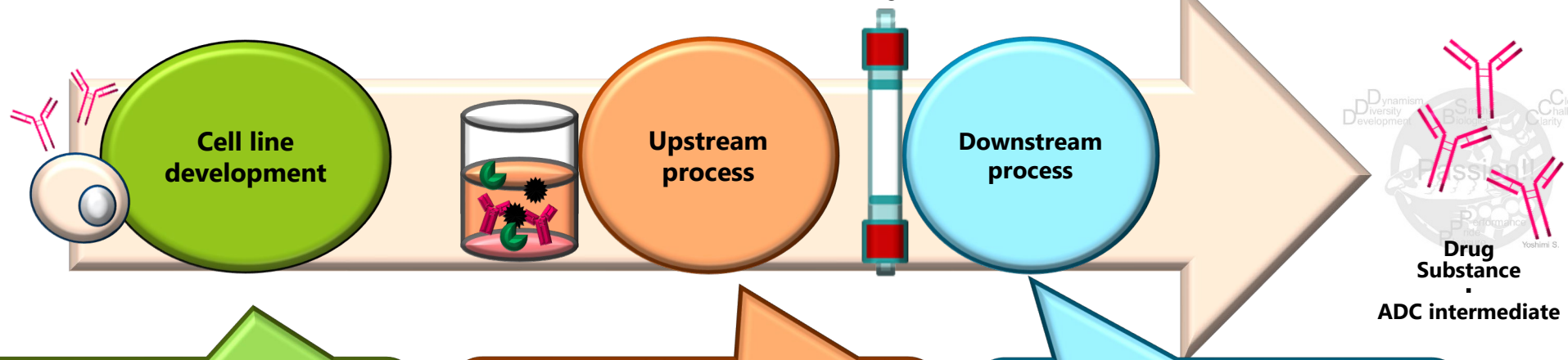
How are antibodies manufactured?

The value chain in antibody manufacturing process development

a) PParS:Process Parameter study
PCS:Process Characterization study

Antibody manufacturing is carried out through the following process: "manufacture of antibody producing cells", "expansion of the cells", and "collection of antibodies produced by these cells".



- Construction of expressing vectors
- Screening of high producing cells
- Cell banking
- Development of single cell isolation methods
- Improvement of cell cloning methods
- Development of in-house expression system

- Media selection
- Assessment of culture conditions
- Scale up studies
- Media development
- Introduction of new technologies
- Streamlining of data acquisition

- Recovery method development
- Purification resin screening
- Virus removal conditions, etc.
- Platform improvement
  Evaluation and selection of novel resins
  Process optimization
  Introduction of new technologies

How are antibodies manufactured?
3 major process: CLD-upstream-downstream

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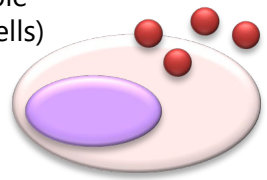
Cell line development Cell bank manufacturing

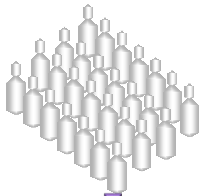
Transfection

Isolation of stable cell line (CHO cells)



Screening of high producing cells

MCB manufacturing (Master Cell Bank)



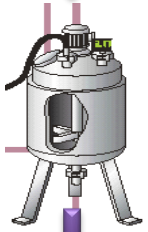
WCB (Working Cell Bank)

Upstream process

Thawing of WCB

Expansion culture

Production culture



Recovery of culture Fluid

Unprocessed cell culture fluid

Downstream process

Unprocessed cell culture fluid

harvest

Column chromatography

Virus inactivation

Column chromatography

Column chromatography

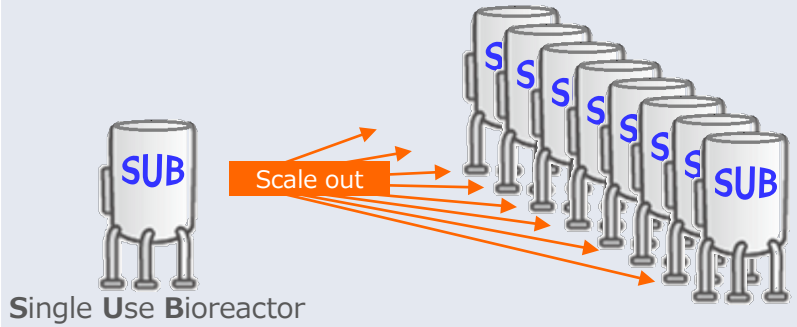
Virus removal

Antibody

Drug substance
·
ADC intermediate

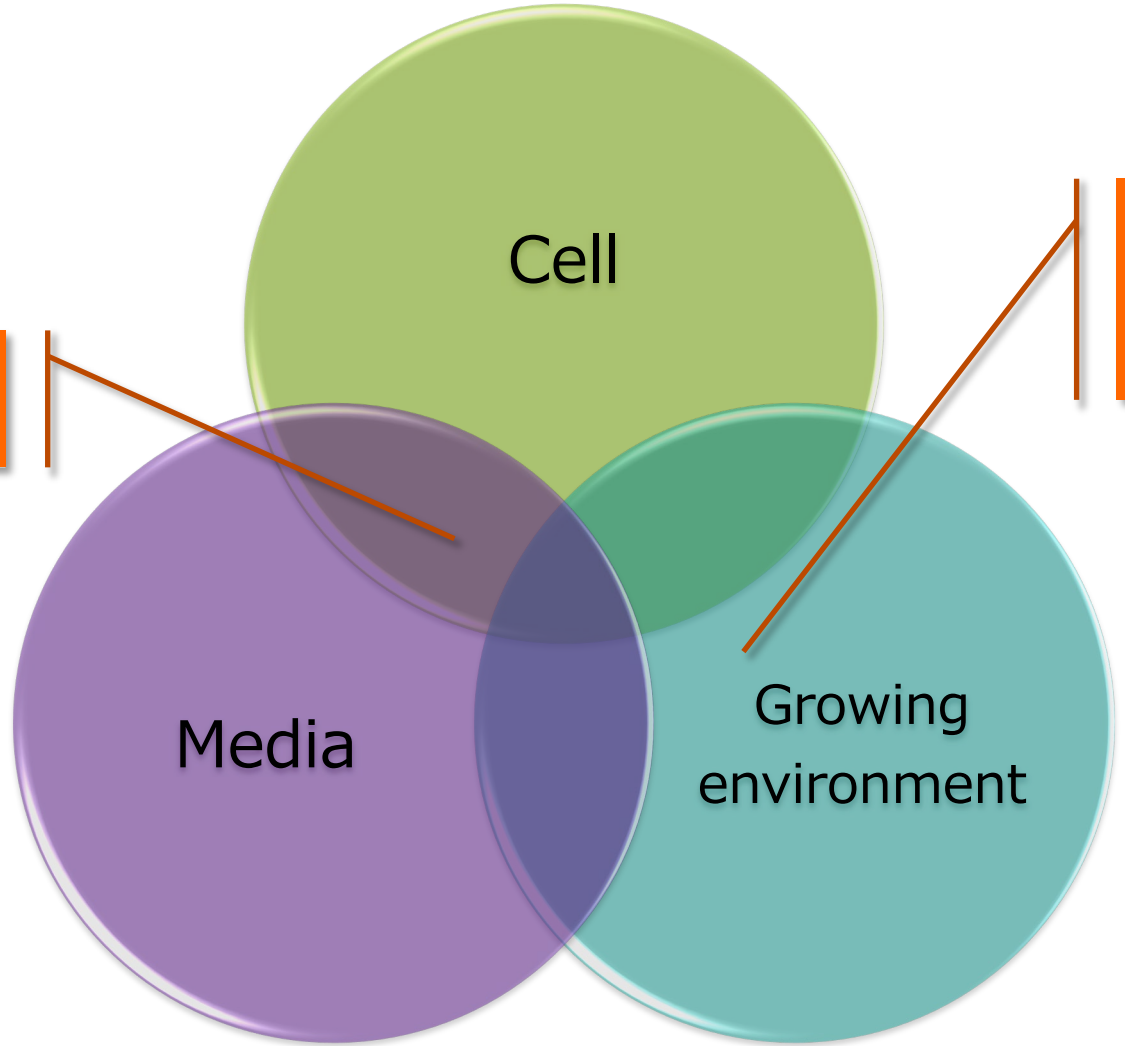
Partially modified “Andrew D,et al.Journal of the National Comprehensive Cancer Network(JNCCN).2011;9(suppl4):S1-S22”

Establishment of the manufacturing infrastructure
Expansion strategy -scale out and scale up-

Expansion strategy			Pros./ Cons.
Scale out	Large scale manufacturing by increasing the number of the same bioreactors	 Single Use Bioreactor	■ Tech transfer (incl. outsourcing) can be completed smoothly using the same bioreactor ■ Low comparability risk ■ Need more bioreactors and batches for expanding the manufacturing volume
Scale up	Large scale manufacturing by changing the bioreactor (upsizing)	 Stainless Steel Bioreactor	■ Increasing the manufacturing scale per a batch (productivity increase per a period) ■ Different bioreactor for scale up may take longer time to complete a tech transfer ■ May have comparability risk Achievement of a targeted producibility Management of cultivation profile Control in antibody quality Control of impurity profile

Establishment of manufacturing infrastructure by selectively applying or combining scale-out and scale-up strategies

Establishment of manufacturing infrastructure
Upstream process development



Media screening

- Spent media analysis
- Cell metabolism analysis
- Additives
- Trace elements

Determination of culture conditions

- Confirmation of cell responsiveness
- Parameter selection
- Aeration/sparging, stirring

Establishment of manufacturing infrastructure
An example of culture process development

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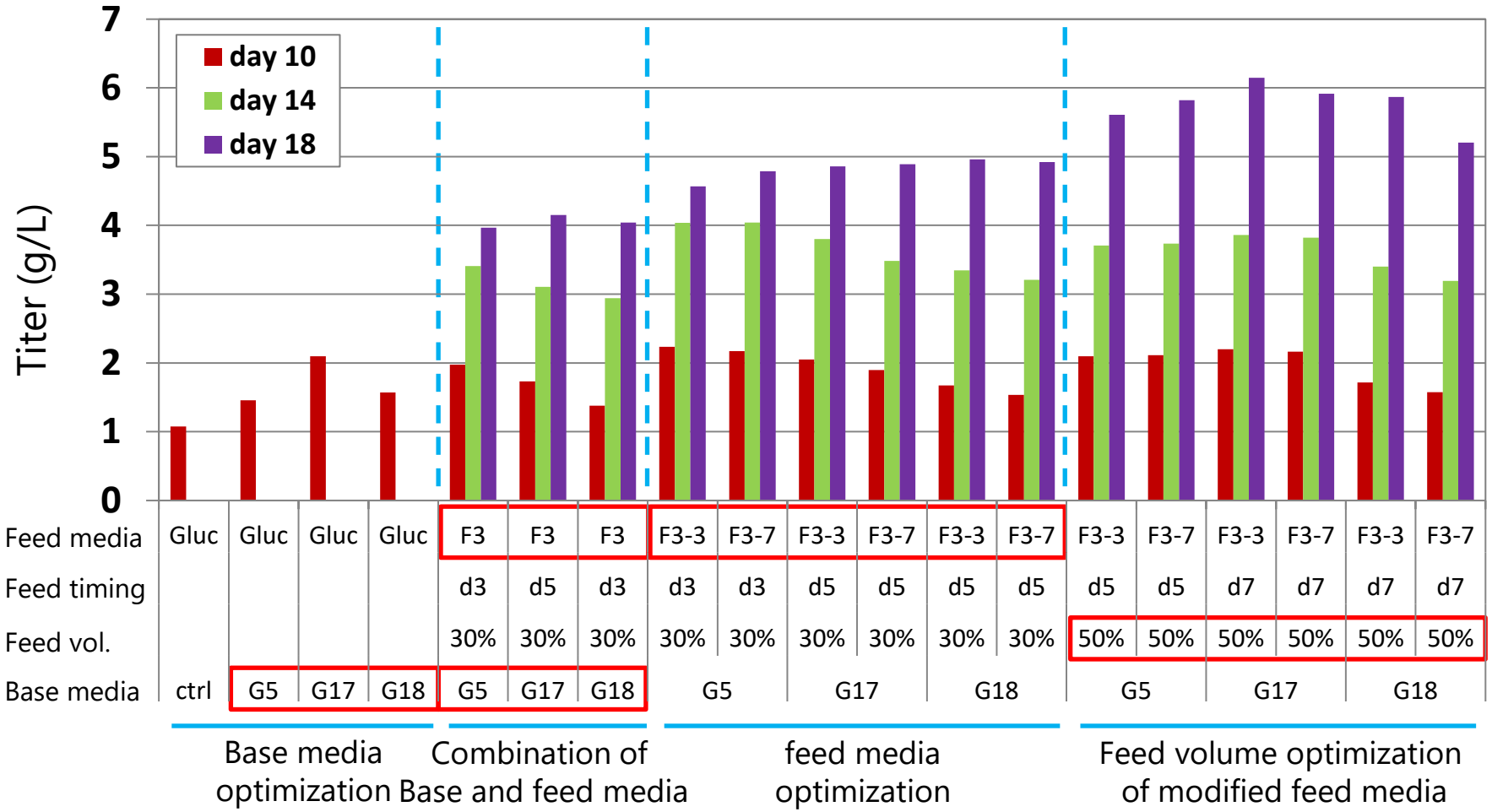
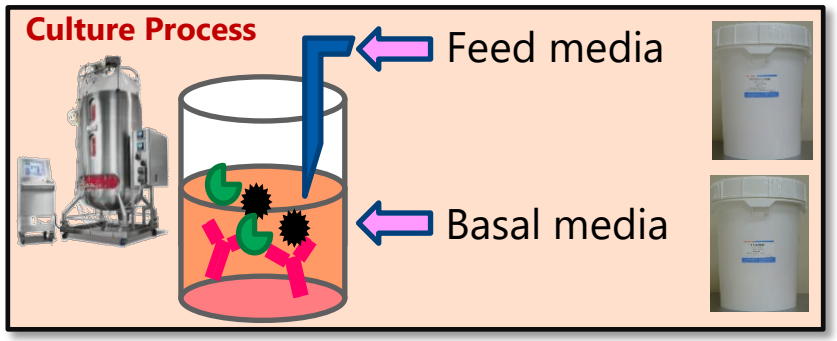
Consider media development and culture conditions to enhance productivity



Establishment of manufacturing infrastructure
Platform Technology ～for upstream process～

■ **Custom medium development**：quality control, cost reduction and effective supply and inventory management



Optimal media was selected for each antibody producing cell so far

Development wide-use and highly productive medium which can be applied to multiple projects

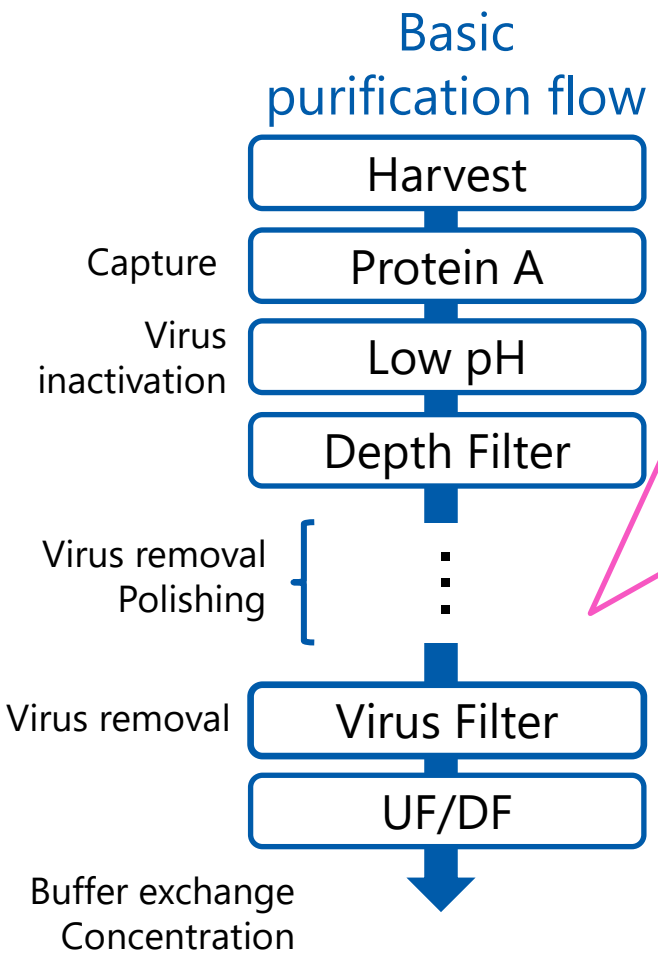
Benefits by development and usage of DS original media

- Enable to control “medium and product quality” and optimize “media compositions and culture conditions” in a short period of time based on the understanding of media component
- Improvement on supply
  - Easy to manage medium stock
  - Control and manage lead time from order to delivery by inventory
- Enable to reduce costs by bulk order

Stable supply/Cost reduction/Price reduction

- Platform media for multiple projects
- Shortening of period for upstream process development
- Cost reduction by scale economics
- Reduction of back-up/waste(expired)
- Emergency response (inventory management)

Establishment of manufacturing infrastructure
Platform Technology ～ for downstream process ～



Polishing step

Process	Purpose
AEX	Virus removal HMWS, HCP and DNA removal
AC Activated Carbon	Virus removal LMWS and HCP removal
HIC Hydrophobic Chromatography	HMWS, HCP and specific HCP removal
CEX	HMWS and HCP removal

Suitable *Polishing step* depends on characteristic of each antibody

- Process design considering internal and external manufacture
- Correspondence for problematic HCP
- Correspondence for increase of amount of throughput by improvement of cells and culture technology
- Process optimization for applying diversified next-generation antibodies
- Correspondence for problems on raw material procurement

Manufacturing process of antibodies

- The final candidate antibody to be developed will be manufactured using recombinant mammalian cells (CHO cells).
- The manufacturing process consists of cell line development, upstream process (including cell removal steps), and downstream process.
- Manufacturing capacity is expanded by scaling out or scaling up depending on the demand and development stage.
- High-quality antibodies will be manufactured (supplied) by an establishment of stable (robust) manufacturing process.
- The development of platform technologies will greatly contribute to stable manufacturing.

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CHO cells/CHO cells gene expression system

History of antibody production quantity by CHO cells

1980's：1-100 mg/L・・・batch culture

1990's：1g/L, 10-14 days・・・fed-batch culture (following the same)

2010：Biogen, 10g/L on day18 in CD media

American Institute of Chemical Engineers Biotechnol. Prog., 26, 1400-1410, 2010 DG44

2013：Genentech, over 9g/L on day18 in CD media

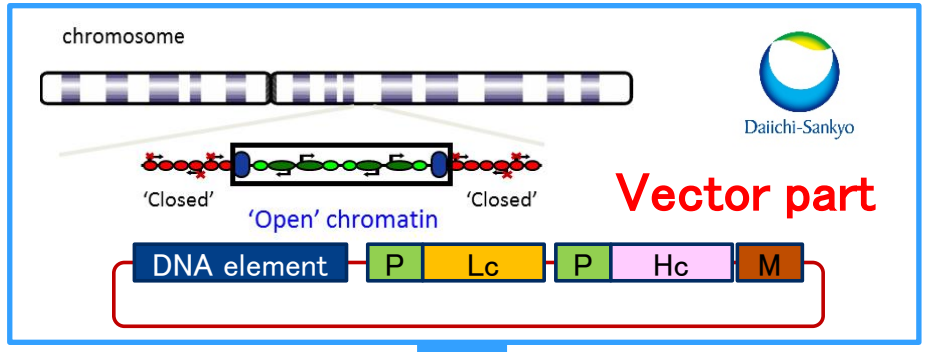
Biotechnology and Bioengineering, Vol. 110, No.1, 2013 CHO

2017：Osaka Univ., over 9g/L on day16 in CD media

Cytotechnology, Vol. 69, 511-521, 2017 GS-CHO

CHO cells/CHO cells gene expression system

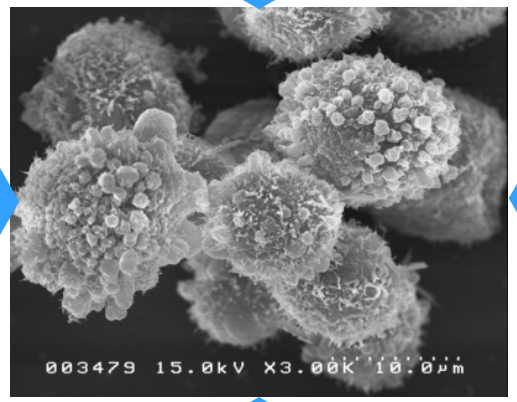
Development of CHO cell gene expression system



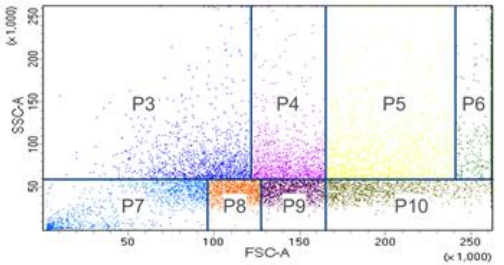
Novel cell line development strategy for monoclonal antibody manufacturing using translational enhancing technology

Kenji Masuda et al.,
J. Bioscience and Bioengineering, 133(3), 273-280, 2022

High performance host improvement part



Concentrating high productivity clone by FCM



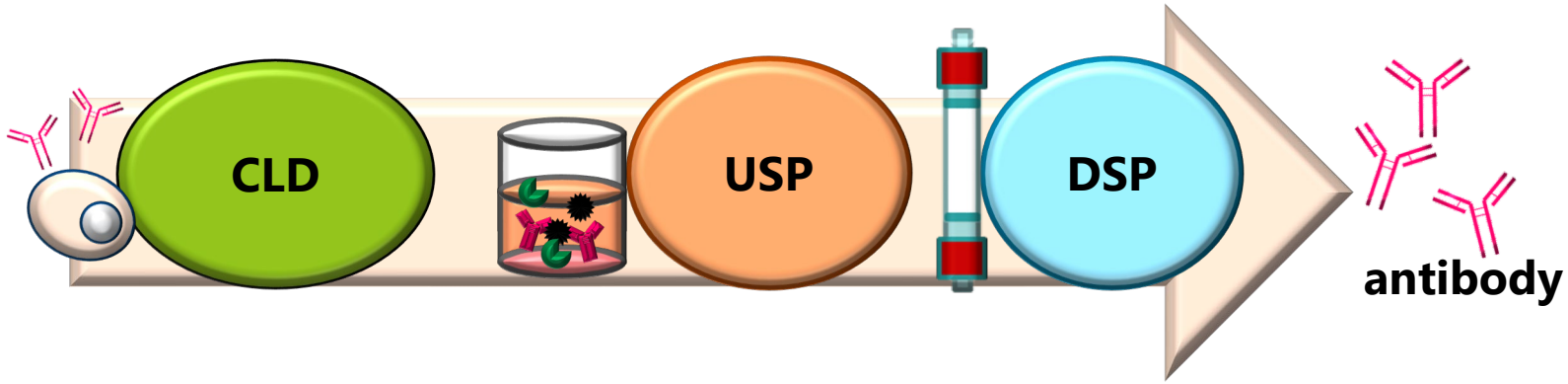
Screening method development

Customized media development

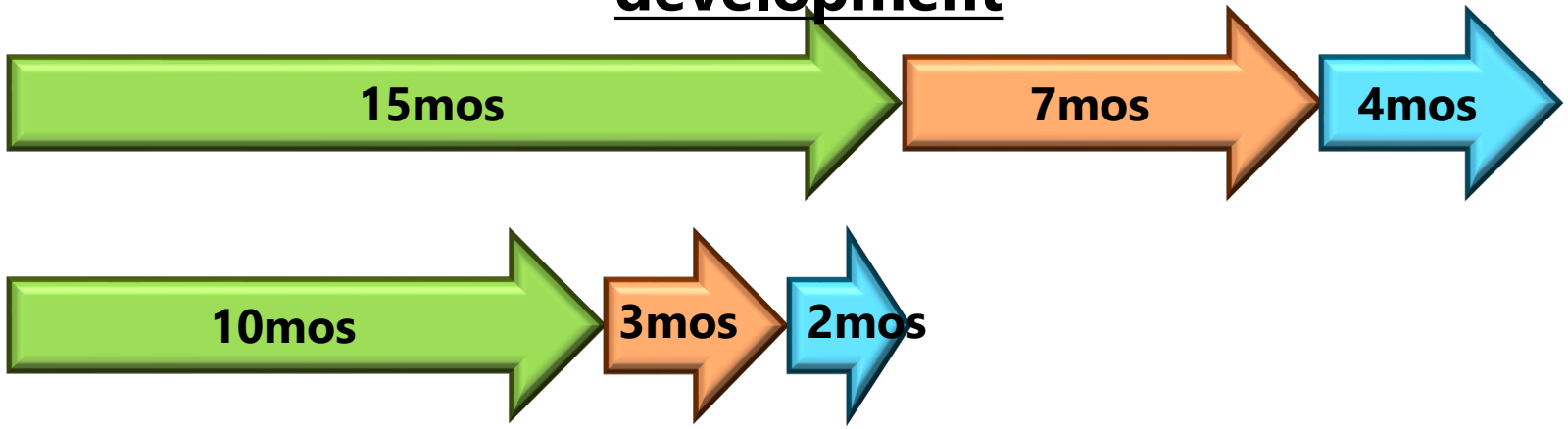
CHO cells/CHO cells gene expression system

Acceleration of early-stage process development

Accomplished to save 11mos in early-stage process development



Period for early-stage process development



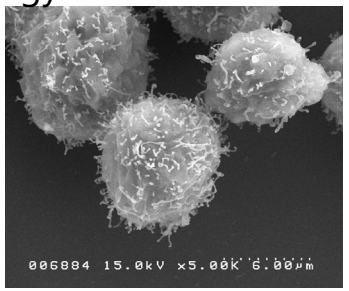
26mos
(2010)

15mos
(2016)

CHO cells/CHO cells gene expression system

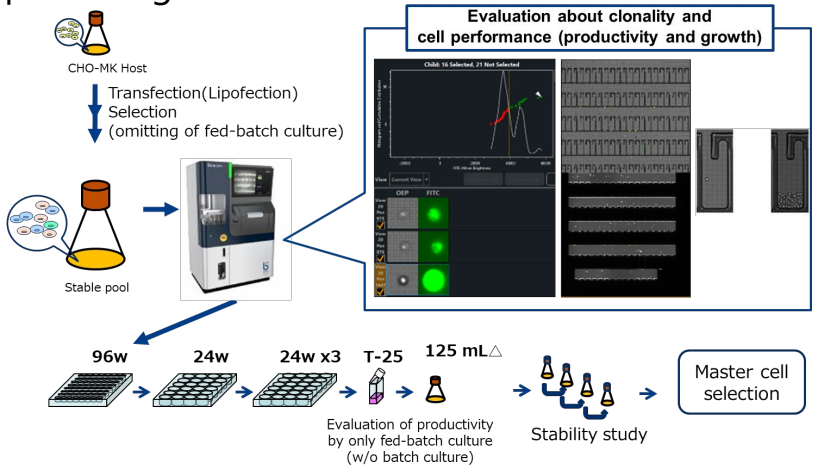
For further development of highspeed manufacturing process

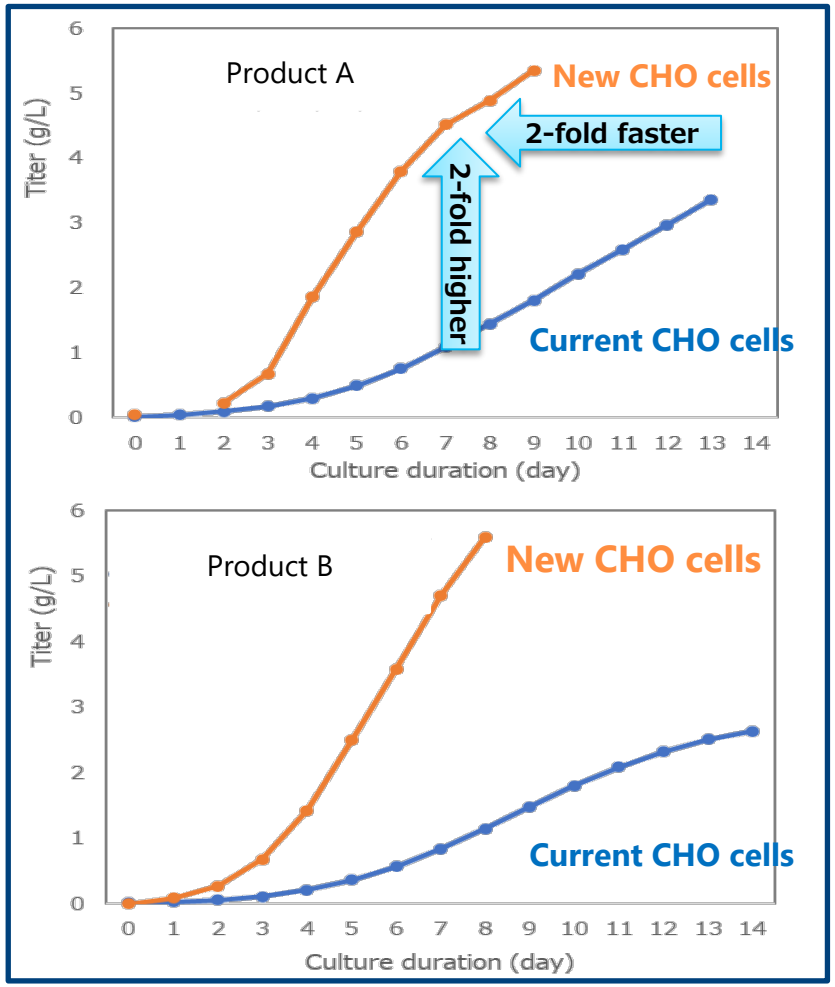
Establishing antibody producing cells by DS original technology



・toolbox A
・toolbox B
・・・・・

Establishing DS original highspeed screening system for cloning high producing cells

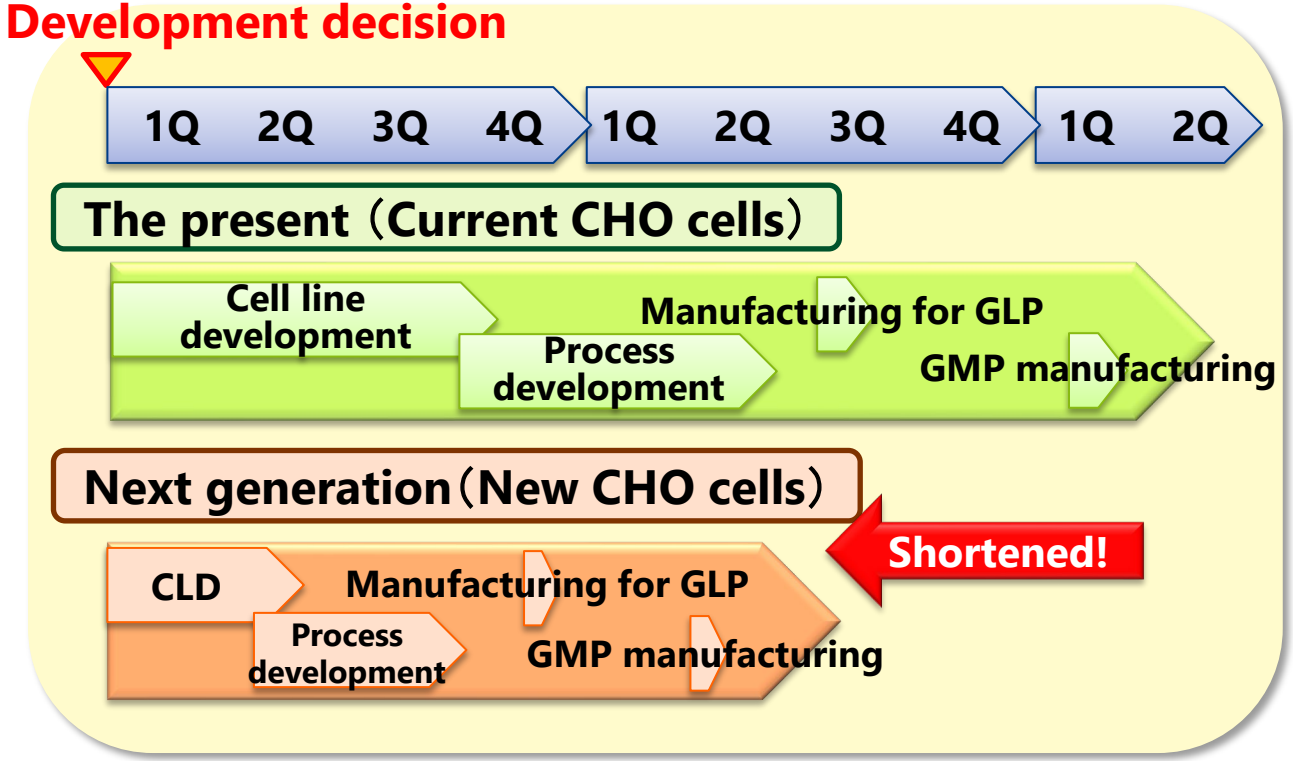


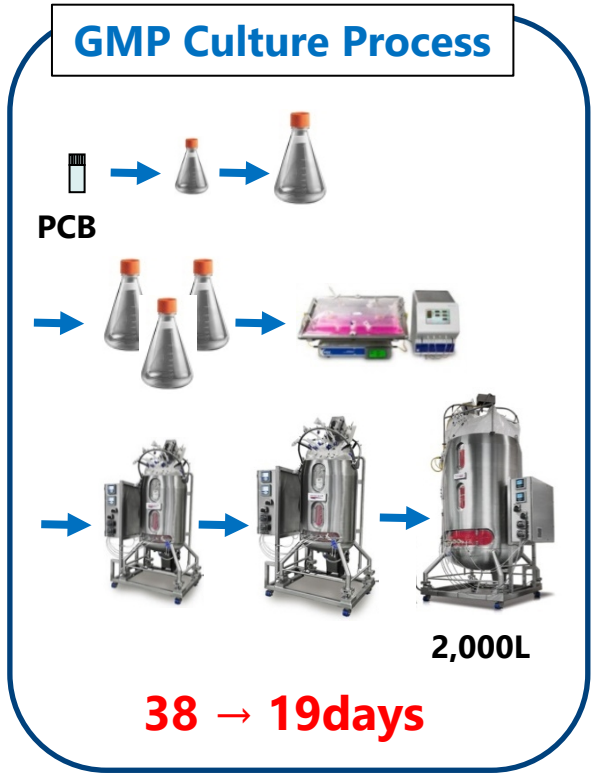


CHO cells/CHO cell gene expression system

Next Challenge - Next generation DS gene expression system

- ✓ Shorten period from development decision to the 1st GMP manufacturing (halve the length of time for establishing producing strain)
- ✓ Improve efficacy of production of biologics by shortening manufacturing period（halve the length of time for expansion culture and manufacturing culture）





CHO cells/CHO cells gene expression system

- The CHO cell gene expression system has been safely used in biologics manufacturing.
- Nowadays the system can demonstrate ~10g/L productivity in manufacturing antibodies.
- As such platformization progresses, it can contribute to shorten the process development period.
- Development of new CHO cells can provide a high-speed process that cannot be achieved by an effort for seeking an effective manufacturing process alone.
- Utilizing new CHO cells expects to accelerate a research and development, speed up process development, and shorten the manufacturing period.

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