An Industry Perspective on CHO Cell Product Virus Safety

Shohei Kobayashi
API Process Development Dept. Bio 5G(Purification)
Manager

CHUGAI PHARMACEUTICAL CO., LTD.

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Agenda

01 Viral Clearance Strategy in Chugai

02 Prior Knowledge Utilization

03 Expectation for Q5A Revision

04 Future DSP and Viral Clearance

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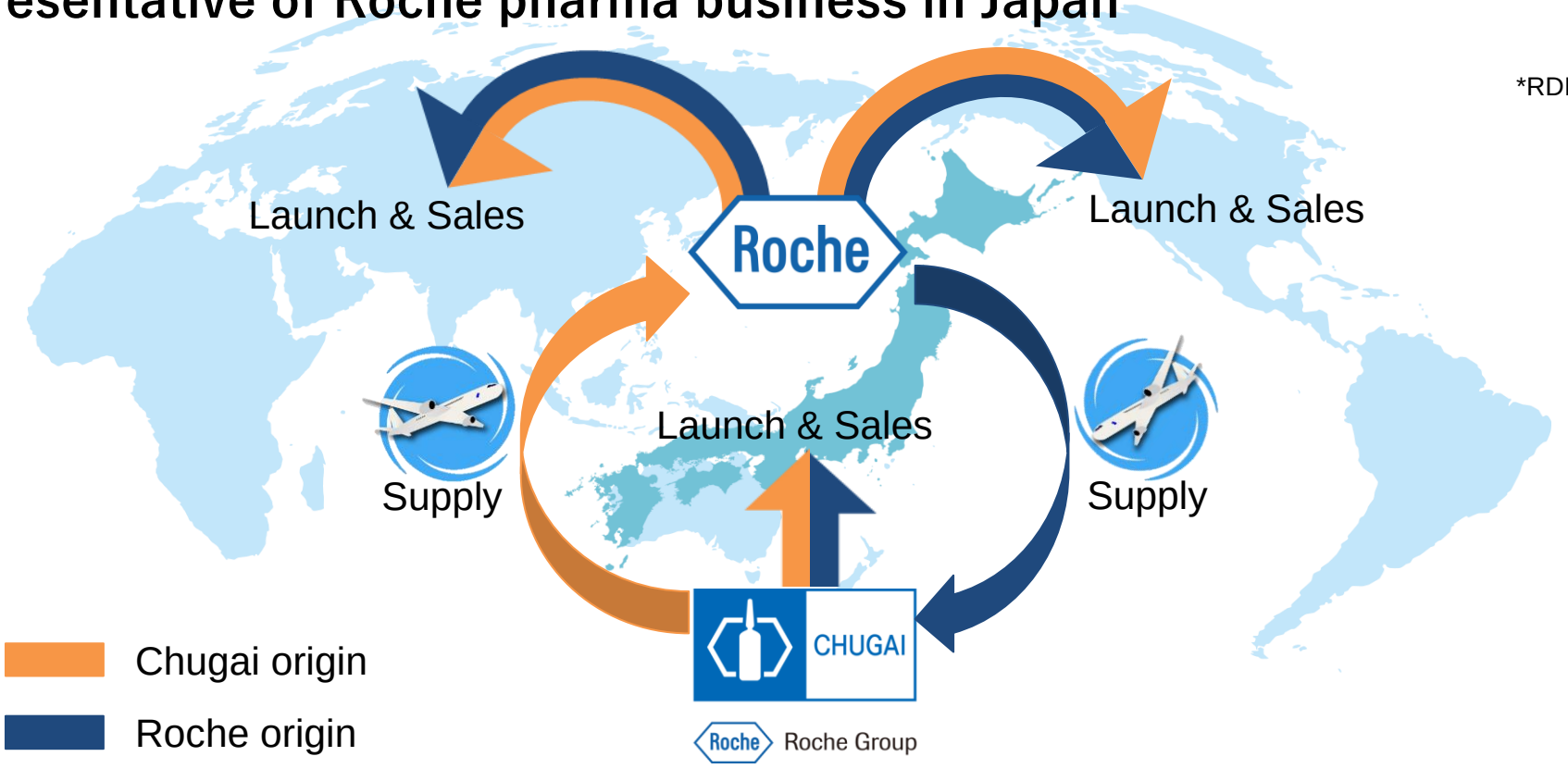
Chugai - Roche Strategic Alliance

- **Independent pharma with RDPM* functions**
- **Global clinical development and sales of Chugai original drugs executed using Roche infrastructure**
- **Sole representative of Roche pharma business in Japan**



*RDPM: R = Research
D = Development
P = Production
M = Marketing

Antibody Pipeline in Chugai

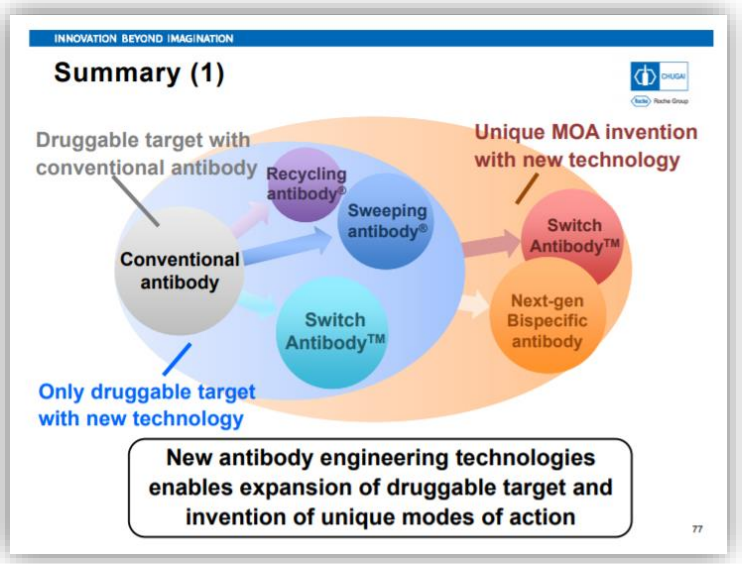
Advanced therapeutic antibody with engineering technology (e.g. bispecific, recycling, sweeping, switch), enabling more effective and desirable functions for the mode of action in the body, are in commercial and clinical phase.

Pipeline	Technology	Stage
		Research / P1~P2 / P3 / Approval
FDA BTD Actemra®		
FDA BTD Hemlibra®	Bi-Specific	
FDA BTD Enspring®	Recycling	
FDA BTD Nemolizumab	Half-life extension	
ERY974	Bi-Specific	
GC33		
SKY59	Recycling	
AMY109	Recycling	
GYM329	Sweeping	
NXT007	Bi-Specific	
STA551	Switch	
SOF10		
Several mabs	Confidential	

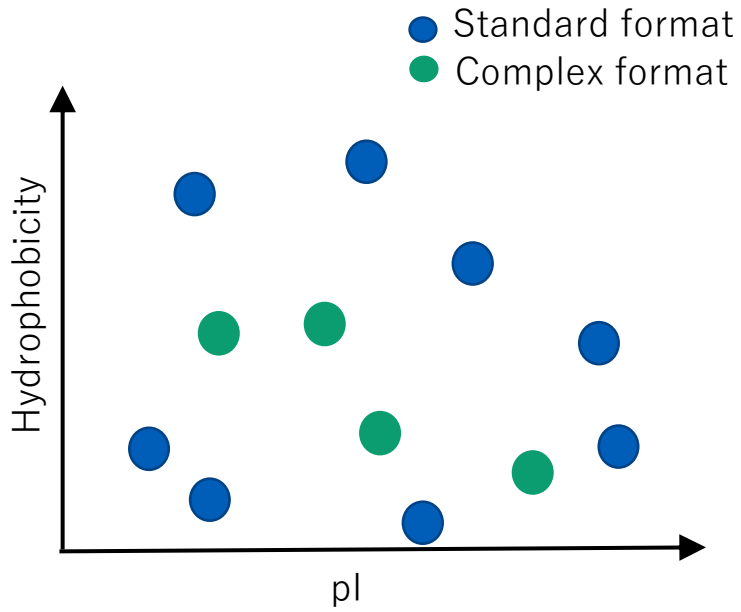
Physicochemical Property of Chugai's Antibody

Making full use of antibody engineering technology, the molecules have become increasingly complex.
Purification process platforming becomes difficult when the physicochemical properties of the molecules are various.

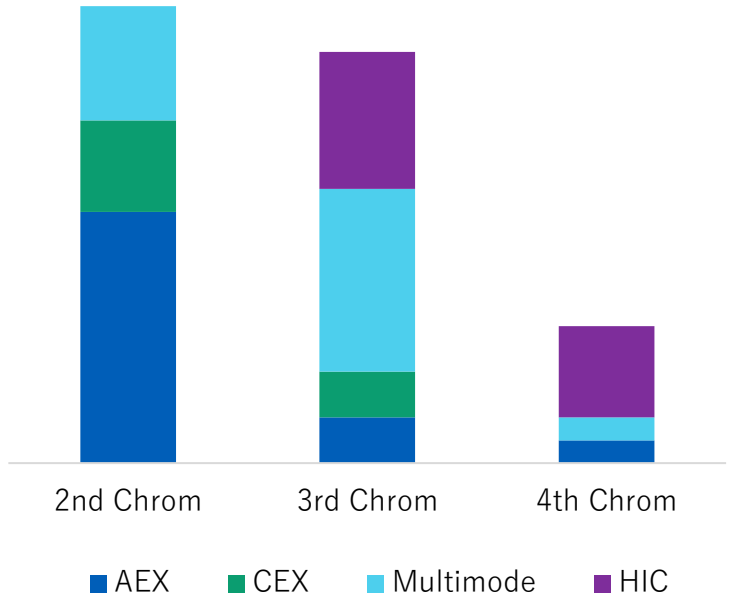
Antibody Engineering



Physicochemical Property



Chromatography Mode

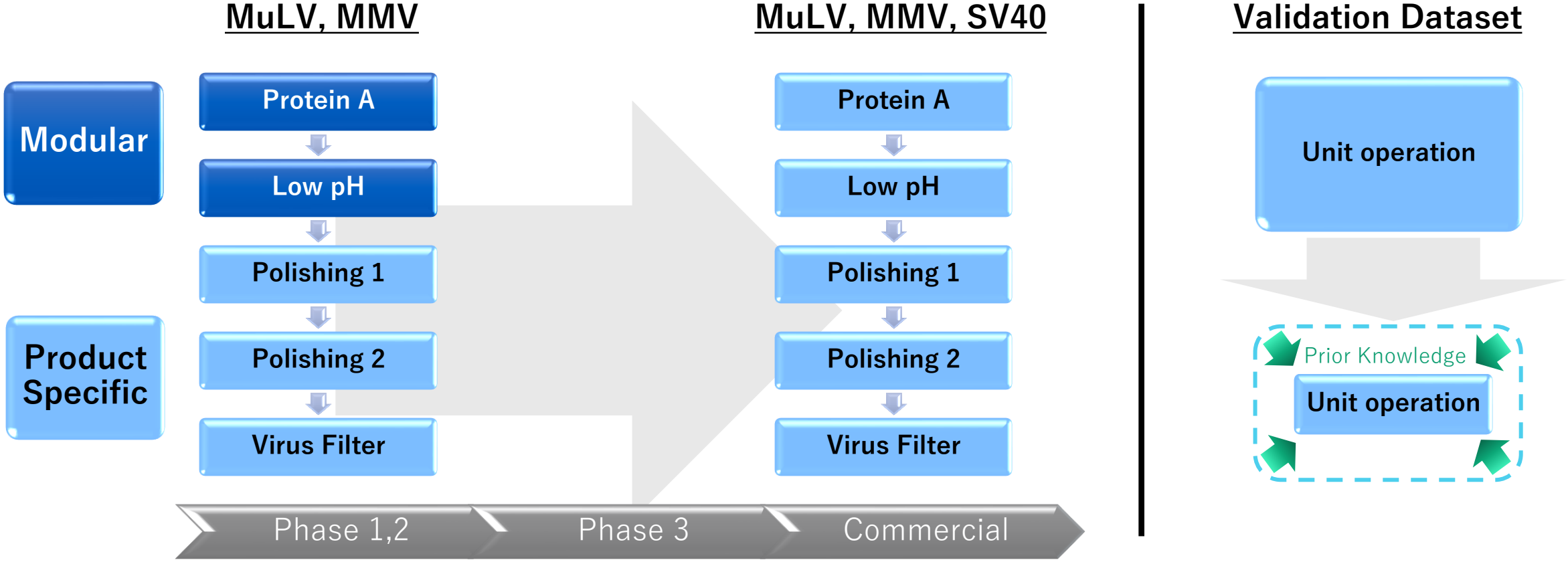


Chugai Information Meeting on Antibody Engineering Technologies (2019 Dec.)
https://www.chugai-pharm.co.jp/english/profile/media/conference.html

Viral Clearance Strategy in Chugai

In early phase, more Modular approach and less product specific data with two model viruses is employed. In late phase, more Product specific data with three model viruses is adopted.

Prior knowledge supports to reduce the product specific validation dataset.



Model Virus Selection

Considering the mode of action and Q5A requirement, appropriate model viruses, covering broad range, are selected.

Process Scope Viral clearance is affected by the exterior characteristics of the virus

Unit Operation	MoA	Physicochemical property			
		Envelope	Size	pI	Genome
Protein A	Ligand Affinity				
Low pH / Detergent	Chemical reaction by acid or detergent	✓			
Polishing	Charge and/or Hydrophobicity			✓	
Virus Filter	Size sieving		✓		
UV	Chemical reaction by UV irradiation				✓

Model Virus Selection

Considering the mode of action and Q5A requirement, appropriate model viruses, covering broad range, are selected.

Low pH disrupts virus envelope.
Comparable LRV has been shown in other enveloped virus (e.g. PRV)

1. Mattila J, Clark M, Liu S, et al. PDA J Pharm Sci and Tech 2016.
2. Mieseages G, Lute S, Brorson K. Biotechnol Bioeng 2010.

VF is size sieving and smallest virus is worst-case (See to Slide13)

Viruses with similar pI to Mab are more difficult to remove in IEC.
E.g. Reo3, pI is 3.8, results in tightly binding to AEX same as CHO DNA

Category	Model Virus	Envelope	Size	pI	Resistance
Specific model virus	X–MuLV	+	80-110	**5.8**	Low
Relevant model virus	MMV	–	**18-24**	**6.2**	Very High
Non-specific model virus	SV40	–	40-50	**5.4**	Very High

Note: Expression system is CHO cell

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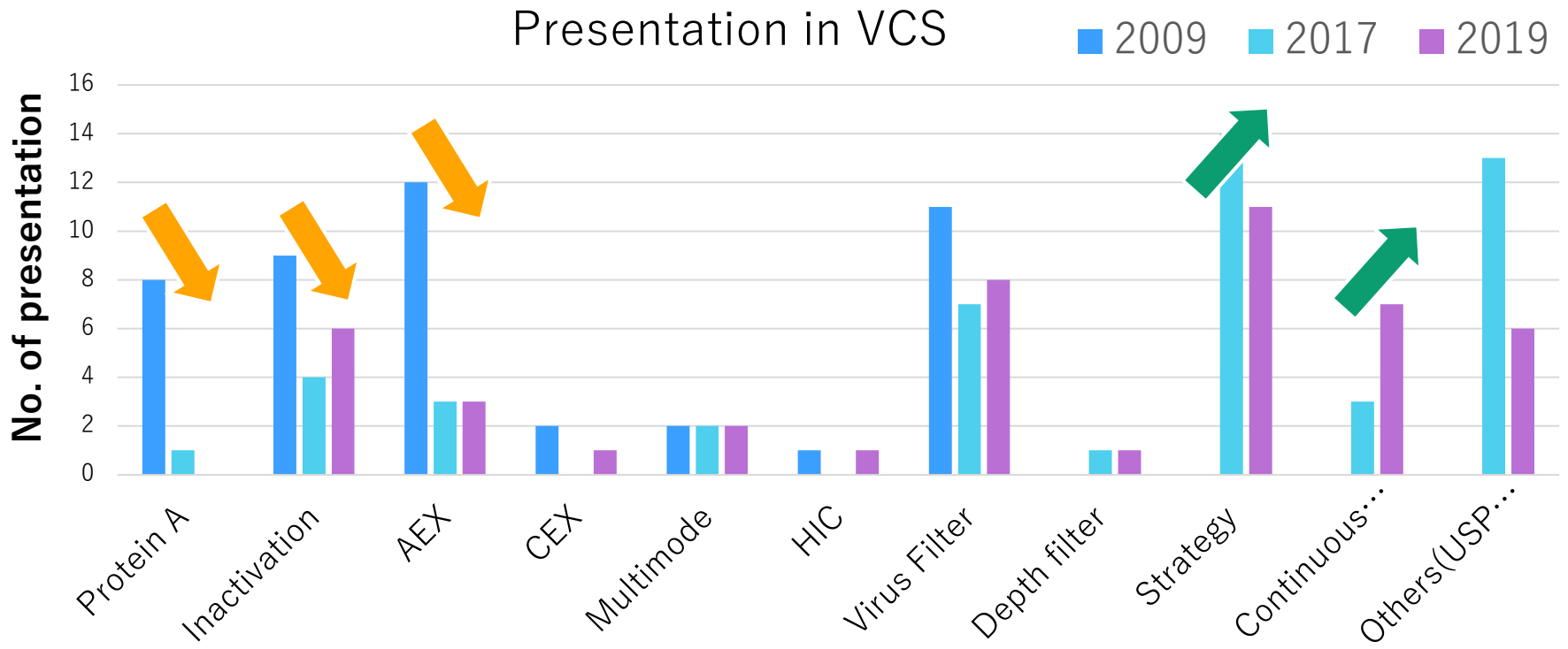
Trend in Viral Clearance

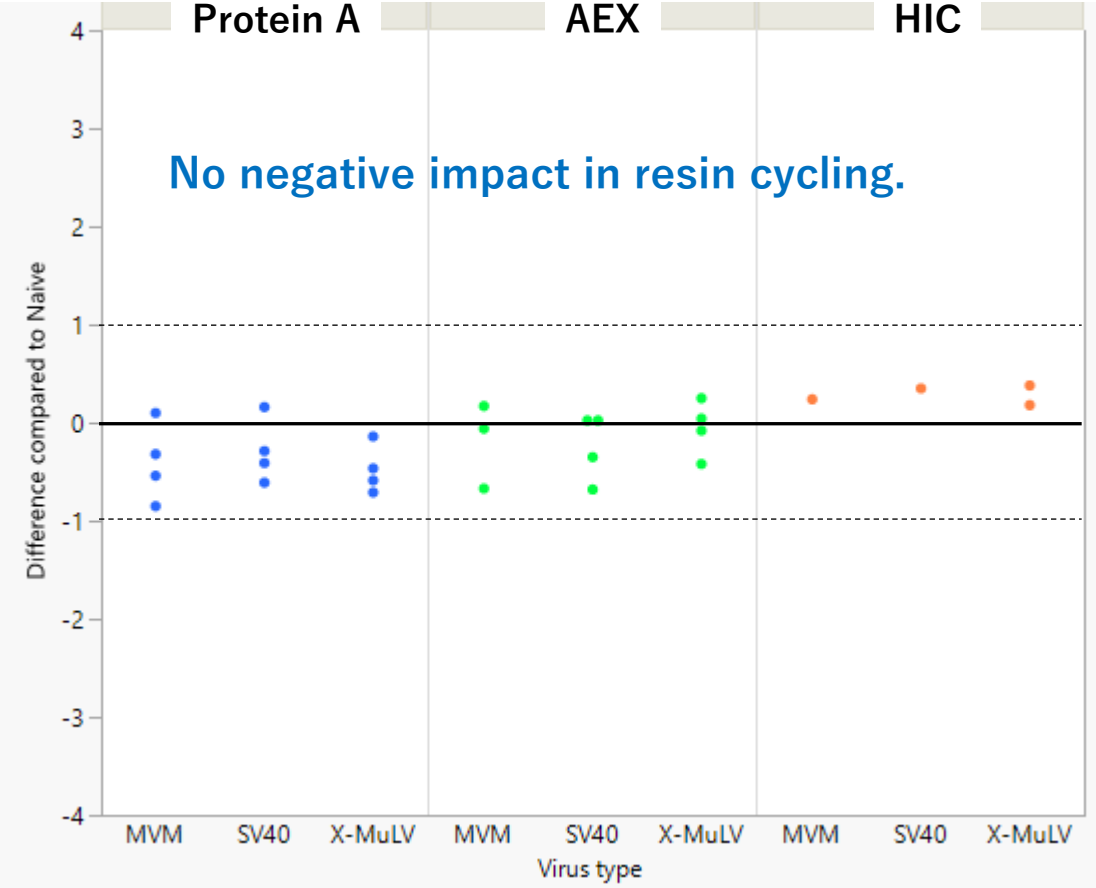
Understanding of each unit operation, such as Protein A, Low pH and AEX step, is deepened in the last 10 years. Recently, Strategy and Continuous process are more discussed.



VCS: Viral Clearance Symposium
A global conference where pharmaceutical companies and authorities gather to share information and discuss, every 2-3 year.
1st conference was in 2009, next one will be in May 2023 in Austria.

Prior Knowledge: Column Aging

Because column aging does not show any impact on viral clearance in several resins, number of spiking runs w/ aged resin are reduced.



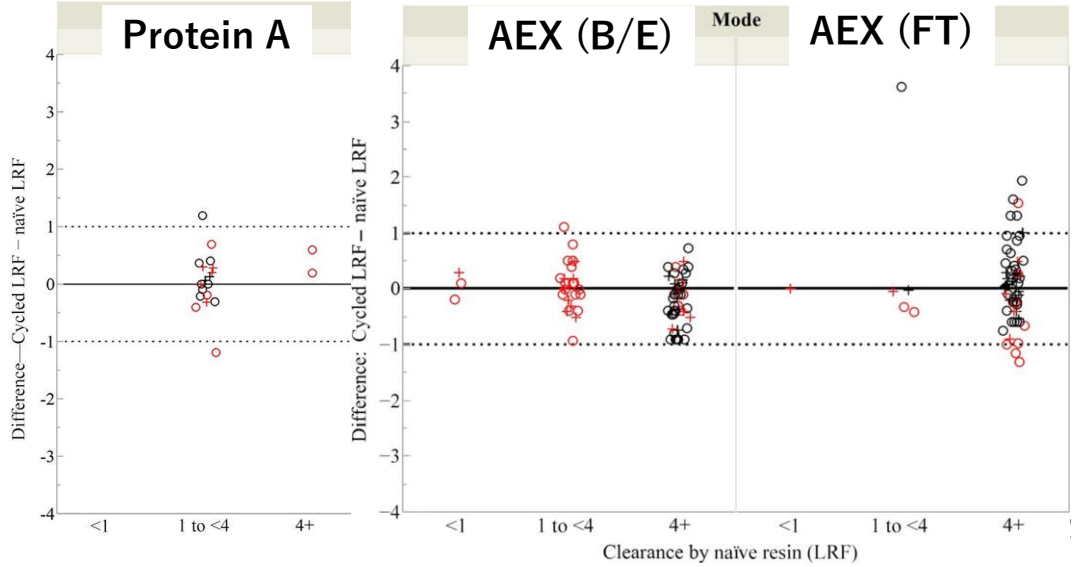
PDA Journal of Pharmaceutical Science and Technology

Retrospective Evaluation of Cycled Resin in Viral Clearance Studies—A Multiple Company Collaboration

John Mattila, Sherrie Curtis, Yenny Webb-Vargas, et al.

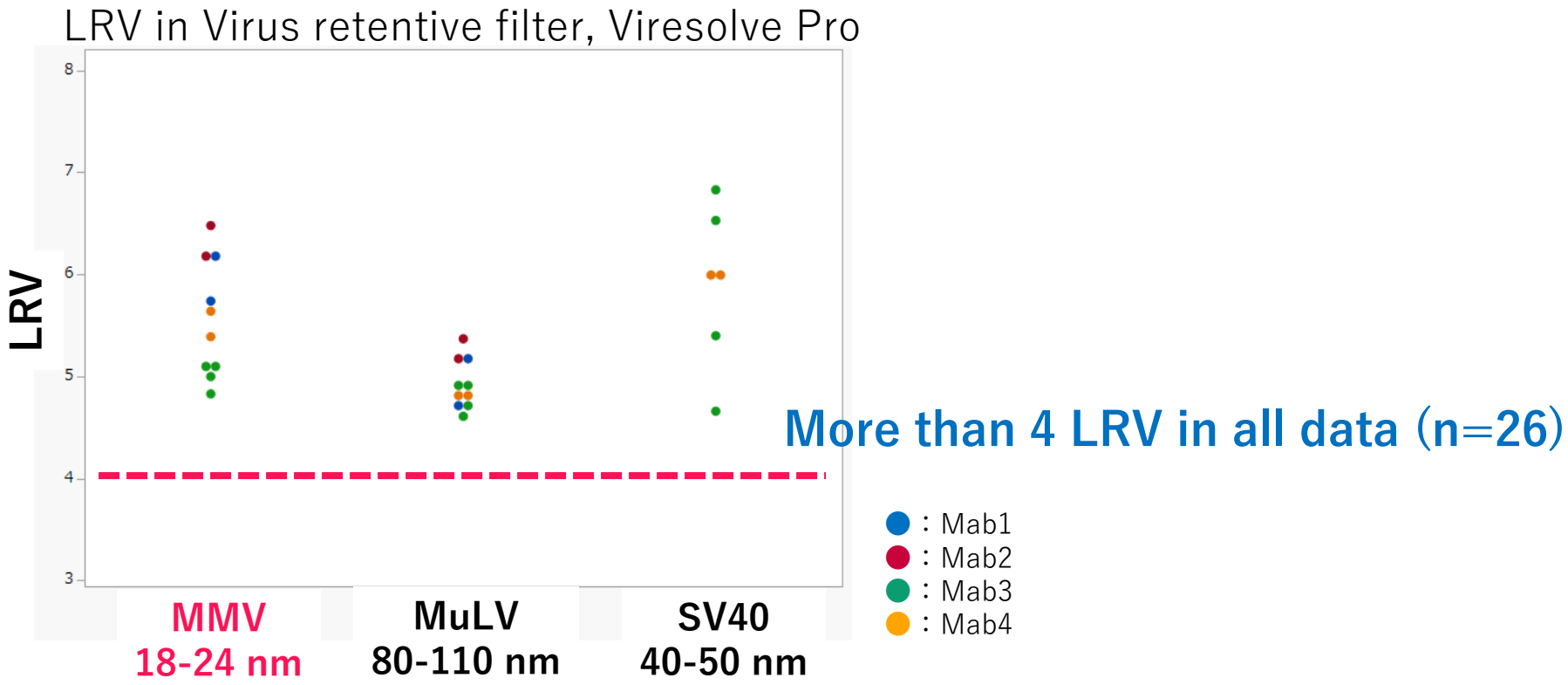
PDA J Pharm Sci and Tech **2019**, *73* 470-486
Access the most recent version at doi:10.5731/pdajpst.2018.009605

No negative impact in resin cycling.
(Data from 12 global company)



Prior Knowledge: Extrapolation of MMV Data

Because MoA[1), 2)] of VF and historical data support the extrapolation of MMV LRV to other viruses, extrapolated value is used for RVLP assessment.



In addition to the data above, effective removal in both MMV and MuLV are validated in more than 10 Mabs in Roche Group.(Data not shown)

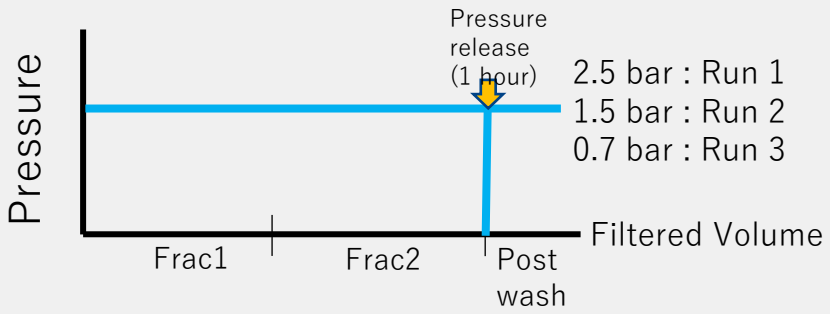
LRV: Log Reduction Value

1)Technical Report No. 41. PDA J Pharm Sci Technol 2008, vol 62 No.S-4.
2)George M, Scott L,Hazel A, Kurt B Virus Retentive Filters. Encyclopedia of Industrial Biotechnology: Bioprocess, Bioseparation, and Cell Technology 2010, April.

Prior Knowledge: Robustness of Virus Filter

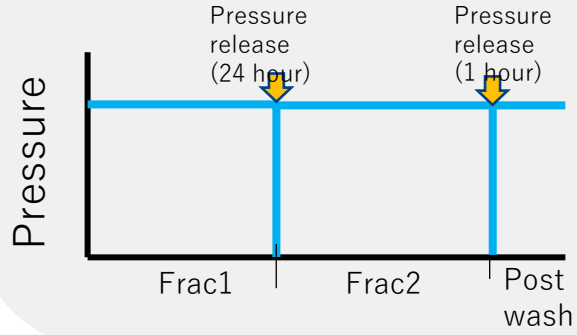
Small virus retentive filter, Viresolve® Pro, shows high robustness even in extreme conditions. Low and high Pressure, Flow Rate, Pressure Release and Process Interruption do not impact on viral clearance.

1. Pressure Range study



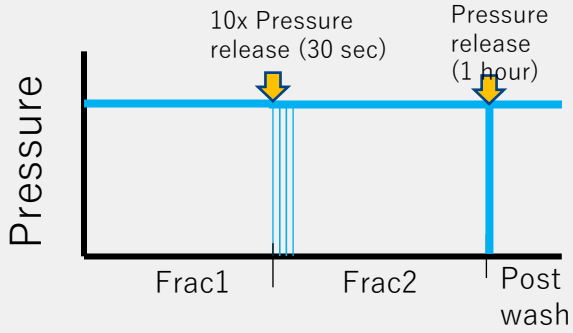
2.5 bar : Run 1
1.5 bar : Run 2
0.7 bar : Run 3

2. Pressure release and hold study



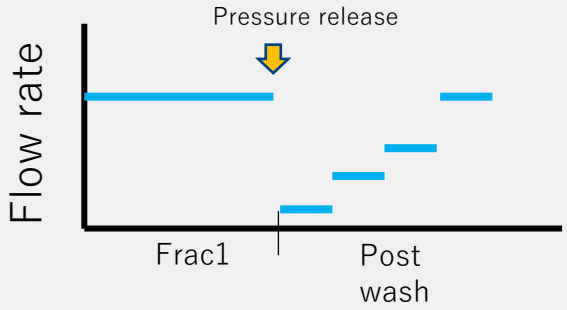
2.5 bar : Run 4
1.5 bar : Run 5
0.7 bar : Run 6

3. Pressure release stress study



2.5 bar : Run 7
1.5 bar : Run 8
1.0 bar : Run 9

4. Low flow rate study



Run 10
200 LMH
90 LMH
30 LMH
10 LMH

More than 5 LRV in all condition

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Expectation for Q5A Revision

✓ Utilization of Prior Knowledge

- How much justification is required as scientific knowledge widespread?
  - Continuing to have open discussion w/ pharmaceutical company, health authority and virus CROs, i.e. Viral clearance symposium, also contributes to global consensus.
- How much raw data is required in filling activity?
  - JP specific: 「抗体医薬品の品質評価のためのガイダンス, Guidance for Evaluating the Quality of Antibody Drugs」薬食審査発1214第1号

4. 抗体医薬品開発におけるプラットフォーム技術の利用

プラットフォーム技術が用いられる場合、論文等の公知情報、又は、自社での抗体医薬品の製法及び評価法確立を通じて蓄積されたデータを利用することにより、開発を合理的に進めることも可能であると考えられる。ただし、論文等の公知情報に関しては、その根拠となっている生データの入手が困難である場合もあると考えられるため、承認申請資料においてはその情報の利用可能性は限定的と考えられる。

When using platform technology it is considered possible to rationally promote development by using public knowledge such as published literature or data accumulated through establishing an in-house antibody drug manufacturing process and evaluation method. However, it may be difficult to obtain the raw data that serves as the evidence for public knowledge such as published literature, therefore the use of this type of information for approval application data may be limited.

✓ Average or Lower LRV

- Because study design is already Worst-case condition besides duplicate(or more) LRVs should be within 1 log considering assay variation, adoption of lower LRV is considered to be excessive Worst-case combination.
- Difference is quite small and no impact on virus assessment.

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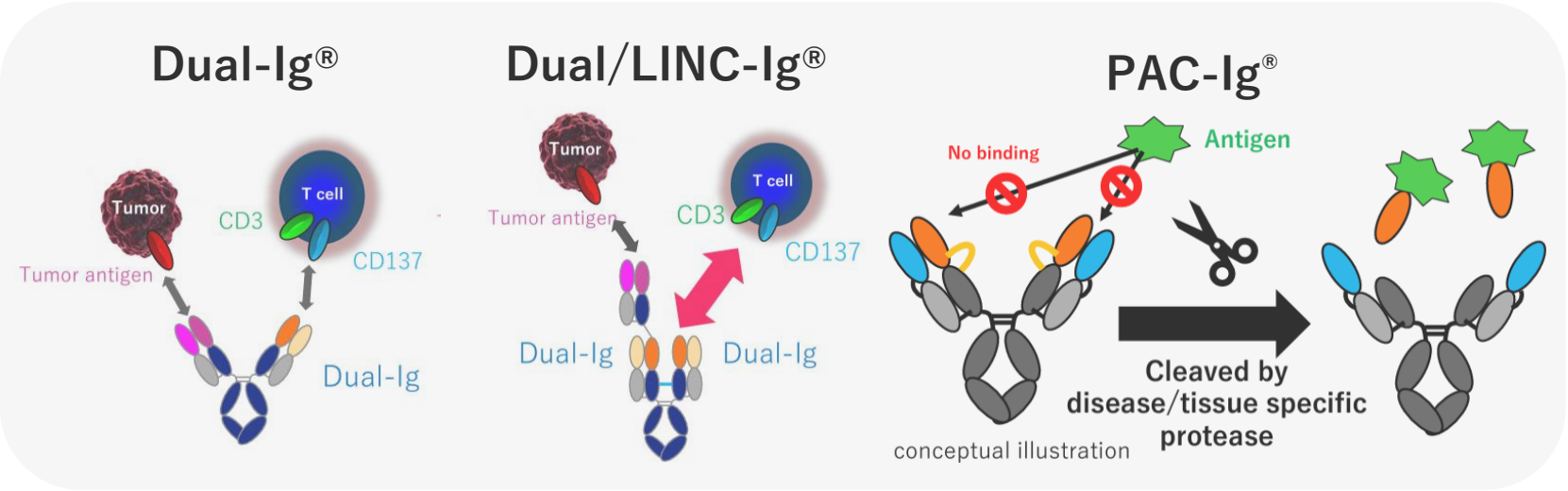
Future DSP: Non-platform Process

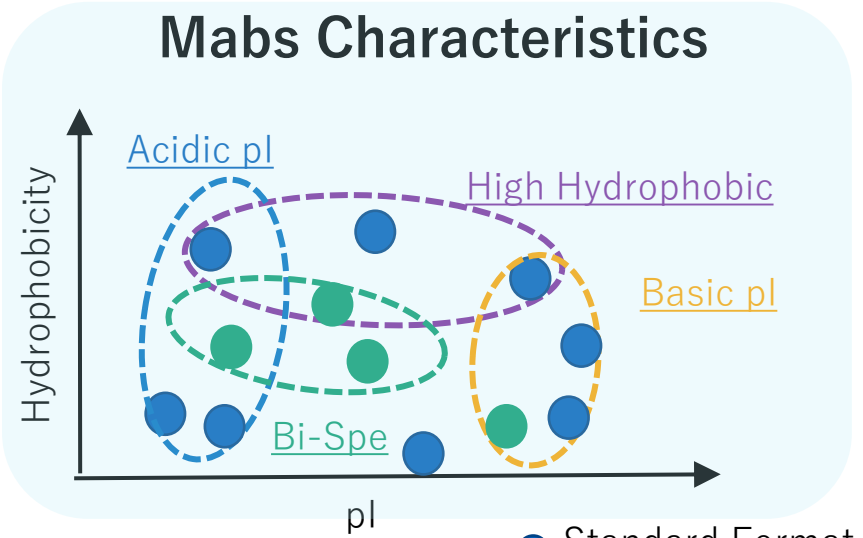
More Non-platform process is required for advanced therapeutic antibody.

- New toolbox development is necessary with stake holders as open innovation.

  i.e. Protein L resin, Multimodal resin, Functionalized depth filter, Additives etc.

- Stacking viral clearance data for each unit operation is continued.



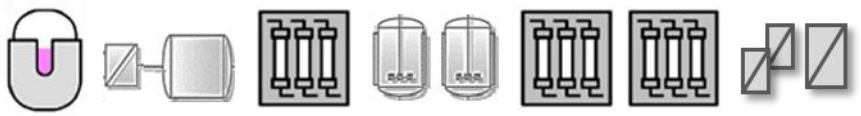


中外製薬 R&D説明会(2021 Dec.)
https://www.chugai-pharm.co.jp/cont_file_dl.php?f=FILE_1_104.pdf&src=[%0],[%1]&rep=139,104

Future DSP: Continuous Process

✓ Definition of “Continuous Process”

- There will be various process flow more than batch process flow. Control strategy of GMP manufacturing and process should be reflected in viral clearance study in small scale.
  - End- to end or Only multi-column in Affinity
  - Surge vessel or Direct loading
  - Surge vessel with every wash or not etc..

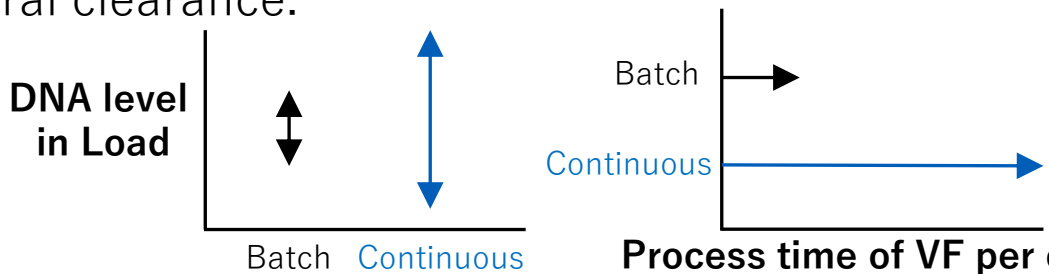


✓ Validation Scale and Equipment

- Since basic mode of action for each unit operation is not changed, conventional scale-down model can continue to be used.

✓ Points to Consider in Continuous Process

- Heterogeneity and extended condition, such as impurity level, flow rate, process time etc., needs to be considered, if it would impact on viral clearance.



Summary

- ✓ In Chugai, Modular approach is employed in early phase, and Product specific data with three model viruses are adopted in late phase, considering the MoA of unit operation and physicochemical property of model viruses.
- ✓ While Prior knowledge is widespread, it would be preferable if it is clear how much justification is required and how much raw data has to be submitted under global consensus.
- ✓ Continuous Process is under development in Chugai. Although there are more parameters to consider than batch process, such as fluctuated impurity level and extended virus filtration process time, the basic MoA remains the same and conventional scale-down model can be used, so we believe that sufficient validation can be achieved.

INNOVATION BEYOND IMAGINATION