An Industry Perspective on CHO Cell Product Virus Safety

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06 December 2022
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
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.

<table>
<thead>
<tr>
<th>Pipeline</th>
<th>Technology</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Research</td>
</tr>
<tr>
<td>Actemra®</td>
<td>Bi-Specific</td>
<td></td>
</tr>
<tr>
<td>Hemlibra®</td>
<td>Bi-Specific</td>
<td>P1~P2</td>
</tr>
<tr>
<td>Enspring®</td>
<td>Recycling</td>
<td>P3</td>
</tr>
<tr>
<td>Nemolizumab</td>
<td>Half-life extension</td>
<td>P3</td>
</tr>
<tr>
<td>ERY974</td>
<td>Bi-Specific</td>
<td></td>
</tr>
<tr>
<td>GC33</td>
<td>Bi-Specific</td>
<td></td>
</tr>
<tr>
<td>SKY59</td>
<td>Recycling</td>
<td></td>
</tr>
<tr>
<td>AMY109</td>
<td>Recycling</td>
<td></td>
</tr>
<tr>
<td>GYM329</td>
<td>Sweeping</td>
<td></td>
</tr>
<tr>
<td>NXT007</td>
<td>Bi-Specific</td>
<td></td>
</tr>
<tr>
<td>STA551</td>
<td>Switch</td>
<td></td>
</tr>
<tr>
<td>SOF10</td>
<td>Confidential</td>
<td></td>
</tr>
<tr>
<td>Several mabs</td>
<td>Confidential</td>
<td></td>
</tr>
</tbody>
</table>
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.
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.
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.

<table>
<thead>
<tr>
<th>Unit Operation</th>
<th>MoA</th>
<th>Physicochemical property</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Envelope</td>
</tr>
<tr>
<td>Protein A</td>
<td>Ligand Affinity</td>
<td></td>
</tr>
<tr>
<td>Low pH / Detergent</td>
<td>Chemical reaction by acid or detergent</td>
<td>✓</td>
</tr>
<tr>
<td>Polishing</td>
<td>Charge and/or Hydrophobicity</td>
<td></td>
</tr>
<tr>
<td>Virus Filter</td>
<td>Size sieving</td>
<td></td>
</tr>
<tr>
<td>UV</td>
<td>Chemical reaction by UV irradiation</td>
<td>✓</td>
</tr>
</tbody>
</table>
# Model Virus Selection

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Model Virus</th>
<th>Envelope</th>
<th>Size</th>
<th>pl</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific model virus</td>
<td>X-MuLV</td>
<td>+</td>
<td>80-110</td>
<td>5.8</td>
<td>Low</td>
</tr>
<tr>
<td>Relevant model virus</td>
<td>MMV</td>
<td>-</td>
<td>18-24</td>
<td>6.2</td>
<td>Very High</td>
</tr>
<tr>
<td>Non-specific model virus</td>
<td>SV40</td>
<td>-</td>
<td>40-50</td>
<td>5.4</td>
<td>Very High</td>
</tr>
</tbody>
</table>

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


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

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

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

Note: Expression system is CHO cell
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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.
Because column aging does not show any impact on viral clearance in several resins, number of spiking runs w/ aged resin are reduced.
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 in Virus retentive filter, Viresolve Pro**

- MMV: 18-24 nm
- MuLV: 80-110 nm
- SV40: 40-50 nm

More than 4 LRV in all data (n=26)

- \(\bullet\): Mab1
- \(\bullet\): Mab2
- \(\bullet\): Mab3
- \(\bullet\): Mab4

LRV: Log Reduction Value

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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. Pressure release and hold study

3. Pressure release stress study

4. Low flow rate study

More than 5 LRV in all condition
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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

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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04. Future DSP and Viral Clearance
Future DSP: Non-platform Process

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

- New toolbox development is necessary with stakeholders 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.

Dual-Ig®, Dual/LINC-Ig®, PAC-Ig®

Mabs Characteristics

Acidic pI

Basic pI

High Hydrophobic

Standard Format
Complex Format

Bi-Spe

Hydrophobicity

https://www.chugai-pharm.co.jp/cont_file_dl.php?f=FILE_1_104.pdf&src=,%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.

![Diagram showing DNA level in Load and process time of VF per cassette between Batch and Continuous processes.](image-url)
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