独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

# ICHQ5Aの改定を踏まえた
# 遺伝子治療用製品のウイルス安全性の考え方について

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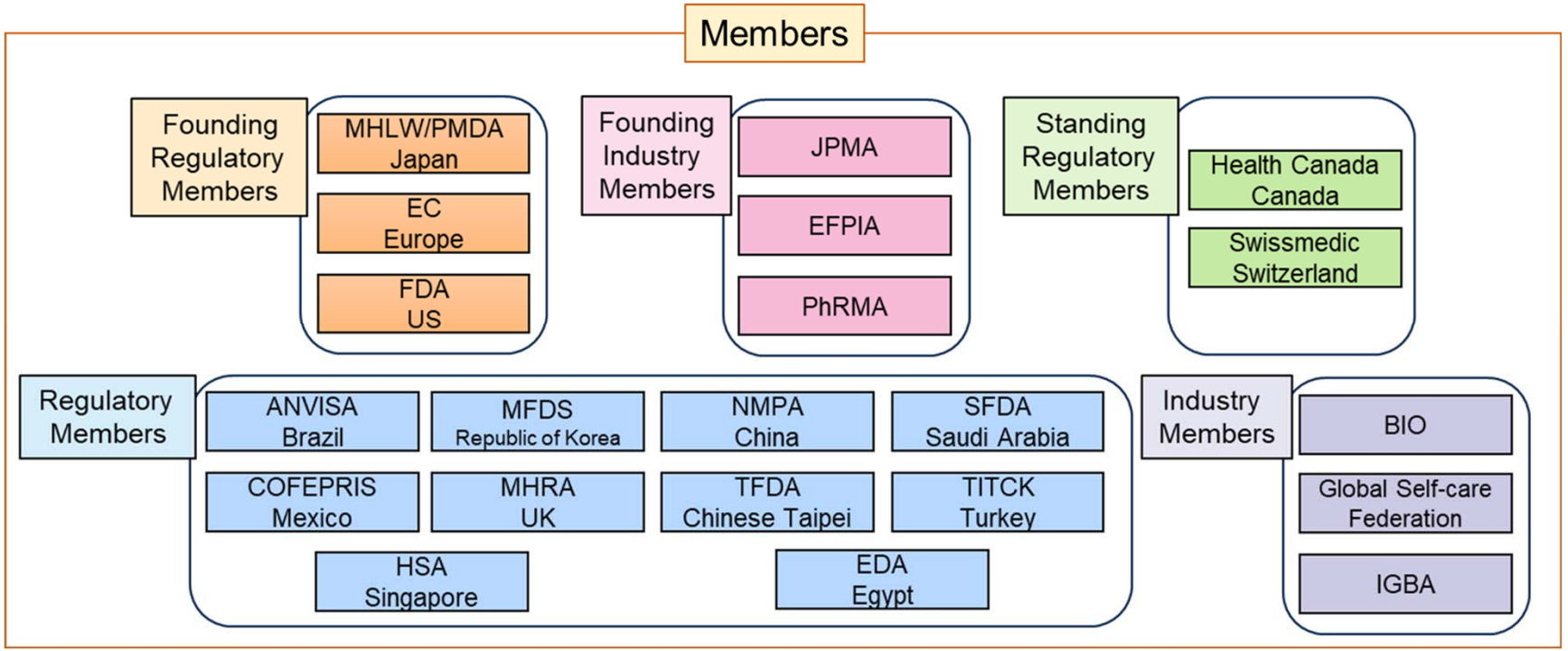
# ICHとは

ICH: 医薬品規制調和国際会議
International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use




医薬品規制当局と製薬業界の代表者が協働して、医薬品規制に関する
**国際的に調和された**ガイドラインを科学的・技術的な観点から作成する国際会議

医薬機審発 1023 第 1 号
令 和 5 年 10月 23日

各都道府県衛生主管部（局）長 殿

厚生労働省医薬局医療機器審査管理課長
（ 公 印 省 略 ）

「遺伝子治療用製品の非臨床生体内分布の考え方」について

優れた新医薬品の研究開発を地球規模で促進し、患者へ迅速に提供するため、近年、承認審査資料の国際的な調和の推進を図ることの必要性が指摘されています。当該要請に応えるため、医薬品規制調和国際会議（以下「ICH」という。）が組織され、品質、安全性及び有効性の各分野で、承認審査資料の国際的な調和の推進を図るための活動が行われているところです。

別添の「遺伝子治療用製品の非臨床生体内分布の考え方」は、ICH における合意に基づき、遺伝子治療用製品の開発における非臨床生体内分布試験の実施について、国際的に調和されたガイドラインを提供することを目的としています。つきましては、貴管下関係業者等に対して周知方御配慮願います。

ICH S12
遺伝子治療用製品の非臨床生体内分布試験の考え方


ICH 細胞治療遺伝子治療ディスカッショングループ

遺伝子治療においても国際調和が加速している

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# ICH Quality Guidelines

| | | |
|---|---|---|
| ICH-Q1 | 安定性 | A, B, C, D, E |
| ICH-Q2 | 分析バリデーション | A, B |
| ICH-Q3 | 不純物 | A,B,C,D (E step1) |
| ICH-Q4 | 薬局方 | - |
| ICH-Q5 | 生物製剤の品質 | **A**, B, C, D, E |
| ICH-Q6 | 規格及び試験方法 | A, B |
| ICH-Q7 | GMP（Good Manufacturing Practice） | - |
| ICH-Q8 | 製剤開発 | - |
| ICH-Q9 | 品質リスクマネジメント | - |
| ICH-Q10 | 品質システム | - |
| ICH-Q11 | 原薬の開発と製造 | - |
| ICH-Q12 | ライフサイクルマネジメント | - |
| ICH-Q13 | 連続生産 | - |
| ICH-Q14 | 分析法の開発 | - |

# ICH Q5A (R1) (old version)

## ヒト又は動物細胞株を用いて製造されるバイオテクノロジー応用医薬品のウイルス安全性

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

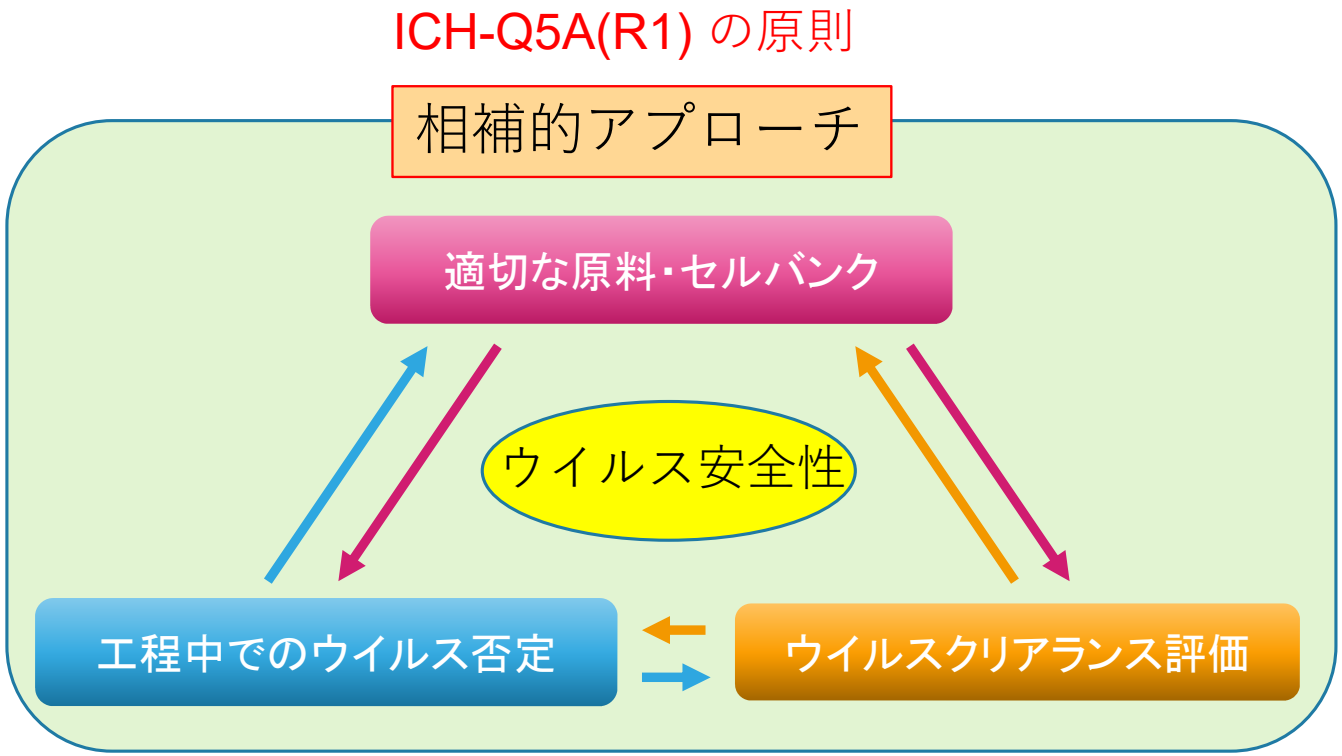
ICH HARMONISED TRIPARTITE GUIDELINE

VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS DERIVED FROM CELL LINES OF HUMAN OR ANIMAL ORIGIN
Q5A(R1)

Current *Step 4* version
dated 23 September 1999

R1の適用はバイオ医薬品

*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.*



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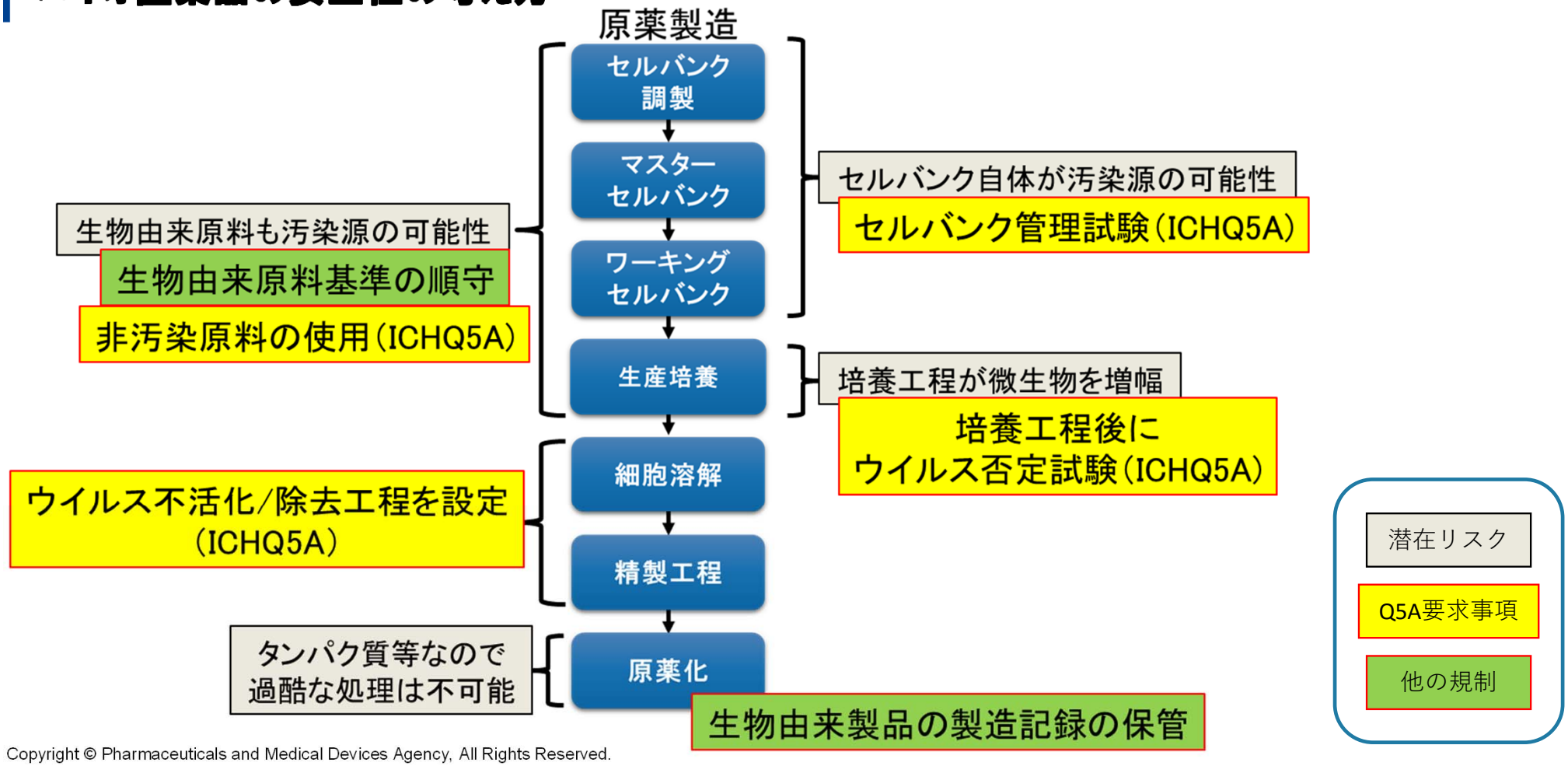
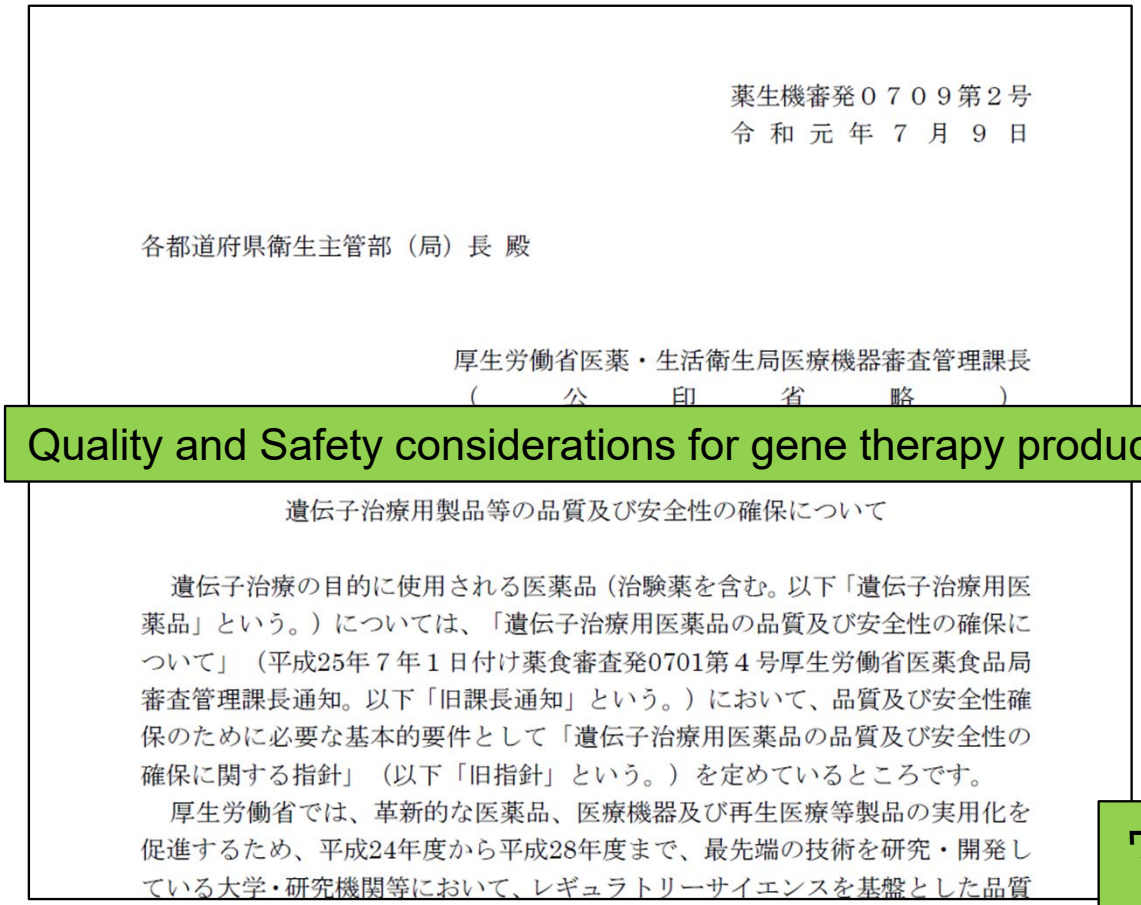
# バイオ医薬品の安全性の考え方





薬生機審発０７０９第２号
令 和 元 年 ７ 月 ９ 日

各都道府県衛生主管部（局）長 殿

厚生労働省医薬・生活衛生局医療機器審査管理課長
（ 公 印 省 略 ）

遺伝子治療用製品等の品質及び安全性の確保について

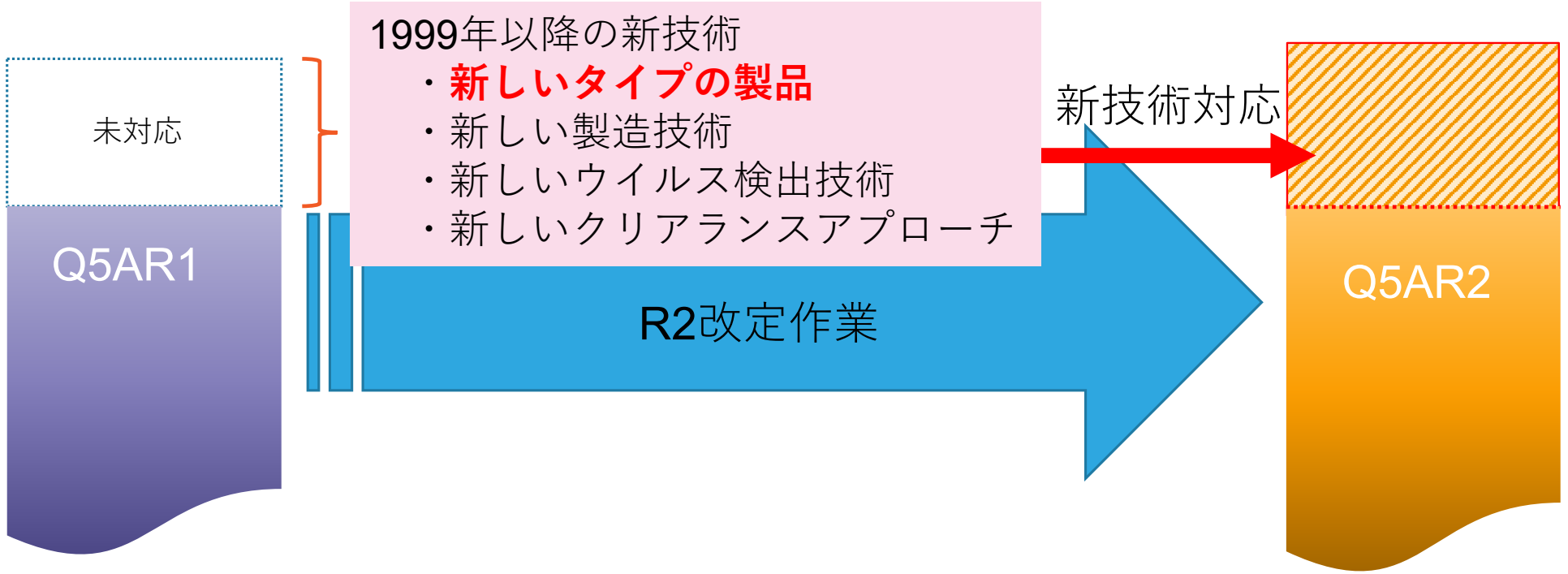
遺伝子治療の目的に使用される医薬品（治験薬を含む。以下「遺伝子治療用医薬品」という。）については、「遺伝子治療用医薬品の品質及び安全性の確保について」（平成25年７年１日付け薬食審査発0701第４号厚生労働省医薬食品局審査管理課長通知。以下「旧課長通知」という。）において、品質及び安全性確保のために必要な基本的要件として「遺伝子治療用医薬品の品質及び安全性の確保に関する指針」（以下「旧指針」という。）を定めているところです。

厚生労働省では、革新的な医薬品、医療機器及び再生医療等製品の実用化を促進するため、平成24年度から平成28年度まで、最先端の技術を研究・開発している大学・研究機関等において、レギュラトリーサイエンスを基盤とした品質

Quality and Safety considerations for gene therapy products

ウイルス安全性について、Q5Aを参考とするよう記載。
本質的な規制が変わったわけではない。

# Q5AR2 Updates




Published in 1999

Reached Step4 in 2023
(国際的合意)

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## 改正後のQ5Aの構成（本文）

| Section | Title | Comment |
|---|---|---|
| Section 1 | Introduction | Major Changes |
| Section 2 | Potential Sources of Viral Contamination | Minor Changes |
| Section 3 | Cell Line Qualification: Testing for Viruses | Major Changes |
| Section 4 | Testing for Viruses for Unprocessed Bulk | Major Changes |
| Section 5 | Rationale and Action Plan for Viral Clearance Studies and Virus Tests on Purified Bulk | Major Changes |
| Section 6 | Evaluation and Characterisation of Viral Clearance Procedures | Major Changes |
| Section 7 | Points to Consider for Continuous Manufacturing | New |
| Section 8 | Summary | Minor Changes |
| Section 9 | Glossary | Major Changes |
| Section 10 | References | New |

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## 改正後のQ5Aの構成（付録）

| Annex | Title | Comment |
|---|---|---|
| Annex 1 | The Choice Of Viruses For Viral Clearance Studies | Minor Changes |
| Annex 2 | Statistical Considerations For Assessing Virus And Virus Reduction Factors | Minor Changes |
| Annex 3 | Calculation Of Reduction Factors In Studies To Determine Viral Clearance | Minor Changes |
| Annex 4 | Calculation Of Estimated Particles Per Dose | Minor Changes |
| Annex 5 | Examples Of Prior Knowledge Including In-house Experience To Reduce Product-specific Validation Effort | New |
| Annex 6 | Genetically-engineered Viral Vectors And Viral Vector-Derived Products | New |

旧Annex1は削除

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# ICH Q5A(R2)の改定ポイント(適用範囲)について

| ICHQ5A(R1) | ICH Q5A(R2) |
|---|---|
| Included:<br>• Products derived from in vitro cell culture:<br>• Interferons<br>• Monoclonal antibodies<br>• Recombinant DNA-derived products<br>• Recombinant subunit vaccines<br>• Products derived from hybridoma cells grown in vivo as ascites | Included:<br>• Products derived from in vitro cell culture:<br>• Cytokines<br>• Monoclonal antibodies<br>• Recombinant DNA-derived products<br>• Recombinant subunit vaccines<br>• Genetically-engineered viral vectors and viral vector derived products provided they are amenable to viral clearance<br>○ e.g., Virus Like Particles (VLPs) and protein subunits |
| Excluded:<br>• Inactivated vaccines<br>• All live vaccines containing self-replicating agents<br>• Genetically-engineered live vectors | Excluded:<br>• Inactivated vaccines<br>• All live vaccines containing self-replicating agents<br>• Products derived from hybridoma cells grown in vivo as ascites<br>• Genetically-engineered viral vectors provided they are not amenable to virus clearance<br>• Cell therapies |

ウイルスベクターのうち
品質へ影響与えずにクリアランス可能なもの

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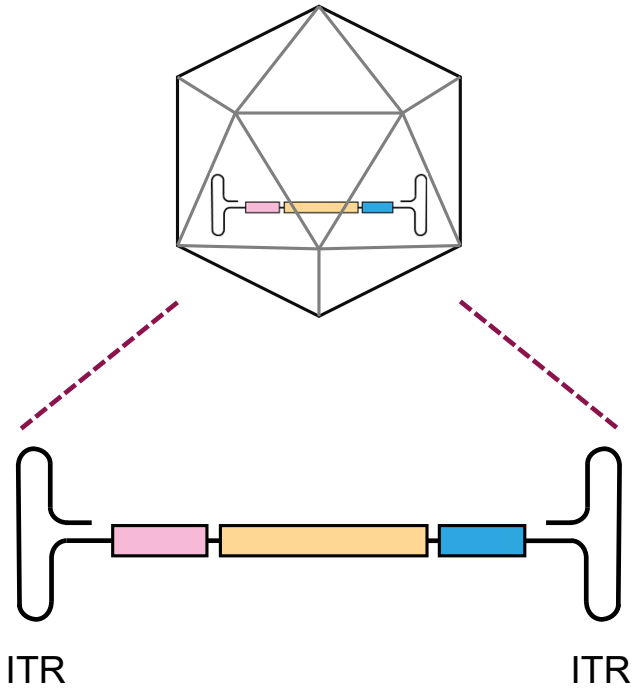
# ICH Q5A(R2)の改定ポイント(適用範囲)の具体例について

| ICHQ5A(R1) | ICH Q5A(R2) |
|---|---|
| Included:<br>• mAbs<br>• Recombinant proteins<br>• Recombinant subunit vaccines<br>• Certain vaccines<br>• Interferons | Included:<br>• MAbs<br>• Recombinant proteins<br>• Recombinant subunit vaccines<br>• Certain vaccines<br>• Cytokines<br>• AAV and adenovirus helper AAV<br>• Baculovirus produced VLP vaccines and gene therapies e.g., baculovirus expressed AAV<br>• Protein subunits expressed in baculovirus |
| Excluded:<br>• Inactivated viral vaccines<br>• Live attenuated vaccines: Measles, Mumps, Rubella<br>• Lentivirus, AAV, and adenovirus vectors | Excluded:<br>• Inactivated viral vaccines<br>• Live attenuated vaccines: Measles, Mumps, Rubella |

アデノ随伴ウイルスベクターが想定

## ICH Q5A(R2)の適用範囲となった「品質に影響を与えずにクリアランス可能」な製品とは？




アデノ随伴ウイルスベクター

- Non-enveloped virusなので界面活性剤や低pHに耐性
- 非常に小型なため、孔径の大きなナノフィルターは通過可能
- 精製が可能なため他のウイルスの除去が可能

抗体ほどではないが一定のクリアランス工程は可能

ICH Q5A(R2) Guideline

**ANNEX 6: GENETICALLY ENGINEERED VIRAL VECTORS AND VIRAL VECTOR-DERIVED PRODUCTS**

**6.1 Introduction**

Advances in biotechnology have led to the emergence of new and advanced production platforms expressing new product types manufactured using characterised cell banks of human or animal origin (i.e., avian, mammalian, or insect). The scope of Annex 6 includes genetically engineered viral vectors and viral-vector derived products that can be produced using helper-virus and viral vectors for protein expression (collectively referred to as production viruses) or from stable or transient transfected cell lines. The products included here are those amenable to viral clearance based on the physicochemical properties of the product. These products include protein subunits and VLPs that are produced using baculovirus/insect cells, nanoparticle-based protein vaccines, and viral vector products such as AAV. These vectors may be applied *in vivo* or *ex vivo*.

AAVベクターなどにバイオ医薬品と同じ規制は限界があるため付録6という形で留意点を記載している。

品質に影響を与えずにウイルスクリアランス工程を設定できる品目に限定。

Viral safety and contamination controls of new product types should be assured through the application of a comprehensive program of material sourcing, virus testing at appropriate steps of the manufacturing process and removal and/or inactivation of adventitious viruses and production viruses by the manufacturing process. If viral clearance is limited, viral safety should focus on the testing and control of the raw materials and reagents and the manufacturing process.

基本原則（管理された原材料、ウイルスクリアランス工程、行程中のウイルス否定試験）はこれまでと同じ。
ウイルスクリアランスに限界がある場合は、後の2つに焦点を当てて管理戦略を立てることが明記。

ICH Q5A(R2) Guideline

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ウイルスシードの要件の明確化

**Table A-5: Virus Tests that Should Be Performed at Applicable Stages**

| *Test* | *MCB, WCB, Cells at the LIVCA* | *Virus Seeds*[i] | *Unprocessed Bulk (Harvest)* | *Drug Substance (purified bulk)* |
|---|---|---|---|---|
| Test for adventitious viruses | | | | |
| *In vitro* Assays or NGS [a,b] | See Table 1 of main guideline | +[g] | +[g] | - |
| *In vivo* Assays or NGS[b] | | +[g] | -[g, j] | - |
| Tests for Specific Virus[c] | | +[h] | + | - |
| Test for Retrovirus and Endogenous virus, Production virus and Replication competent virus, as applicable | | | | |
| Retrovirus and Endogenous Virus | See Table 1 of main guideline | + | -[d, j] | - |
| Production Virus | - | - | +[e] | +[e] |
| Replication Competent Virus | - | +[f] | +[f] | +[f] |

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ICH Q5A(R2) Guideline

**ANNEX 6: GENETICALLY ENGINEERED VIRAL VECTORS AND VIRAL VECTOR-DERIVED PRODUCTS**

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ウイルスベクター使用時の
工程内管理試験の要求事項

**Table A-5: Virus Tests that Should Be Performed at Applicable Stages**

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| Retrovirus and Endogenous Virus | See Table 1 of main guideline | + | -[d, j] | - |
| Production Virus | - | - | +[e] | +[e] |
| Replication Competent Virus | - | +[f] | +[f] | +[f] |

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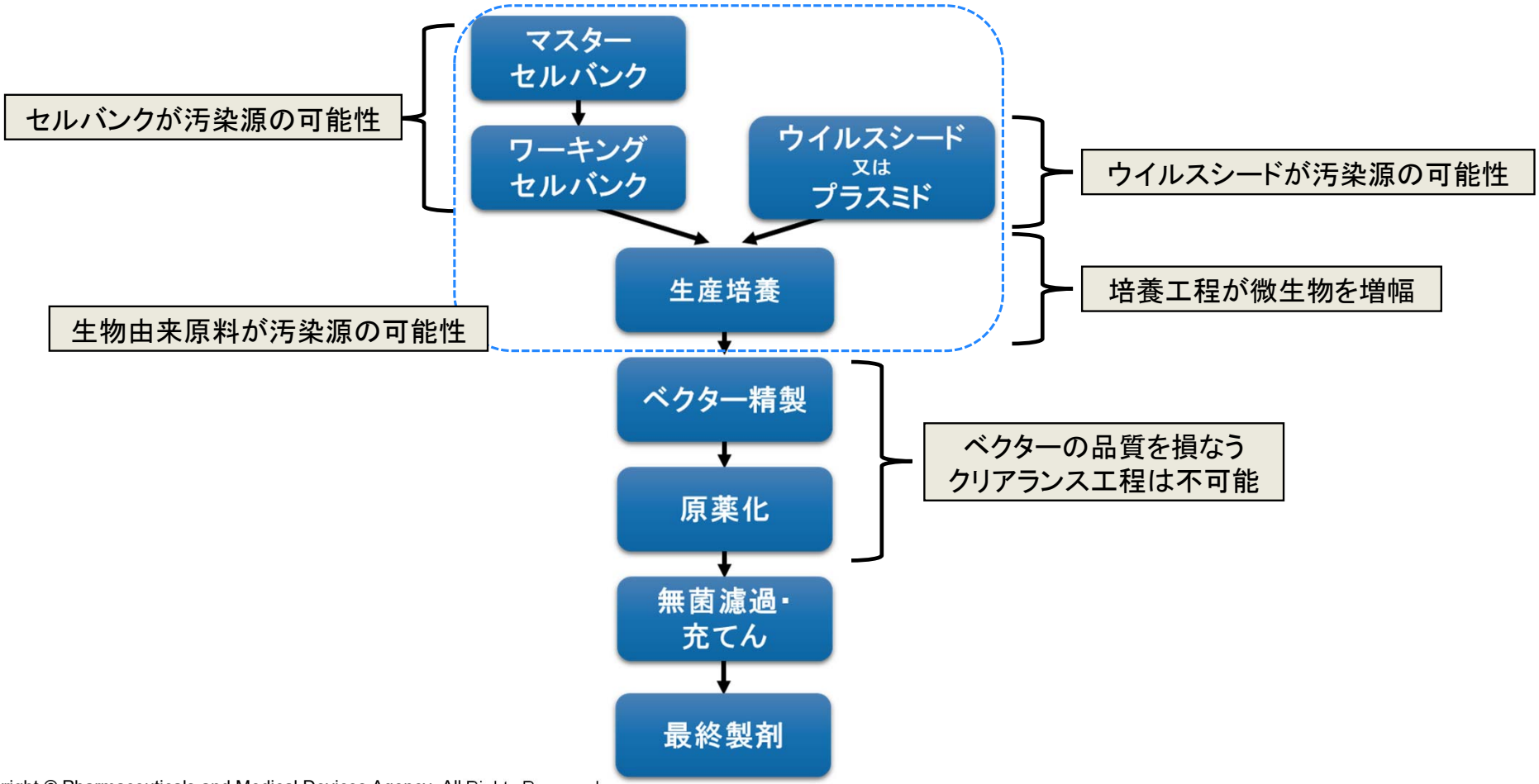
### 6.3 Viral Clearance

The risk of contamination with adventitious viruses, endogenous viruses and residual production viruses should be mitigated following the general principles of this guideline to the extent possible. Some viral-vector products such as AAVs are amenable to viral clearance steps, assuring adventitious and production viral clearance (inactivation or removal).

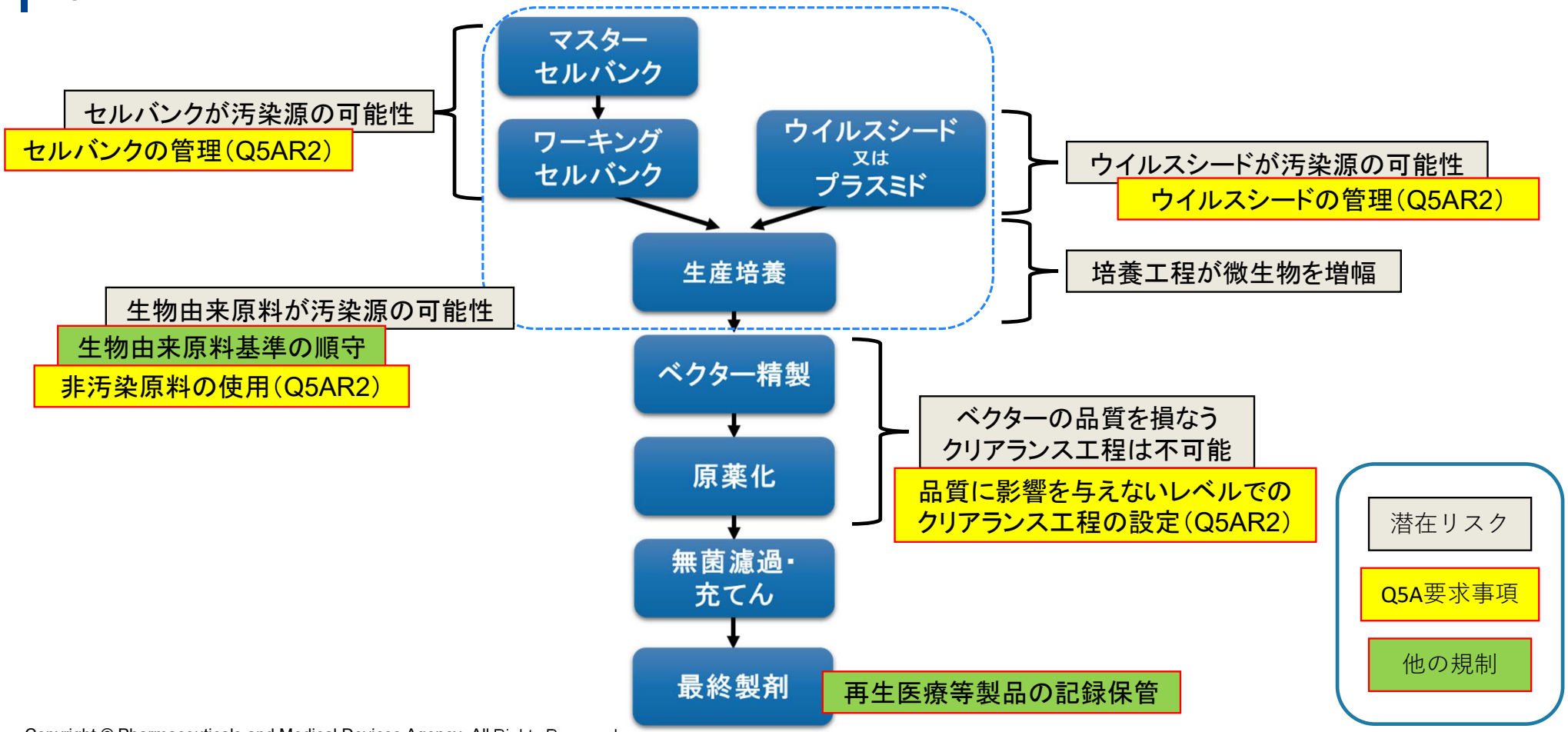
The viral safety of these products may also rely on closed processing, testing and other preventative controls (see Sections 2.2, 3, and 4). Viral clearance steps during production may not achieve the same robustness as for recombinant proteins, therefore viral safety of the products should be supported by a risk assessment.

ウイルスクリアランスの頑健性が他の組換えタンパク等に及ばない場合は
他の安全策を検討した上で、リスク評価を実施する必要がある。

# ウイルスベクター製品のウイルス安全性のリスク



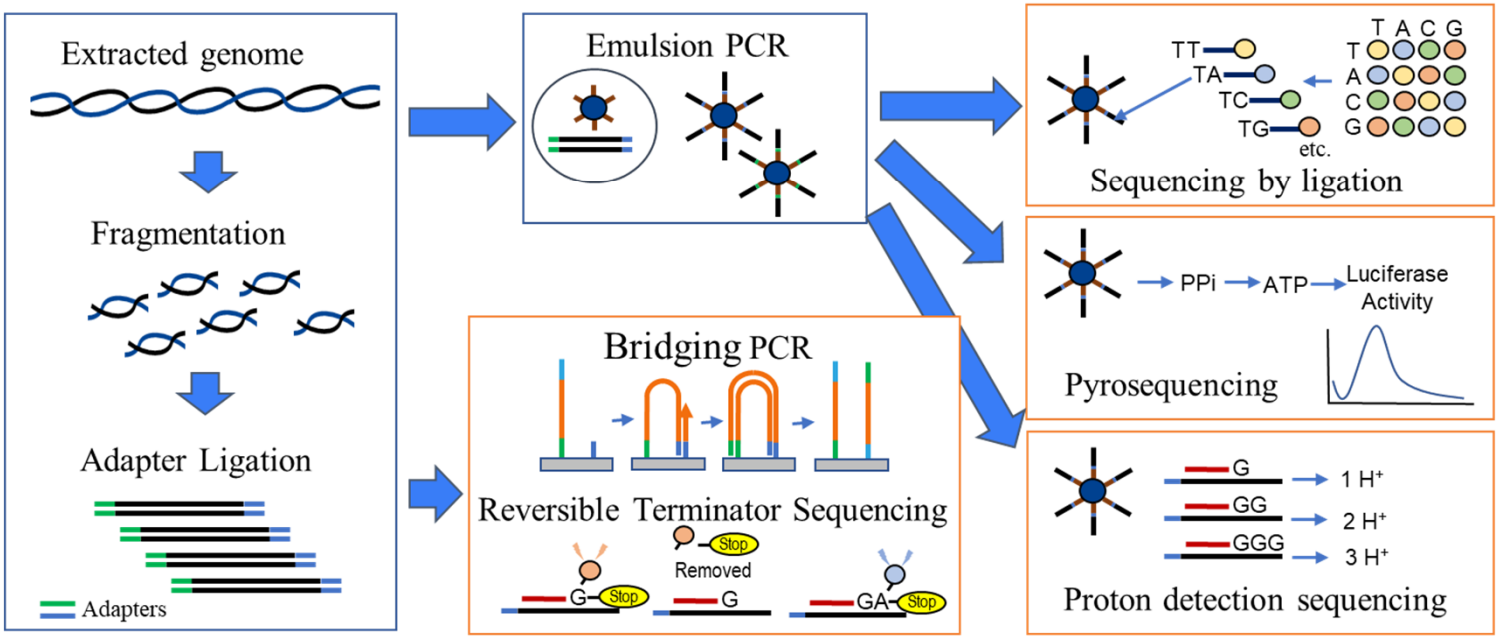
# Q5Aの改定を踏まえたウイルスベクター製品のウイルス安全性管理戦略



# 次世代シークエンシング（NGS）

***3.2.5.2 Next Generation Sequencing***

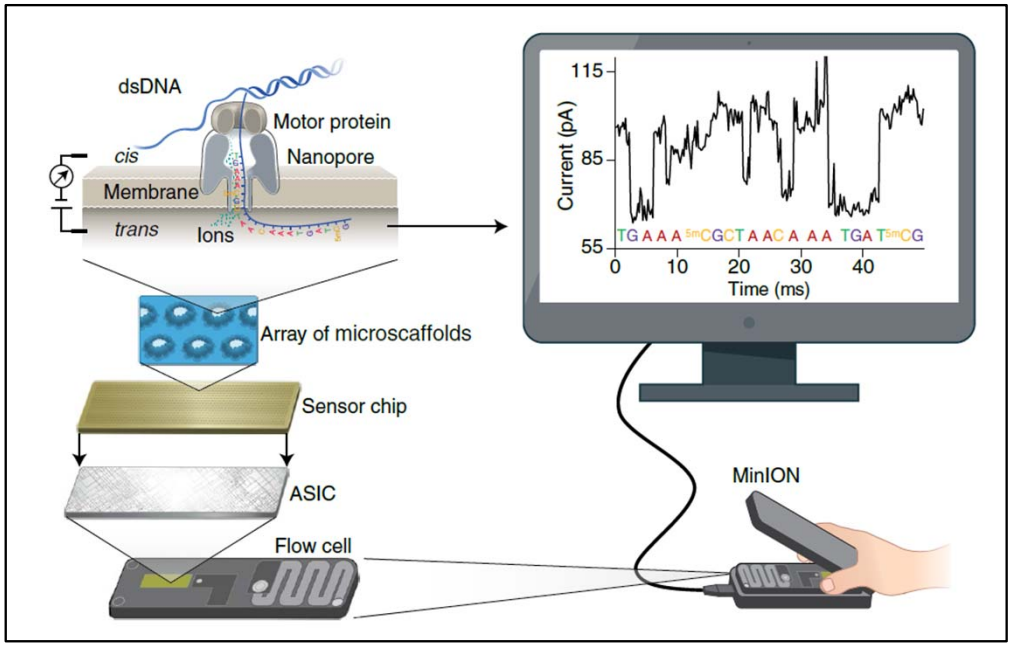
NGS (also known as high-throughput sequencing) is available with demonstrated capabilities for broad virus detection. NGS can provide defined sensitivity and breadth of virus detection and can reduce animal use and testing time. Non-targeted NGS can replace the *in vivo* tests with broad virus detection for unknown or unexpected virus species without a head-to-head comparison.



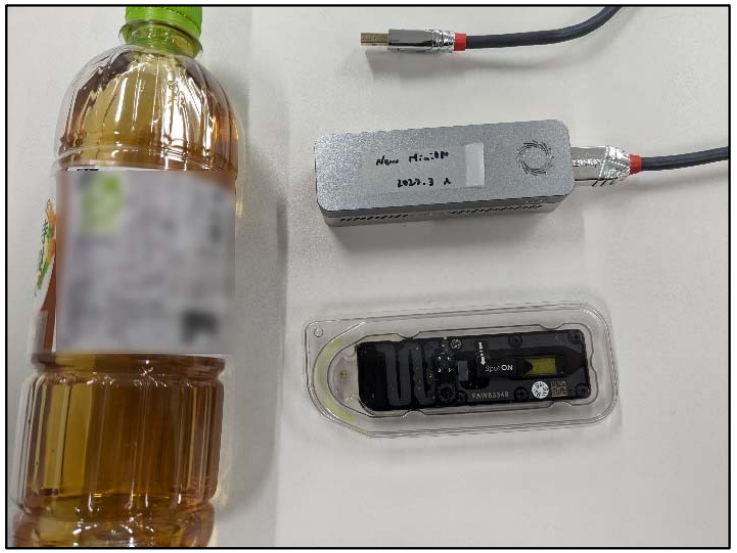
REVIEW ARTICLE
https://doi.org/10.1038/s41587-021-01108-x
nature biotechnology
Check for updates

# Nanopore sequencing technology, bioinformatics and applications

Yunhao Wang[1,3], Yue Zhao[1,2,3], Audrey Bollas[1,3], Yuru Wang[1] and Kin Fai Au[1,2]







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Use of NGS can be considered for characterisation of the cell line or testing of the cell bank, virus seed or unprocessed bulk harvest. This can be particularly useful in case of assay interference as a result of lack of effective neutralization of the viral vector (see Annex 6) or toxicity caused by the product or media components. In such applications, NGS can be applied to analyse all genomic viral nucleic acids (genomics), viral mRNAs (transcriptomics), or encapsidated viral genomes (viromics). When analyzing cell culture-derived materials, nucleic acids prepared from cells are used for genomics and transcriptomics while cell culture supernatants or cell free virus preparations are used for the viromics. The rationale for selecting these different strategies should be provided.

When applying NGS for sensitive and broad detection of known and novel viruses, there are several critical steps in the NGS workflow for consideration: (1) sample pre-treatment (when performed) and virus enrichment steps that may be needed to maximise virus detection based on the type of sample material; (2) efficiency of viral nucleic acid extraction (from enveloped and nonenveloped particles) and library preparation (DNA and RNA viruses); (3) selection of a suitable sequencing platform for sensitive virus detection; and (4) bioinformatics analysis against a database with diverse representation of viral sequences of different viral families using strategies for broad virus detection. A follow up strategy may be needed to confirm the detection of a virus specific signal to distinguish from non-viral sequences that could be present in the database.

Suitable reference materials should be used for method qualification and validation to evaluate performance of the different steps involved in the workflow and to demonstrate sensitivity, specificity, and breadth of virus detection. This can include using currently available reference virus reagents/panels which contain viruses of distinct physical (size, enveloped and non-enveloped), chemical (low, medium, and high resistance), and genomic (DNA, RNA, double- and single-stranded, linear, circular) characteristics to evaluate the performance of the entire NGS workflow or specific steps. A comprehensive viral database should be used with diverse viral sequences for broad virus detection. Other types of reference materials may be used to evaluate the specific technical and bioinformatic steps.

- ✓ Genomics, transcriptomics, or viromics
- ✓ Extract from cells or culture supernatant

The rationale for selection should be provides

Should be evaluated

- ✓ Sample Pre-treatment
- ✓ Viral nucleic acid extraction
- ✓ Sequencing platform
- ✓ Bioinformatic analysis

Reference viruses?

- ✓ Size
- ✓ Enveloped or Non-enveloped
- ✓ Chemical resistance
- ✓ DNA or RNA
- ✓ Double-stranded or Single-stranded
- ✓ Linear or Circular

ICH Q5A(R2) Guideline

**ANNEX 5: EXAMPLES OF PRIOR KNOWLEDGE INCLUDING IN-HOUSE EXPERIENCE TO REDUCE PRODUCT-SPECIFIC VALIDATION EFFORT**

**5.1 Introduction**

According to the general principles for a platform validation approach, robust viral clearance should be demonstrated across products from the same platform and the procedure for viral clearance should follow established and well-characterised conditions. In addition, it should be shown that the composition of the process intermediate is comparable to the intermediates used in viral clearance studies unless prior knowledge indicates robustness of viral clearance with respect to process intermediate composition.

In this context, as opposed to product-specific process validation, platform validation is defined as the use of prior knowledge including in-house (applicant-owned data) experience with viral clearance from other products, to claim a reduction factor for a new similar product. In general, viral clearance claims for a new product based on prior knowledge including in-house experience should include a discussion of all relevant platform data available and the rationale to support the platform validation approach (see Section 6.6). Part of the prior knowledge and in-house data used to reduce product-specific validation could be provided as a comparison of the new product and its manufacturing process with other in-house products, related process conditions, and process intermediates.

**5.2 Inactivation by Solvent/Detergent or Detergent Alone**

Based on the mechanism of action, detergent concentration of Solvent/Detergent (SD) reagents or detergent alone is an important process parameter.

In addition, hydrophobic impurities such as lipids, cell debris, or components of cell culture media such as antifoaming agents can affect virus inactivation by challenging the detergent or SD mixture in solubilizing the virus lipid envelope and therefore should be assessed.

**Table A-2: Summary of Process Parameters or Factors and Their Potential Effect for Detergent Inactivation or SD-Treatment**

| *Process parameter or Factor* | *Potential Effect* | *Rationale* |
|---|---|---|
| **SD or Triton X-100 concentration** | high | Inactivating agent |
| **Incubation time** | high | Mechanism of inactivation is time-dependent |
| **Temperature** | high | Effect on inactivation kinetics |
| **Pre-treatment by ≤ 0.2 µm filtration** | high | Removal from the starting intermediate of aggregates potentially entrapping and protecting viral particles from detergent access |
| **Total lipid content or surrogate parameter in HCCF** | low | Low effect observed with worse-case HCCF |
| **Type of product** | low | No effect on inactivation observed for mAbs, half antibody, fusion protein or recombinant protein |
| **Total protein content** | low | Low effect observed |
| **pH** | low | Triton X-100 is a non-ionic detergent |
| **Ionic strength** | low | Triton X-100 is a non-ionic detergent |
| **Buffer salt in HCCF** | low | Triton X-100 is a non-ionic detergent |
| **Potential interaction between virus particle and product** | low | No effect on inactivation observed and disruption of lipid envelope lowers probability of interaction with product |

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# ありがとうございました