Technical Requirements for Viral Safety Control of Recombinant Biotechnology Products

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Taizhou (Jiangsu), August 2022

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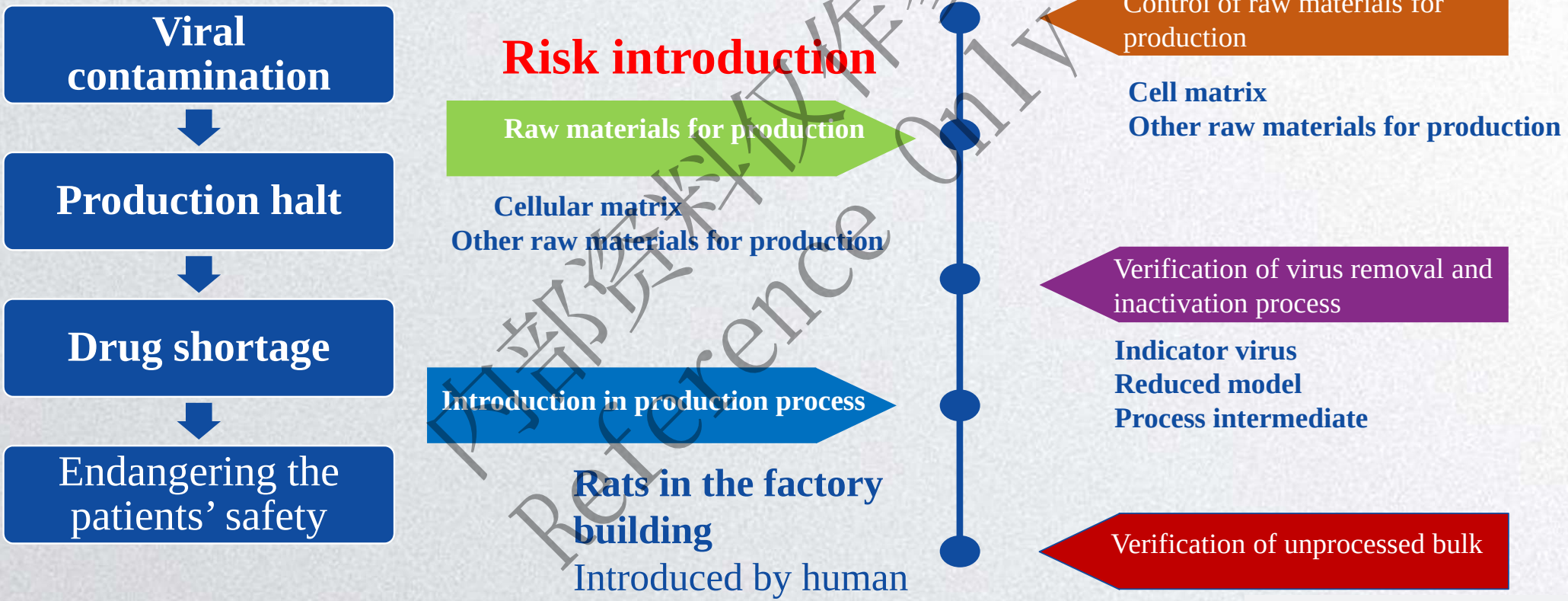
I. Overview

Biological products from different sources have different risks of viral contamination



II. Regulations and Technical Guides

1. Regulations and technical guides in China

General Principles for Technical Review of Viral Safety of Biotissue-Extracted Products and Eukaryotic Expression Products

2005 CDE

General Principles of Chinese Pharmacopoeia:
Preparation and Quality Control of Animal Cell Matrix for Production and Verification of Biological Products and Viral Safety Control of Biological Products

2020 Chinese Pharmacopoeia Commission

2. International regulations and technical guides

Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin

1999 ICH Q5A（R1）

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III. Review Technical Requirements

1. Control of raw materials for production

1.1 Verification of cell bank

Host cells: source information, domestication history and verification of viral exogenous factor of host cell bank;

Cell bank for production: MCB, WCB, and EOPC /LIVCA;

The 2020 edition of Chinese Pharmacopoeia or ICH Q5A (R1) can be followed.

1.2 Other raw materials for production

Fully assess the potential risks according to the source and production methods;

Provide certificate for no TSE or BSE risks;

Perform appropriate pretreatment, such as HTST…

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III. Review Technical Requirements

2. Verification of viral exogenous factors of unprocessed bulk(UPB)

During clinical trials:

Verification should be conducted on each batch of clinical trial samples;

During marketing authorization application:

Verification results of at least 3 batches of UPBs should be provided during the marketing authorization application phase;

It is recommended to verify each batch of process intermediates after marketing;

Selection of virus for verification:

Based on the risks that may be possibly introduced by the product and production process;

Including contamination history of the production site, etc.;

Determine the viral exogenous factors to be determined;

Such as minute virus of mice, porcine circovirus, 2117 calicivirus, etc.

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III. Review Technical Requirements

3. Verification o f virus removal and inactivation

3.1 Selection of indicator virus

Cell matrix for production: such as CHO cells: murine leukemia virus, SF9 cells: baculovirus;

Production process: such as Nanofiltration process: minute virus;

3.2 Reduced model for verification

At least two process steps with different mechanisms: Chromatography, low-pH, nanofiltration…, which should cover the worst conditions;

3.3 Samples of process intermediates for verification

For process intermediates produced with the process under application, 2 independent studies on 1 batch of samples / independent study on 3 batches of samples;

3.4 Calculation of safety factor

Take CHO cells as an example, the assessment is conducted in combination with the RVLP verification results and elimination ability of the production process.

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IV. Special Considerations for Different Application Stages

1. IND phase

Select the production process to be verified and the indicator virus to be used on the basis of the cell matrix for production.

For example:

In combination with the Case B listed in ICH Q5A(R1), that is, there are rodent retroviruses only,

Indicator virus: murine leukemia virus and minute virus of mice;

Verification process: verify the two process steps, low-pH inactivation and virus removal by nanofiltration, respectively.

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IV. Special Considerations for Different Application Stages

2. Post-marketing change phase

CMC change items of recombinant biotechnology products cannot be enumerated one by one

Conduct comprehensive assessment on the viral contamination risks of the product according to different change items

Core

Representative analysis of the studies carried out

Verification of virus removal and inactivation process

Cell matrix for production

EOPC/LIVCA/UPB

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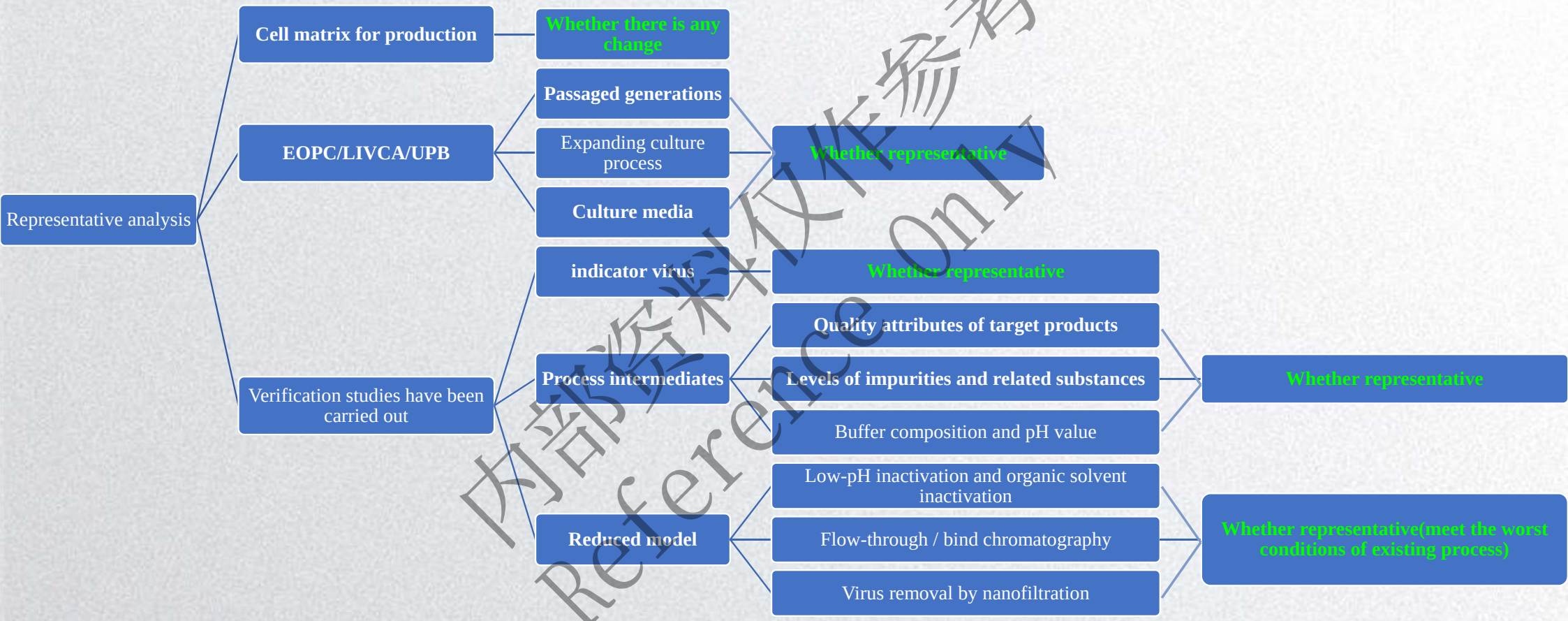
IV. Special Considerations for Different Application Stages



Viral safety studies should be re-conducted when representativeness cannot be adequately assessed

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IV. Special Considerations for Different Application Stages

Examples

- **Change in cell lines for production**

  Considering the limited characterization of recombinant biotechnology products by available technologies, it is recommended to re-conduct comprehensive viral safety related studies.

- **Change in chromatographic media**

  In addition to the verification of virus removal and inactivation for this step, it is also necessary to conduct a comparative study on the process intermediates of the effective steps of subsequent virus removal and inactivation.

- **Change in production site（non-copy production line）**

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V. Development and Challenges

1. Verification of viral exogenous factor based on nucleic acid testing

Advantages: Breadth and speed of verification, especially for **unexpected viruses**;

Challenge: **Methodological study**

Differences in the detection sensitivity for viruses with different attributes (physical, chemical, and genomic);

Depth and precision of the sequencing itself;

Sample testing and determination of results

Effective viral nucleic acid extraction and library preparation;

Select the appropriate sequencing platform;

Comprehensive bioinformatic analysis for diversity databases;

Identification of infected/non-infected particles and decision trees after positive results.

V. Development and Challenges

2. Application of prior knowledge and platform experience

Advantages: Simplify the study and expedite the application;

Challenge: Full experiences and understanding of the product and process

In the event of developing similar products through established and fully characterized processes and using the virus elimination data of the platform, the representativeness of prior knowledge of specific process steps should be clearly demonstrated. The prior composed of external and internal experience should cover the following aspects:

The mechanism of action of potential virus elimination and inactivation processes should be fully understood.

All process parameters that may affect virus removal and inactivation should be fully understood;

It should be clarified that the interaction between the virus and the product has no impact on the virus elimination and inactivation effect;

The composition of process intermediates and their potential impact on virus elimination and inactivation effect should be understood;

General limitations of virus elimination studies should be considered when applying them to specific products.

Establishment and recognition of prior knowledge and platform experience

V. Development and Challenges

3. Control of viral exogenous factor control under continuous manufacture

Advantages: Closed loop production and cost reduction

Challenge: Front control

Special emphasis on the control and verification of viral exogenous factors in raw materials for production;

Long-time cell culture

Setting of sampling points and fluctuation of endogenous retrovirus levels;

Virus elimination and inactivation verification

Depending on the device design and system integration, two or more connected units can be verified simultaneously.

Control of relevant dynamic process parameters, such as low pH treatment or organic solvent inactivation, should be ensured;

Process controls should be defined to allow filter replacement and post-use integrity testing.

Thanks for Listening