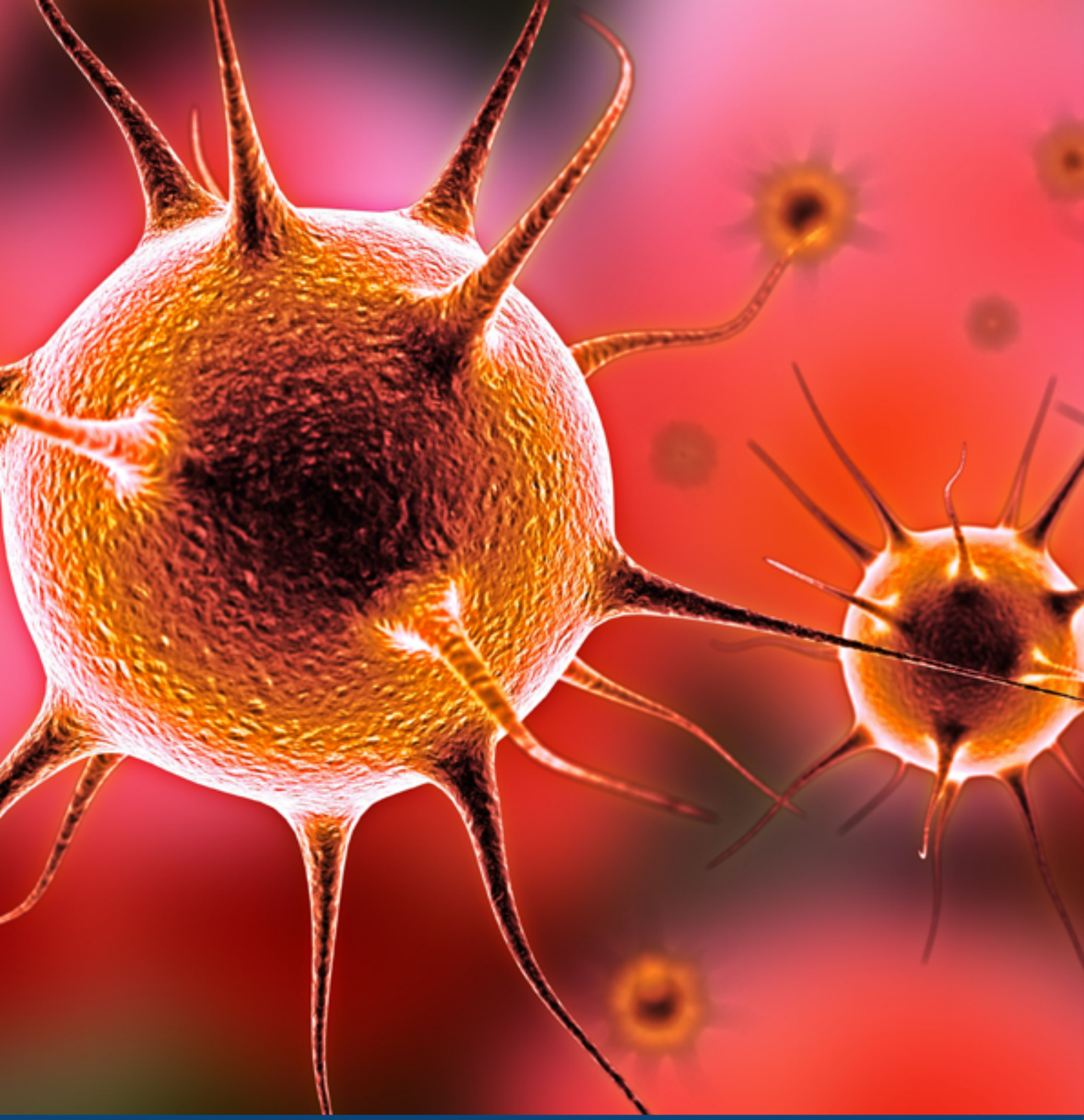


Viral Clearance

Ensure the safety of biopharmaceuticals medical devices

Mérieux NutriSciences

Viral Clearance

Viral clearance studies are required to assess the safety of biopharmaceuticals, such as blood products, monoclonal antibodies, recombinant proteins, tissue derived products, **and medical devices** prior to entering clinical trials and ahead of commercial launch.

Biopharmaceutical manufacturing processes **need to be highly controlled in order to significantly reduce the risk of viruses entering the final product**.

Contamination events in biomanufacturing **can be catastrophic** when they occur: consequences of such events can have impact on patient safety and drug shortages as well as legal, regulatory and financial implications. The impact on manufacturing operations is significant since follow up on contamination events include investigation management, decontamination and other corrective actions which are very expensive and time consuming.

Products from *in vitro* cell cultures

- Interferons
- Monoclonal antibodies
- Recombinant proteins
- Hybridoma cells grown in vivo-derived products (as ascites)
- Medical Devices

Contamination events conseguences

- Impact on patient safety
- Drug restriction
- Implications at regulatory level
- Closure of production facilities
- Economic loss
- Legal consequences

Regulation and guidelines

The **International Conference on Harmonization ICHQ5A guidance** as well as the **EMEA/CPMP/ICH/295/95 guidance**, included **ISO22442-3 specific for Medical Devices**, discuss the risk of potential viral contamination and approaches to apply to ensure viral safety of products derived from raw materials of human or animal origin. Such contamination could arise from infecteded cell lines, raw materials or from adventitius viruses introduced during production.

Potential sources of Viral Contamination

Viruses that could infect Master Cell Banks (MCB) by several routes, as:

- Derivation of cell lines from infected animals
- Use of virus to establish the cell line
- Used of contaminated biological reagents such as animal serum components
- Contamination during cell handling

Adventitius viruses that might contaminate the raw material:

- Blood and plasma derived products
- Medical Devices obtained from animal tissues
- Proteins and recombinant proteins of animal origin or produced in animals

Adventitius viruses that could be introduced during production by several routes:

- The use of contaminated biological reagents such as animal serum components
- The use of a virus for the induction of expression of specific genes encoding a desired protein
- The use of a contaminated reagent
- The use of a contaminated excipient during formulation
- Contamination during cell and medium handling
- Use of contaminated tissues or organs of human or animal origin

Study plan with the Customer

It is extremely important that the design, planning and execution of the viral clearance study are discussed in details with the customer.

Process Steps

The process **steps able of inactivating/removing viral agents need to be selected before starting** the Viral Clearance testing. Among others some of the most commonly applied are:

- Treatment with strong acids and bases
- Heat treatment
- Filtration
- Use of solvents

Virus Selection

Viruses for clearance evaluation and process characterisation studies should be **model virus** that can resemble viruses which may contaminate the product. The model viruses should also cover a wide range of physical-chemical properties in order to test the ability of the system to remove or inactivate viruses.

Thanks to the wide experience of **Mérieux NutriSciences Specialists**, we are able to assist you from the very beginning for outlining the whole study and we **will guide you** through the selection of the steps to challenge for **demonstrating Viral Clearance**.

What kind of Virus?

- Virus that could contaminate the raw material
- Model viruses that can be easily propagated on cell cultures
- Viruses that can be propagated to high titers
- Resistant viruses
- Virus whose infection is easily recognizable in the laboratory
- Viruses that meet different biochemical characteristics:
  - DNA virus with envelope
  - DNA virus without envelope
  - RNA virus with envelope
  - RNA viruses without envelope

01 Control of viral absence in the raw material

It is necessary to **assess viral absence in raw material prior to begin with the study**.
The customer can provide a certificate of viral absence if this is available or otherwise it is possible to perform a preliminary test (e.g. Antibody labeling, RT-PCR, specific staining).
Essential information about the raw material:

- **origin** - animal, human, etc.
- **type** - blood, bile, tissue, organ, plasma, cell line, etc.

02 Scaling down

The client should share the information concerning the step(s) of the manufacturing process selected for the clearance study. The downscaled steps must be validated to **represent as closely as possible the same steps of the full-scale manufacturing process**.

03 Scaling down validation of the selected steps

Check of equivalence of full scale and small scale processes and **perform Quality Controls (QC)** decided in accordance with the client on the basis of the steps to be validated for viral clearance activity.

04 Preliminary cytotoxicity assay

Cytotoxicity assay is performed to demonstrate whether process materials are toxic to the indicator cells used for virus titration.

05 Spiking

A key aspect in the study is the introduction of viruses (spiking) into selected steps of the manufacturing process **to demonstrate the ability and the capability of the process to remove or inactivate known and unknown viruses**. This is achieved by the **addition of significant amounts of at least 4 different viruses** into the crude material and/or into production intermediates and demonstrating the removal or inactivation during the execution of the steps to be validated.

- **Virus introduction**. The addition of 4 different viruses either to the crude material and/or to production intermediates before the execution of the step. A negative control in the absence of virus is also performed.
- **Execution in worst case** conditions to challenge the robustness of the system.
- **Residual viral titer determination**. Checking of the inactivation/removal kinetics by quantitative infectivity assays such as plaque assays, cytopathic effects, endpoint titrations (TCID50 assays), detection of virus antigens, qPCR.

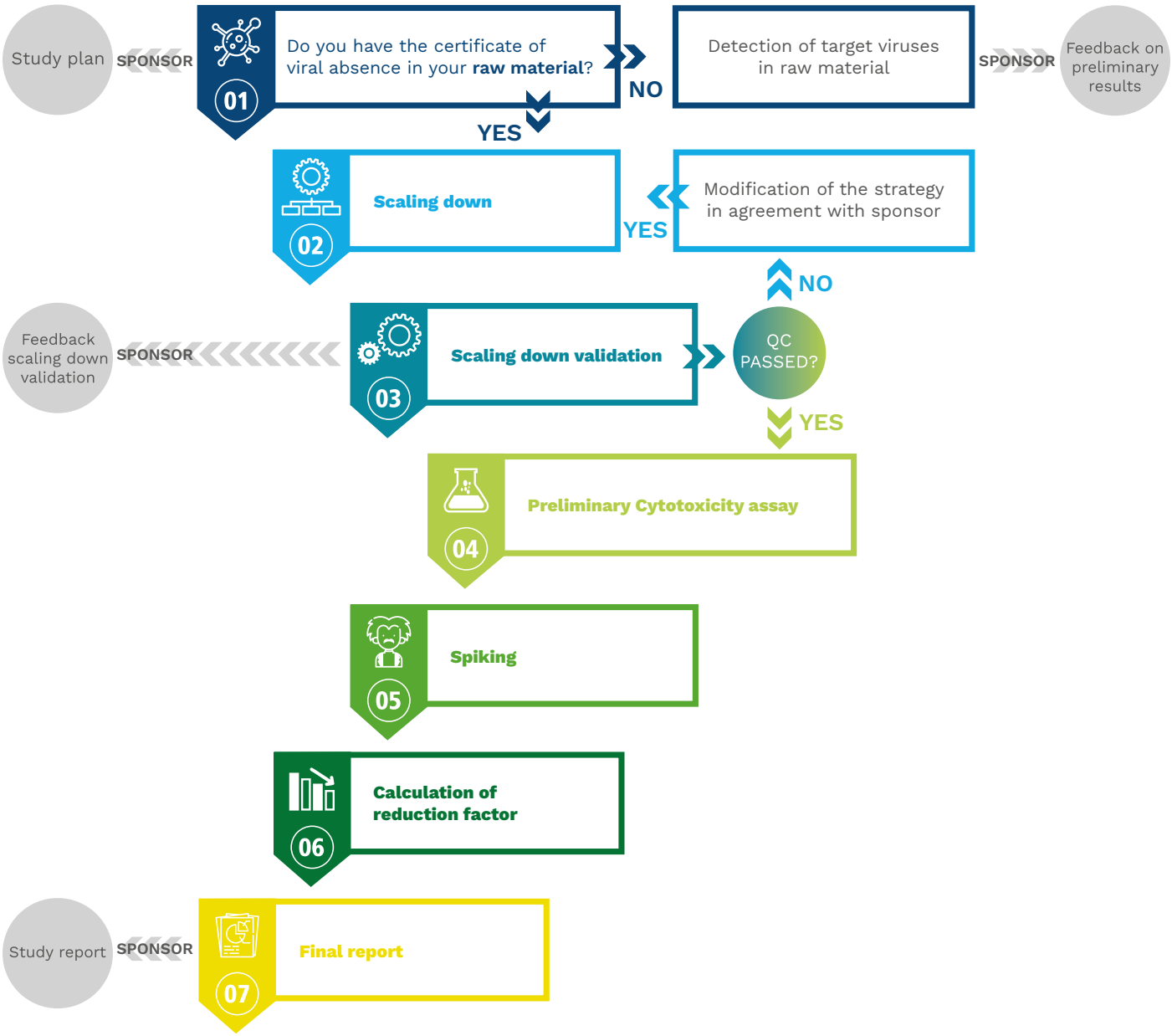
06 Calculation of the reduction factor

For each step the **Reduction Factor (RF)** is determined. RF indicates the ability of a process to remove/inactivate viruses. The sum of the RF calculated for each of the step under study, determines the **Global Reduction Factor**. The reduction necessary to **demonstrate the safety of a manufacturing process** must be assessed on a case-by-case basis, considering the following factors:

- Risks associated with the raw material used in the process
- Product therapeutic indications
- Dosage and frequency of administration

07

The objective of viral clearance studies is to evaluate the ability of the manufacturing process to **inactivate/remove known viral contaminants**, and to **estimate process robustness** by characterizing its ability to clear different model viruses.



The control of the contamination of Biopharmaceuticals and Medical Devices must take place at 3 levels:

1. Selecting and testing cell lines and other raw materials, including media components, for the absence of undesirable viruses which may be infectious and/or pathogenic for humans
2. Assessing the capacity of the production processes to clear infectious viruses
3. Testing the product at appropriate steps of production for absence of contaminating infectious viruses

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A STRONG PRESENCE IN EUROPE AND WORLDWIDE

Viral safety process

Viral safety of a manufacturing process can be ensured with an integrated approach thanks to multiple control and risk reduction strategies, but it is impossible to totally eliminate the risk. A high level of viral safety can be reached through:

- the careful control of raw materials
- the knowledge of the global reduction factor
- an effective monitoring system

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