Operational Controls to Mitigate the SARS-CoV-2 Challenge to the Virus Control Framework in Industrial GMP Manufacturing Facilities

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Speaker

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Dr. Anne Stokes is a Virologist. She is a GlaxoSmithKline (GSK) Senior Fellow, a member of the Council of Fellows and currently the Director of TSE and Virus Control within GMP Operations, Biopharmaceutical Product Development and Supply in Pennsylvania, USA.

For the past 22 years, she has worked for GSK in the development and manufacture of Biopharmaceuticals and cell and gene therapy products. She has managed Cell Banking activities and is currently the Director of TSE and Virus Control, responsible for the oversight of TSE and virus safety of a clinical Biopharm GMP manufacturing facility.

She received a Doctorate in Viral Immunology whilst at the Pirbright Institute Surrey, UK. As a Fogarty Fellow at the NIH she worked on a vaccine for human parainfluenza virus 3. She is currently a member of ISPE. She has 20 publications and has presented posters and talks at many scientific meetings. She is committed to fostering scientific talent through the GSK Fellows Program.

Operational Controls to Mitigate the SARS-CoV-2 Challenge to the Virus Control Framework in Industrial GMP Manufacturing Facilities

Anne Stokes (PhD) GSK Senior Fellow TSE and Virus Control GlaxoSmithKline

Introduction

SARS-CoV-2 Characteristics and Virus Control Framework

- Coronaviruses Background and the Science of SARS-CoV-2
- ICH-Q5A three pronged approach to virus safety in Industrial GMP Manufacturing Facilities
  - Sourcing and testing of raw and starting materials, in process virus testing and virus clearance
- Control Framework in the Production of Cell Banks and Mitigation of Risk of SARS-CoV-2
- Configuration of a Typical Manufacturing Facility and the challenges of a Virus Contamination Event and Facility Risk Assessment
  - Facility and Process Controls
  - Vendor Management and control
  - Transport, distribution and storage of raw materials and consumables
  - Governance, Quality, Compliance and Certification, segregation and disinfectant procedures

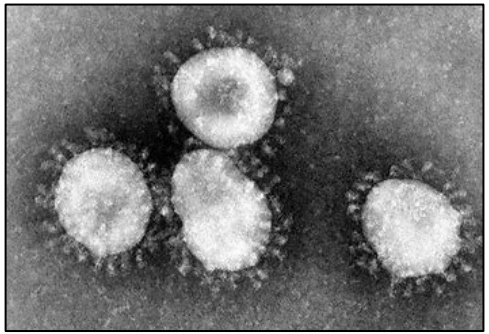


Image from Centers for Disease Control and Prevention (CDC)

Coronaviruses

Background

- **Coronavirus general:** There are hundreds of coronaviruses, that infect animals including pigs, camels, bats and cats. Sometimes those viruses jump to humans—called a spillover event—and can cause disease.
- **Coronavirus Disease:** Coronaviruses cause a variety of diseases in mammals and birds ranging from enteritis in cows and pigs and upper respiratory disease in chickens to potentially lethal human respiratory infections.
- **Human strains of Coronavirus:** Seven coronaviruses are known to cause human disease, four of which are mild: Three have more serious outcomes in people, and those diseases are SARS (severe acute respiratory syndrome) which emerged in late 2002 and disappeared by 2004; MERS (Middle East respiratory syndrome), which emerged in 2012 and remains in circulation in camels; for SARS-CoV-2 a global effort is under way to contain its spread. COVID-19 is caused by the coronavirus known as SARS-CoV-2.
- **SARS-CoV-2** presents a new challenge to the virus control framework in Industrial GMP Manufacturing Facilities

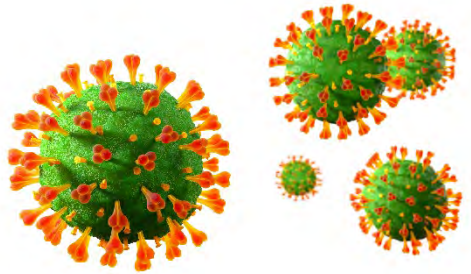
The Science of SARS-CoV-2

Scientific knowledge can make a difference in Mitigating impact of SARS-CoV-2

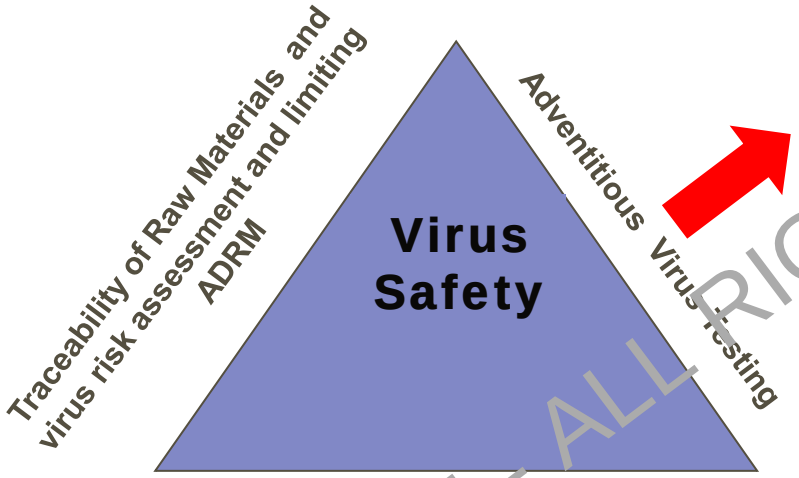
- Knowledge of the **physicochemical** features and surface survival of the virus will help inform how to effectively **inactivate** the agent by disinfectant other means and the environmental conditions that the virus thrives in (i.e. heat and humidity)
- The **RNA sequence** of the genome of the virus (which was determined very early in the pandemic) provides key information on how the components of the virus can be used in the Science of **vaccine or therapeutic development**
- The **protein sequence** and structure of the virus enables the development of **immunotherapies** against those proteins and receptors which the virus uses to infect a cell
- Knowledge about the **viral antigens** is used in the development of ELISA based methods for **serological detection**.
- The **mode of spread** (droplet or aerosol) can be used to determine the transmission (person to person or surface) and the actions to be taken including **social distancing** and **donning of masks**

Characteristics of SARS-CoV-2

- Medium sized 120-160nm in diameter comprising a nucleocapsid surrounded by a lipid envelope and spike proteins, positive-sense RNA viruses, an unusually large RNA genome, and a unique replication strategy.
- Due to the presence of a lipid envelope the virus is easily susceptible to inactivation by e.g. 70% alcohol
- Expected to be inactivated by low pH and nanofiltration but not by sterilizing filters, in the same way as the CHO retrovirus but this is not a retrovirus
- The viruses can persist on surfaces and remain infectious at room temperature for several days. Low temperature and high air humidity further affect their lifespan

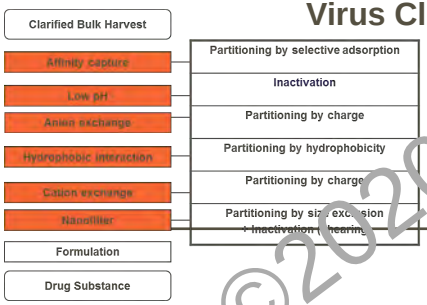


ICH Q5A The 3-pronged Approach to virus safety of Biopharmaceuticals (a holistic approach)



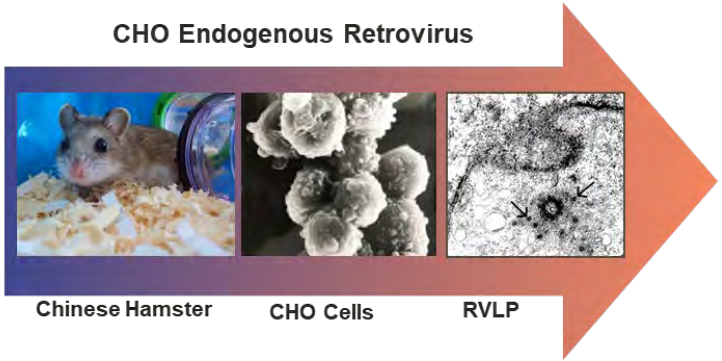
- Cell Banks
- Bulk Harvest
- IVCA testing

Vero cells are susceptible to SARS-CoV-2 reducing the severities for local risk assessment for recombinant products



Virus Clearance Validation of enveloped viruses expected to clear SARS-CoV-2

Process Intermediates

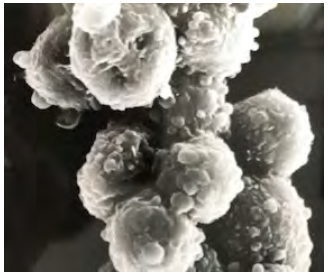


Poll #1

Is your company performing any additional studies of the virus e.g. cell line infectivity?

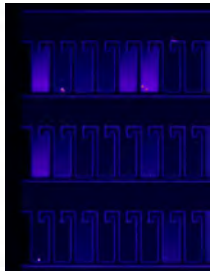
- ❑ Yes
- ❑ No
- ❑ I'm not sure

Control Framework in the Production of Cell Banks and Mitigation of Risk of SARS-CoV-2

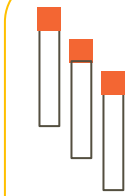


Well Characterized CHO Host Cell Line transfected with DNA construct manufactured pre-SARS-CoV-2 (Pre-2019 low risk)

Clone Selection



Expansion and scale up in BSC

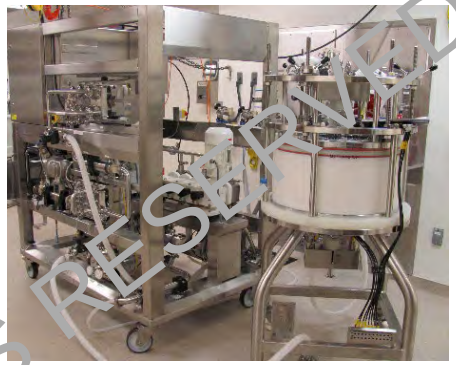


Pre-Master Cell Bank

Expansion in ISO-5 GMP facility (BSC)

GMP Master and Working Cell Bank Production

Split Storage in Liquid Nitrogen for Life of Product ICH Testing SARS-CoV-2 unable to replicate in CHO



Configuration of a Manufacturing Facility and Primary Equipment Used for Bulk Drug Manufacture

- Single-Use Bioreactors (SUB) & Harvest Vessels
- Chromatography Systems
- Ultra Filtration/ Diafiltration Systems
- CIP systems
- Parts Washers & Autoclaves
- Environmental and Stability Chambers
- Water Purification Equipment
- Likelihood of Virus Contamination is **Low** but Impact is **Very High**

Virus Control Framework in the Manufacture of Biopharmaceuticals

Raw Materials and Components transport to Manufacturing Facility

- Vendor audit and approval procedures
- Chemically defined media
- Gamma irradiation of components
- Control of transportation
- Certification

Buffer, media, cell bank and manufacture and Filling

- Media and Buffer filtration (0.1/0.2um)
- Cell Bank and EOP testing
- Virus Clearance validation/segregation
- Drug Substance purification
- Resin usage and storage
- Facility de-contamination procedure

cGMP Manufacturing of Biopharmaceuticals

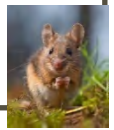
- ICH, FDA and JP Guidelines
- GMP Philosophy and Facility reviews
- Quality Risk Management and Compliance
- QA Oversight

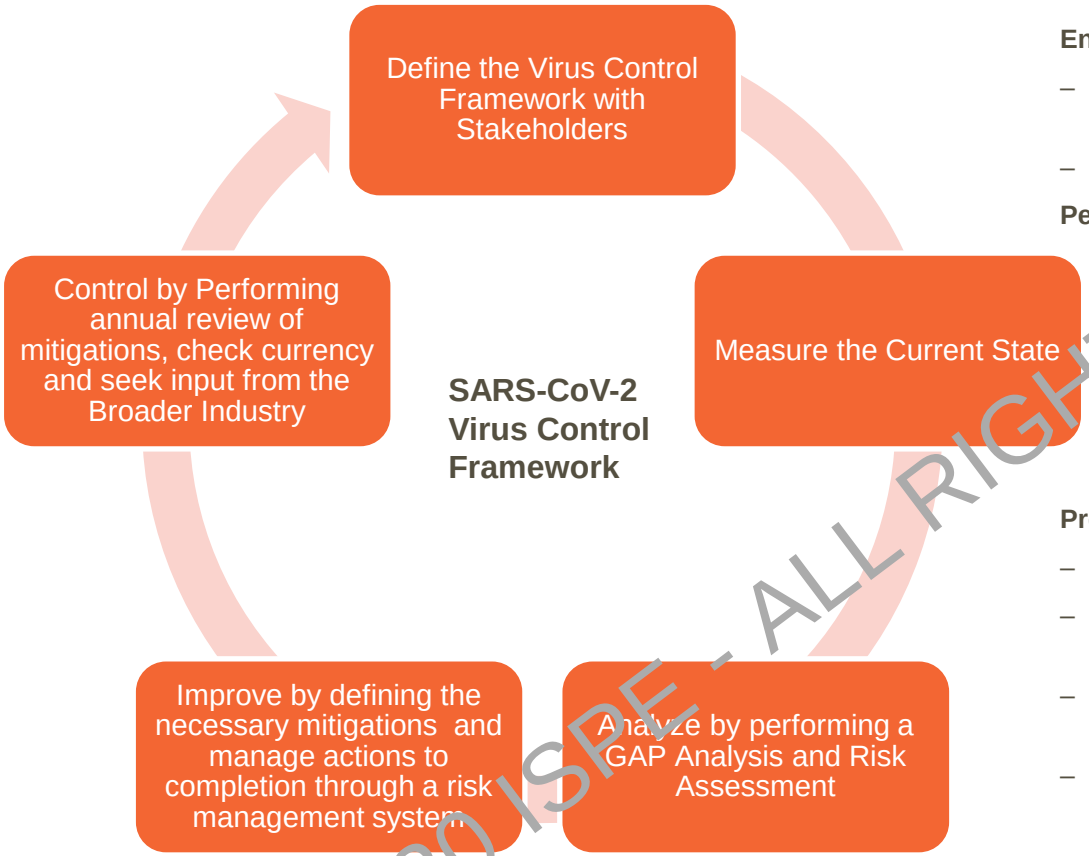
Movement of Materials and Equipment into Manufacturing Facility

- Spray/clean down Procedures
- Materials, personnel and equipment flow
- Pest Control/cleaning program
- Disinfectant and operator health policy
- Segregation and iso classification

Receipt of Materials at Manufacturing Facility

- Warehouse Receipt Procedures
- Warehouse monitoring
- Pest Control program
- Cleaning Program





Facility risk assessment

Engineering Controls and Facility Design

- HEPA-filtered air and environmental conditions- temperature and humidity are closely controlled and monitored.
- Surfaces were designed for highest degree of cleanability.

People, Gowning and Material Flow

- Personnel regularly sanitize their hands and practice good aseptic behaviors throughout work which protects against SARS-CoV-2. Operator Health Policy to mitigate infected individuals in facility
- Personnel gowned in clean scrubs, hairnet and beard cover, surgical mask and clean facility-dedicated footwear for access to the GMP Facility. Contractors are subject to the same gowning and are supervised at all times

Process and Product Controls

- Functionally Closed Processing and single use equipment
- In vitro and in vivo virus testing of cell banks and intermediates and Virus Clearance validation.
- GMP areas subject to routine disinfection and a sporicidal as needed confirmed effective against SARS-CoV-2.
- Materials that enter the GMP facility are certified and enter via controlled routes and are disinfected with bleach and/or 70% isopropyl alcohol solutions effective against SARS-CoV-2.
- Equipment cleaning, sterilization and gamma irradiation

Poll #2

Has your company performed a risk assessment to assess the potential impact of SARS-CoV-2 on your manufacturing processes and facility?

- ❑ Yes
- ❑ No
- ❑ In progress
- ❑ N/A

Conclusions

The SARS-CoV-2 Control Framework

- Biopharmaceuticals are produced from cells with the potential to become infected with viruses including SARS-CoV-2 and virus risk assessments need to be in place and risk managed holistically to ensure patient safety, facility and personnel safety in line with ICHQ5A and Q5D by a combination of:
- **Virus Detection:** Data indicate how CHO cell substrate is not susceptible to SARS-CoV-2 virus replication and cytopathology, reducing the severities for local risk assessment for recombinant products. Data less clear for human derived HEK-293. Detectability for Cell Banks and EOPCB through standard AVA per batch using permissive Vero cell line.
- **Virus Clearance:** Reliance on orthoganol virus clearance and known robustness and mechanism of action for Detergent and Virus Filtration steps for this large enveloped virus. (<1 virus like particle per 10^6 doses).
- **Disinfection:** Routine and enhanced cleaning considerations (if an operator is diagnosed as positive)
- **Open cell culture support operations controls:** As for all respiratory-borne viruses.
- **General:** Tiered controls for illness management, raw materials and component sourcing, gowning and hygiene practices for cleanroom controls as standard contamination control measures, closed systems for cell culture and use of virucidal disinfectants.
- Companies in broad alignment with the layers of product protection controls required and already in place. Companies are business as usual, with the consistent (and regional) infection control measures

Poll #3

Are the control measures in your facility appropriate to meet the SARS-CoV-2 challenge or has anything additional been done during the pandemic?

- ❑ Controls were sufficient
- ❑ Controls not sufficient and further actions taken
- ❑ N/A

Q&A

Contact Information

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