

PDA COVID-19 Webinar Series – Applying the New June 2020 FDA Guidance on Responding to COVID-19 Infection in Employees in Mfg.

August 24, 2020

Sponsored By:



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PDA COVID-19 Task Force Webinar Series

- As part of the ongoing work by the COVID-19 Task Force a series of webinars are being created.
- The webinars are focused on the COVID-19 pandemic and its current and future impact on pharmaceutical manufacturing.
- Some of the future webinar topics in the series will cover areas such as:
 - ✓ Performing remote assessments and audits
 - ✓ Keeping manufacturing facilities safe and productive during a pandemic
 - ✓ Preparing for post COVID-19 inspection (the importance of documenting and explaining the actions taken to ensure continued operations to prevent drug shortages)

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Today's Webinar



- This webinar is intended as a discussion with regulators and industry leaders on the topic of: *The 2020 FDA Guidance for Industry - GMP Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing*
- This webinar is intended to provide attendees the opportunity to better understand the expectations outlined in the guidance through a general discussion of the guidance as well as an open Q&A session.
- The panel will consist of both FDA and Industry representatives.

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Format for Today's Webinar



- This will be a general discussion format
- We will begin with introductory comments from each panelist on the June 2020 FDA Guidance on responding to COVID-19 infection in employees in manufacturing
- We will then transition into a general Q and A discussion

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Moderator - Anil Sawant, PhD



SVP, Global Quality Compliance,
Merck & Co. Inc., Kenilworth, NJ, USA

Beyond his work at Merck & Co

- PDA member, frequent volunteer, and Task Force member since 1991.
- Member of PDA Board of Directors
- Member of Mind Your Brain Foundation Board of Directors
- Previous member of Board of Directors of Georgia State University Alumni Association
- Numerous publications in antimicrobial, infectious disease, and pharmaceutical quality in American Society for Microbiology, American Medical Association, and PDA journals.

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Panelist - Peter Qiu, PhD



Division Director (Acting), Office of Pharmaceutical
Manufacturing Assessment, US FDA

- Dr. Qiu is the Director in the Division of Biotechnology Manufacturing, Office of Pharmaceutical Manufacturing Assessment, CDER, FDA. The Division oversees the scientific assessment and quality evaluation of the manufacturing and control and facilities for biological product applications. The Division is also responsible for conducting pre-license inspections for CDER's biotech products. Prior to his current position, he was an acting Division Director in the Division of Microbiology Assessment and a Branch Chief in the Division of Inspectional Assessment, Office of Process and Facilities, CDER. He joined CDER as Branch Chief in the Biotech Manufacturing Assessment Branch in the Office of Compliance, where he managed the microbiology review and pre-license inspection program for CDER regulated BLAs. Dr. Qiu joined FDA as a facility reviewer and pre-license inspection investigator in the Office of Compliance and Biologic Quality, CBER. He then joined the Center for Devices and Radiological Health (CDRH) as an Associate Director in the Division of Chemistry and Toxicology Devices. Dr. Qiu holds a Ph.D. in Biological Sciences from the University of Southern California.

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Panelist - Joel Welch, PhD



Associate Director for Biosimilar and Regulatory Policy (Acting),
Office of Biological Products, US FDA

- Joel Welch is the Associate Director for Biosimilar & Regulatory Policy (Acting) in the Office of Biotechnology Products in the Office of Pharmaceutical Quality at CDER. He is responsible for assessing emerging, complex, or precedent-setting issues impacting science policies of the office with particular emphasis on the biosimilar program. He also serves as the Rapporteur for the ICH revision to Q5A(R1). Prior to his current role, he served as a Review Chief where he oversaw as many as 20 assessors who evaluate CMC information for monoclonal antibodies and therapeutic proteins. In his time at FDA, he has worked as a regulatory project manager, a product quality reviewer, and a product quality/CMC team leader. He is a trained chemist and prior to joining FDA in 2010, he spent six years in industry supporting late state analytical development of small molecules.

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Panelist - Alonza Cruse



Director, Office of Pharmaceutical Quality Operations, FDA

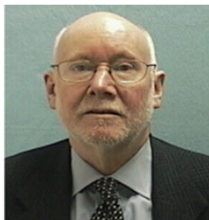
- Alonza Cruse is Director, Pharmaceutical Quality Program Operations within FDA's Office of Regulatory Affairs. His office is responsible for all pharmaceutical quality inspections & investigations, both foreign & domestic working in conjunction with FDA's Center for Drug Evaluation & Research and the Center for Veterinary Medicine.
- From 2013 - 2015 Mr. Cruse served as the Director, (Acting) of the Office of Medical Products & Tobacco Operations (OMPTO) within FDA's Office of Regulatory Affairs where he coordinated ORA's activities associated with the Generic Drug User Fee Act (GDUFA) implementation and oversaw headquarters inspectional operations associated with pharmacy compounding. Mr. Cruse works with the Center for Drug Evaluation and Research (CDER)'s senior leadership on initializing ORA's role in the new drug application review process and the development of a New Inspection Protocols Program.
- In 2000, Mr. Cruse was named Director, FDA's Los Angeles District Office, where his responsibilities included providing executive leadership to implementing, managing and evaluating FDA's regulatory operations. Prior to this Mr. Cruse was Director, New York District Import Operations.
- Mr. Cruse first joined ORA in 1983 where he began as a microbiologist. He received his Bachelor of Science degree in Medical Technology from York College (City University of New York).

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Panelist - Tony Cundell, PhD



Principal Consultant, Microbiological Consulting, LLC

- Dr. Tony Cundell consults in the pharmaceutical industry in the areas of microbial risk assessment, regulatory affairs, and microbiological testing. Prior to November 2013 he worked for Merck Research Laboratories in Summit, New Jersey, as a Senior Principal Scientist in early phase drug development. Earlier in his career, he worked as a director level in Quality Control and Product Development organizations at the New York Blood Center, Lederle Laboratories, Wyeth Pharmaceuticals, and Schering-Plough.
- He is a member of the 2015-2020 U.S.P. Microbiology Committee of Experts where he takes a leadership role in the area of modern microbiology methods.
- He has a PhD in Microbiology from the Lincoln University, New Zealand.

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Panelist - Thomas R. Kreil, PhD



Associate Professor of Virology
VP, Global Pathogen Safety, Takeda

Beyond his work at Takeda

- Chairman, Pathogen Safety Steering Committee
Plasma Protein Therapeutics Association's (PPTA)
- Steering Committee member
Consortium on Adventitious Agent Contamination in Biomanufacturing (CAACB),
coordinated by the Massachusetts Institute of Technology (MIT)
- Associate Professor at the Institute of Virology, Medical University of Vienna

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Panelist - Paul Barone, PhD



Director, Consortium on Adventitious Agent Contamination in Biomanufacturing (CAACB);
Co-Director, Biomanufacturing@MIT-CBI;
MIT Center for Biomedical Innovation

- Paul W. Barone has been at the Massachusetts Institute of Technology's Center for Biomedical Innovation (CBI) since 2010. He is currently the Director of the Consortium on Adventitious Agent Contamination in Biomanufacturing (CAACB) and Co-director of Biomanufacturing@MIT-CBI, both housed at MIT's Center for Biomedical Innovation. The CAACB is a pre-competitive biopharmaceutical industry consortium focused on identifying and sharing best practices to mitigate the risk of adventitious agent contamination in biopharmaceutical manufacturing. In his role as Co-Director of Biomanufacturing@MIT-CBI, Dr. Barone manages a variety of sponsored research activities related to biopharmaceutical manufacturing, including the development of novel analytical technologies for the rapid assessment of protein product quality, the development of a process for the continuous production of viral vectors, and the development of an online course on the principles of cell therapy manufacturing.
- Prior to joining CBI, Dr. Barone earned an M.S and Ph.D. in Chemical and Biomolecular Engineering from the University of Illinois, Urbana-Champaign and completed a Postdoc at MIT where his research focused on the development of novel nanoscale sensors for the detection of a variety of biologically relevant analytes, such as nitric oxide, glucose, and troponin.

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Risk Assessment Considerations for Biomanufacturing during the SARS-COV-2 Pandemic



Peter Qiu, PhD



Joel Welch, PhD

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Risk Assessment Considerations for Biomanufacturing during the SARS-COV-2 Pandemic

Joel Welch, Ph.D.
Associate Director for Biosimilar and Regulatory Policy
(Acting)
Office of Biotechnology Products
OPQ/CDER/FDA

Zihao Peter Qiu, Ph.D.
Director, Division of Biotechnology Manufacturing
Office of Pharmaceutical Manufacturing Assessment
OPQ/CDER/FDA

PDA Webinar August 24, 2020

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Pharmaceutical Quality

**A quality product of any kind consistently
meets the expectations of the user.**



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Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Drugs are no different.

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Patients expect safe and effective medicine with every dose they take.

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Pharmaceutical quality is
assuring *every* dose is safe and
effective, free of contamination
and defects.

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It is what gives patients confidence
in their *next* dose of medicine.

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Introduction

- The coronavirus family are Positive-sense single-stranded RNA (+ssRNA) viruses
- They are large viruses ranging in size from 120-160 nm
- SARS-CoV-2 is in the same beta-coronavirus genus as the respiratory SARS-CoV and MERS-CoV viruses seen in previous years
- Given known characteristics of the SARS-CoV-2, opportunities exist to understand potential mitigation and risk assessment approaches in manufacturing
- For some biological products, such as cellular and gene therapy products, there may be additional considerations for risk assessments and some of the factors mentioned may not be applicable to those products.
- Remarks will focus on CDER-regulated biotechnology products



Biotechnology Products have Susceptibility to Contamination

- Biotechnology products have processes and raw materials that are inherently susceptible to viral contamination
- Contamination may occur from a variety of sources
- Culture performance may or may not reveal contamination

Table 2 | Viruses reported to have contaminated mammalian cell culture operations for the production of vaccines or recombinant proteins, the number of events where the virus source was identified, and the source of the contaminant

| Contaminated cell line | Contaminating virus | Pathogenic to humans | Suspected and confirmed sources of contamination | | | | | |
|---|----------------------------|----------------------|--|------------------------------|-------------------------------|----------|----------------|-----------|
| | | | Serum | Recombinant medium component | Undetermined medium component | Operator | Host cell line | Not found |
| Viruses found to contaminate CHO cell culture | | | | | | | | |
| CHO | Blue tongue virus | No | 1 | | | | | |
| CHO | Cache Valley virus | Yes | 2 | | | | | |
| CHO | Minute virus of mice | No | | 1 | 3 | | | 1 |
| CHO | Vesivirus 2117 | No | 4 | | | | | |
| Viruses found to contaminate human or primate cell lines | | | | | | | | |
| Primary monkey, Vero | Herpesvirus | Yes | | | | 1 | 1 | |
| HEK293 | Human adenovirus type 1 | Yes | | | | 1 | | |
| MRC5 | Parainfluenza virus type 3 | Yes | | | | 1 | | |
| MRC5 | Reovirus type 3 | Yes | | | | 1 | | |
| Primary monkey | Simian adenovirus | No | | | | | 1 | |

Table adapted from Nature Biotechnology | VOL 38 | May 2020 | 563–572 | www.nature.com/naturebiotechnology

Risk Principles in ICH Q5A(R1)

- Scientific Basis for assessing Risk of Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin cell lines is presented in ICH Q5A (R1)
- The risk is not defined by a single consideration (e.g., the type of production cell line)
- Three principal, complementary approaches have evolved to control the potential viral contamination of biotechnology products:
 - 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;
 - assessing the capacity of the production processes to clear infectious viruses;
 - testing the product at appropriate steps of production for absence of contaminating infectious viruses.

Key Recommendations from Guidance for Biotech Products

- Processes already have stringent viral control strategies in place
- FDA recommends that manufacturers perform a risk assessment of the current viral control strategy in light of SARS-CoV-2 and implement appropriate mitigation strategies
- This should include, but not be limited to, leveraging available information to assess:
 - The potential for the production cell line to replicate SARS-CoV-2
 - Testing strategies that would detect SAR-CoV-2
- The effectiveness of the manufacturing process to remove or inactivate SARS-CoV-2
- Controls in place for procedures taking place in open systems (e.g., buffer and media preparation areas)
- Risk assessment should scientifically re-considered as more information is obtained

Examples of Assessing Risk – Unit Operations



- Viral filtration is traditionally one of last steps in DS manufacturing.
 - Consider likelihood that virus can pass through filter
 - Examine possible data that may be leveraged from model viruses
 - Evaluate and monitor process performance
- Chromatographic steps may provide additional possible source of viral clearance
 - Should consider the nature of the chromatographic conditions (pI of virus, use of alkaline buffers)
 - Many purification schemes use the same or similar buffers or columns routinely and may operate under such conditions. Where data are not available, process specific buffers may be assessed for inactivation potential.
- Detergent inactivation and Solvent/Detergent inactivation can also provide viral clearance

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Examples of Risk Assessment – Cell Bank/Testing Considerations



- As described in ICH Q5A(R1), testing is only one of the principal approaches for control
- Testing occurs throughout the process, including cell banks early on, as well as during routine manufacture
- Risk for previously established cell bank is lower
- Consider susceptibility of production cell lines for transmission
- Current testing may include *in vitro* testing for cytopathogenic effects (CPEs) on a panel of indicator cells, including VERO cells
- Current testing may include *in vivo* testing methods which are known to detect other viruses within the coronavirus family

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**GMP Considerations for Responding to
COVID-19 Infection in Employees in Drug and
Biological Products Manufacturing**
Guidance for Industry



Recommendations to drug manufacturers regarding:

1. Manufacturing controls to prevent contamination of drugs
2. Risk assessment of SARS-CoV-2 as it relates to drug safety or quality
3. Continuity of manufacturing operations to avoid drug shortage

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**GMP Considerations for Responding to
COVID-19 Infection in Employees in Drug and
Biological Products Manufacturing**
Guidance for Industry



Recommendations to drug manufacturers regarding:

1. Manufacturing controls to prevent contamination of drugs
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CGMP Regulations and Guidance Concerning Ill Employees



- 21 CFR 211.28(d) Personnel responsibilities
- 21 CFR 212.30 Facilities
- 21 CFR 600.10(c)(1) Restrictions on personnel
- ICH Q7 Section III. Personnel

Drug manufacturers are expected to exclude employees who test positive for COVID-19 (regardless of whether they have symptoms) or have symptoms of COVID-19 from drug production areas.

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Manufacturing Controls to Prevent Contamination of Drugs



- Evaluate current CGMP controls to protect materials and drugs from operators in context of this novel coronavirus; mitigate if needed
- Assessment SARS-CoV-2 risk as it relates to drug safety or quality
 - Impact on product if contaminated
 - Consider known characteristics of this family of viruses
 - Consider drug types (e.g., drug product or API, sterile, non-sterile, solids, powders, liquids, large or small molecule)

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Risk Evaluation of Existing Manufacturing Controls



- Manufacturing Facilities
 - facility and equipment cleaning and sanitation
 - Cross contamination procedures
- Manufacturing Process
 - Open vs closed process system
 - Manufacturing steps susceptible for viral contamination
- Control of Raw Materials, APIs, drug product, and other components
 - Additional testing
 - Handling of affected materials; quarantine.
 - Do not distribute lots/batches of drugs determined to be adversely affected in terms of safety or quality

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Continuity of Manufacturing Operations



- Prevent or Minimize Risk of Covid-19 Transmission among Employees
 - Institute more frequent cleaning, sanitization, and/or sterilization of surfaces in the production areas
 - Clean and sanitize nonproduction areas more frequently (non-GMP areas)
 - Expand existing procedures on PPE
 - Follow CDC guidance for businesses and workplaces
 - <https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/businesses-employers.html>

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Considerations for Implementation of Contingency Production Plans

- Address unique considerations at each location
- Identify high risk areas and ensure that appropriate risk control measures are identified
- Prioritizing plans for medically necessary products

Guidance for Industry Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products (March 2011).

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Summary

- Protect drugs from sick employees
- Prevent transmission between employees to avoid high absenteeism and drug supply interruptions

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Discussion of FDA Guidance

Alonza Cruse



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Overview of Industry Aspects

Tony Cundell, PhD



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PDA COVID-19 Webinar

- A technology review co-authored by Tony Cundell, Dennis Guilfoyle, Thomas Kreil and Anil Sawant entitled *Controls To Minimize Disruption Of The Pharmaceutical Supply Chain During The Covid-19 Pandemic* was published in the July-August 2020 issue of the PDA J. Pharm. Sci. & Technol.
- We concluded that **employee absenteeism** and the unavailability of critical materials, and **not product contamination** were the greatest risks to the pharmaceutical supply chain.
- Does the FDA panelists concur?

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The major areas for clarifications from this panelist are:

- The lack of emphasis on self exclusion of employees in the GMP regulations and the published guidance document.
- The extent of the expected risk assessment of the current viral control strategies for SARS-CoV-2 virus, especially studies supporting biological manufacturing using mammalian cell culture.
- The expected documentation level of the risk mitigation steps implemented in non-GMP areas.
- The response to discovery of employees who are implicated in COVID-19 infection, i.e., a viral event.

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Self Exclusion by Employees

- Although not emphasized in 21 CFR 211.23(d) and 600.10 (c)(1), this reviewer believes that self-exclusion of employees from the workplace is a major risk mitigation tool that should be addressed in the guidance.
- Reasons for self-exclusion might include recent travel to areas with high COVID-19 infection rates, recent contact with individuals known to be infected with SARS-CoV-2 viruses, display of multiple symptoms, and testing positive for the virus.

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Control Strategies for SARS-CoV-2 Virus



According to the guidance, this risk assessment may include, but not be limited to the leverage of existing available information on the following:

- The potential of the SARS-CoV-2 virus to replicate in production cell lines.
- Whether current cell bank and harvest viral testing would detect SARS-CoV-2.
- The effectiveness of viral clearance and inactivation steps for SARS-CoV-2.
- Controls in buffer and media preparation areas.

The recommendations in the guidance are too open-ended, making it more difficult for companies to meet agency expectations. Will the agency be satisfied with risk assessment provided by industry groups and peer-reviewed scientific articles?

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Risk Assessment in Non-GMP areas



- Cleaning methods and schedules in non-GMP areas are not documented in standard operating procedures (SOPs) as in GMP areas.
- Because of the known effectiveness of disinfectant and hand sanitizers, to extend GMP documentation requirements to non-GMP areas is not necessary and would be an undue burden of pharmaceutical companies already stressed to the COVID-19 pandemic.

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Response to Viral Events



- Reactions to reports of potential or actual viral contamination events are problematic. How are viral contamination events defined by the agency?
- Do events include exposure of employees to others infected with the virus, exhibiting multiple symptoms of infection, testing positive to the SARS-CoV-2 virus, or being emitted to hospital?
- Is the event associated with the employee being merely on the manufacturing site, working in a GMP areas, or being directly exposed to product?
- Would applying an investigation paradigm to low risk viral events be expected by the FDA?

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Discussion on Research Topics

Thomas R. Kreil, PhD



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- Risk assessment of SARS-CoV-2 & drug safety or quality

Contains Nonbinding Recommendations

**Good Manufacturing Practice
Considerations for Responding to
COVID-19 Infection in Employees in
Drug and Biological Products
Manufacturing**

Guidance for Industry


June 2020

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- Potential for the production cell line to replicate SARS-CoV-2
→ manufacturing cell susceptibility ?
- Cell bank and harvest testing ... detect SARS-CoV-2
→ AAT detectability ?
- Effectiveness of viral clearance & inactivation for SARS-CoV-2
→ removal & inactivation


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SARS-CoV-2 Test Systems



Charité (Institute of Virology, Berlin)
BetaCoV/German/BavPat1/2020
GPS / TAKEDA → Currently at NGS, genome sequencing
SARS-CoV-2/GPS-001/human/2020/AT
SARS-CoV-2/GPS-002/human/2020/AT
SARS-CoV-2/GPS-003/human/2020/AT

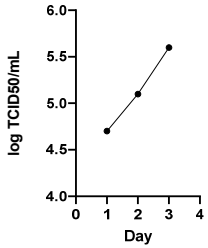




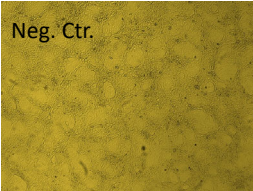
Cell Line

Vero cells
African green monkey kidney epithelial cells


Virus Replication



CPE in Vero Cells



Neg. Ctr.




SARS-CoV-2

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SARS-CoV-2 & (Biological) Drug Safety



- 1) Susceptibility of production cell lines
- 2) Detectability by adventitious virus testing (AAT)
- 3) Virus removal & inactivation

| 1) Production Cell Lines | 2) AAT Detection Cell Lines | | | |
|----------------------------|-----------------------------|-------|-----------|-----|
| CHO | CHO | MRC-5 | Vero | |
| HT-1080 | HT-1080 | MRC-5 | Vero | CHO |
| HEK-293 | HEK-293 | MRC-5 | Vero | |
| ↓ | ↓ | ↓ | ↓ | ↓ |
| Not infected by SARS-CoV-2 | No | No | CPE & HAD | No |

3) Lipid-enveloped → easily inactivated
Large (~120 nm diameter) → easily removed

CPE...Cytopathic Effect
HAD...Haemadsorption

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Presented information is available online

SARS-CoV-2 and the safety margins of cell-based biological medicinal products

Jens Modrof, Astrid Kerschbaum, Maria Farcet,
Daniela Niemeyer, Victor Corman, Thomas R. Kreil

under review

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Discussion on Research Topics

Paul Barone, PhD



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What is the CAACB?



- A biopharmaceutical industry consortium housed at the Massachusetts Institute of Technology



* founding members

- The broad mission of the CAACB is to pool biomanufacturing expertise in the area of adventitious agent contamination

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Industry virus contamination experience



The CAACB performed a **confidential collection** and analysis of industry-wide viral contamination data

nature biotechnology PERSPECTIVE
<https://doi.org/10.1038/445587-020-0509-2>
[Check for updates](#)

Viral contamination in biologic manufacture and implications for emerging therapies

Paul W. Barone¹, Michael E. Wiebe¹, James C. Leung¹, Islam T. M. Hussein¹, Flora J. Keumurian¹, James Bouressa^{2,25}, Audrey Brussel^{1,26}, Dayue Chen^{4,27}, Ming Chong¹, Houman Dehghani^{2,28}, Lionel Gerentes⁷, James Gilbert^{4,29}, Dan Gold³, Robert Kiss^{30,32}, Thomas R. Kreil³, René Labatut¹, Yuling Li^{32,33}, Jürgen Müllberg³, Laurent Mallet³², Christian Menzel³⁴, Mark Moody^{35,37}, Serge Monpoeho³⁶, Marie Murphy³, Mark Plavsic^{37,38}, Nathan J. Roth³⁹, David Roush³⁹, Michael Ruffing²⁹, Richard Schicho^{33,39}, Richard Snyder²², Daniel Stark²³, Chun Zhang^{24,36}, Jacqueline Wolfrum¹, Anthony J. Sinskey¹ and Stacy L. Springs^{41,42}

Recombinant protein therapeutics, vaccines, and plasma products have a long record of safety. However, the use of cell culture to produce recombinant proteins is still susceptible to contamination with viruses. These contaminations cost millions of dollars to recover from, can lead to patients not receiving therapies, and are very rare, which makes learning from past events difficult. A consortium of biotech companies, together with the Massachusetts Institute of Technology, has convened to collect data on these events. This industry-wide study provides insights into the most common viral contaminants, the source of those contaminants, the cell lines affected, corrective actions, as well as the impact of such events. These results have implications for the safe and effective production of not just current products, but also emerging cell and gene therapies which have shown much therapeutic promise.

In the twentieth century, several vaccine products were unintentionally contaminated with unwanted viruses during their production¹⁻³. This included the contamination of poliovirus vaccine with simian virus 40 (SV40)⁴, for which the health impacts were not fully known for many decades⁵. In the early 1980s, unknowingly contaminated therapeutic proteins from human plasma caused human pathogens. The lessons of the past have led to the current best practice, which relies on three pillars: the selection of appropriate starting and raw materials with a low risk of containing adventitious virus; testing of cell banks and in-process materials to ensure they are free from detectable viruses; and finally, the incorporation of steps to remove and inactivate potential undetected adventitious

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Virus contamination lessons for COVID-19



1. **Virus contamination events**
 - are rare (18 reported to the CAACB over 35 years) based on volume
 - but not rare on a per-company basis
2. **CHO cell cultures were contaminated by different viruses from different sources compared to human/primate cells**
3. **Virus safety testing has clear limitations, but when used in a targeted way can prevent virus spread in a facility**
4. **Given limitations of testing, some companies have focused on prevention**
5. **Viral clearance in downstream protein purification is effective for large-scale manufacturing processes.**

Barone, PW et al. Viral contamination in biologic manufacture and implications for emerging therapies. Nature Biotech. (2020) <https://doi.org/10.1038/s41587-020-0507-2>

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Sources of risk are cell line dependent



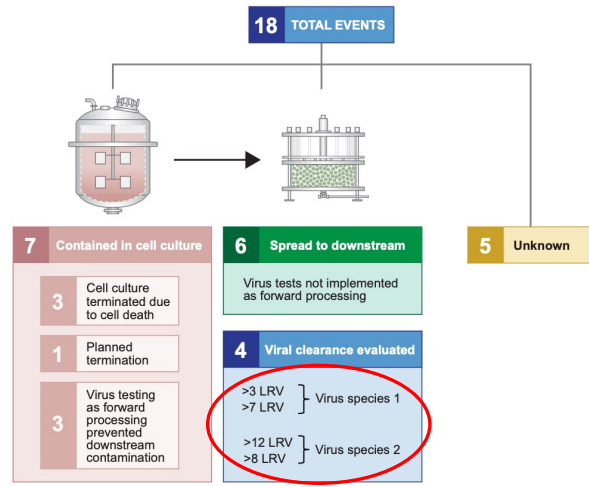
- Virus contaminations in:
 - CHO cell culture were attributed to raw materials
 - Human or primate cell culture were attributed to operators or the cell line itself

| Contaminating Virus | Bovine Serum | Recombinant Media Component | Undetermined Media Component | Operator | Host Cell Line | Not Found |
|----------------------------|--------------|-----------------------------|------------------------------|----------|----------------|-----------|
| Vesivirus 2117 | 4 | | | | | |
| Cache Valley Virus (CVV) | 2 | | | | | |
| Blue Tongue | 1 | | | | | |
| Mouse Minute Virus (MMV) | | 1 | 3 | | | 1 |
| Herpes Virus | | | | 1 | 1 | |
| Human Adenovirus Type 1 | | | | 1 | | |
| Parainfluenza Virus Type 3 | | | | 1 | | |
| Reovirus Type 3 | | | | 1 | | |
| Simian Adenovirus | | | | | 1 | |

Viruses in **black** were found in CHO cell lines.
Viruses in **red** were found in human or simian derived cell lines.

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Downstream viral clearance was effective



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Impact of SARS-CoV-2 on biomanufacturing



The CAACB held a web-meeting in April with key conclusions published in August.

The Impact of SARS-CoV-2 on Biomanufacturing Operations

August 1, 2020
 Paul W. Barone, Flora J. Keumurian, Michael E. Wiebe, Jacqueline Wolfrum, James C. Leung, Anthony J. Sinskey, Stacy L. Springs
 Volume 33, Issue 8
 Page Number: 34-38



Relevant Topics ▾

This article presents the results of a survey conducted to gain insight on the impact of the COVID-19 pandemic on biomanufacturing operations.



Barone, PW et al. The Impact of SARS-CoV-2 on Biomanufacturing Operations. *Biopharm Int.* (2020) Vol. 33 Iss 8 pg. 34-38.

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Key conclusions from web-meeting



- **The risk of SARS-CoV-2 contaminating a cell culture manufacturing process is likely low if:**
 - The cell lines do not replicate SARS-CoV-2, such as CHO cells.
 - The processes use validated robust downstream viral clearance.
 - Viral safety testing that utilizes Vero cells as indicator cell lines is routinely conducted.
- **The risk is significantly higher for products that do not meet these requirements.**
 - For example, autologous T-cell immunotherapies have a large number of open operations that increase the possibility of introducing the virus from operators, utilize cells that have been demonstrated to be permissive to SARS-CoV-2, and lack downstream viral clearance.

Barone, PW et al. The Impact of SARS-CoV-2 on Biomanufacturing Operations. *Biopharm Int.* (2020) Vol. 33 Iss 8 pg. 34-38.

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New CAACB project in 2020



***Collaboration to address emerging viruses
and pandemic preparedness***

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Q&A
Please submit your questions!

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Thank You For Attending Today's Webinar

Our next PDA COVID-19 Task Force Webinar will be:

Utilization of Modular Manufacturing to Enhance/Upscale
Capacity During COVID-19

Tentatively Scheduled for: 23-SEP-2020 at 11:00 AM EDT

Stay informed of all PDA events at: [PDA.org](https://www.pda.org)

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