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SUPPLEMENTARY INFORMATION

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Viral contamination in biologic manufacture and implications for emerging therapies

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Survey

for

Consortium on Adventitious Agent Contamination in Biomanufacturing

Company Information

Company completing survey:_____
Date survey completed:_____
Company individuals completing survey: _____

CAACB on-site interview

Date: _____
Conducted by: _____
Participating individuals from company: _____
_____

Instructions: Please use this electronic pdf to provide answers for each question in as much detail as possible. If the question cannot be answered, please give the reason, e.g. 1) question is irrelevant given the company's circumstances, 2) answer is unknown, 3) company chooses not to answer, etc. Each question needs either an answer or a reason that it cannot be answered. Feel free to attach documentation, if appropriate.

Contamination Events at the Company

1. Has your company had one or more virus contaminations during biomanufacturing (including R&D, pre-clinical, clinical and commercial operations) at anytime during the past 30 years?

2. Has any company with which you have merged or acquired, had a virus contamination event during biomanufacturing during the past 30 years?

3. Has your company experienced a virus contamination while manufacturing your product at a contract manufacturing facility (CMO)?

4. Has your company had one or more mycoplasma contaminations during biomanufacturing (including R&D, pre-clinical, clinical and commercial operations) at anytime during the past 30 years?

   If so, how many mycoplasma contamination events has your company experienced?

5. Has any company with which you have merged or acquired, had a mycoplasma contamination event during biomanufacturing during the past 30 years?

If the answer to all three of questions 1-3 is no, please answer only questions 30-59, 133-141 and 157-166; otherwise continue with question 6 and answer all survey questions.

6. How many total virus contamination events have occurred at your company (including at acquired or merged companies, and at CMOs)?

Answer each of the following questions separately for each contamination event at your company and any company that you have acquired through merger or acquisition. Include contaminations that have occurred at CMOs while manufacturing your product. ***Use a separate survey form for each contamination event****.*

Detection of the Virus Contamination Event

7. At which facility did the contamination event occur (place, type of facility)?

8. What type of cell culture process was employed (e.g., batch, perfusion, roller bottle, etc.)?

9. When was the contamination event first detected (date)?

10. What was the initial indication of a possible virus contamination? Did changes in measured cell culture process parameters indicate possible virus contamination? Was the initial indication of possible virus contamination a result from laboratory testing? Please describe.

11. How was the contamination confirmed?

12. What QC virus lot release tests were performed on each lot to detect virus contamination?

13. Were the QC virus lot release tests positive for virus?

14. How were false positive QC virus lot release tests ruled out?

15. Were the QC virus lot release tests being conducted in-house or outside the company by a contract testing laboratory?

16. Were the virus positive testing results received in sufficient time to limit the contamination to only upstream processes?

17. Was the contaminating virus identified?
    If so, how?

18. What was the contaminating virus?

19. What cell strain or cell line was used in the contaminated manufacturing process?

20. Approximately how many liters of cell culture fluid had been successfully processed with this cell line prior to contamination?

    With all cell lines in the manufacturing facility before the contamination?

21. Which host species is the virus known to infect? Known to cause disease?

22. Does the virus infect humans? Is it a human pathogen?

23. Were any newly emerging methods for virus detection / identification employed during the investigation (current examples: PCR, massively parallel sequencing, degenerate PCR, Plex-ID, Virus microarrays, etc.)?

24. Of all the methods employed to identify the virus, which were the most useful? Why?

25. How long did it take to identify the virus contaminant following the initial detection of contamination?

26. Was a new virus contaminant-specific assay developed/implemented to help facilitate the investigation?
    If so, what was the assay?

27. Was the virus contaminant characterized?
    In what way (possible examples: electron microscopy, serology, nucleic acid sequencing, host cell range, etc.)?

28. Is the nucleotide sequence of the contaminating virus known?

29. Were stocks of this virus contaminant prepared and stored for future study?

    Would company consider making virus available for CAACB Consortium collaborative study?

Virus "False Positive" Test Results

30. Has your company ever had an out of specification (OOS) virus test (in-process or lot release OOS result) that your company has later shown to be a "false positive"?
    a. What type of assay (in vitro, PCR, other)?

    b. Was the assay run in-house or at a contract testing laboratory?

31. How many such instances have occurred over the past 30 years?

Answer the following questions for each "false positive" instance.

32. Was the root cause of the "false positive" result identified?
    If so, describe the root cause.

33. How long did the investigation into the OOS take before it was closed out?

34. What actions relating to manufacturing operations were undertaken by the company during the OOS investigation?

35. In the absence of identifying an OOS root cause, on what basis did the company decide to restart/continue cell culture operations and/or release lots implicated by the OOS?

36. Did the OOS investigation lead to changes in cell culture processes, sample acquisition and/or transfer, or virus testing procedures? Please describe.

37. Describe and quantify (if possible) the overall impact to the company of the OOS virus test result and subsequent actions.

38. Were regulatory agencies informed of the OOS result?

Virus Controls in Place at the Time of Contamination

For companies that have never had a virus contamination, please answer questions 39-59 for virus controls historically in place. Also describe how these may have changed over time. For companies that have had virus contamination events, please answer questions 39-59 for controls in place at the time of the contamination.

39. What virus tests were performed on the Master Cell Bank and Working Cell Bank to demonstrate freedom from virus contamination?

40. What in-process controls in cell culture operations were in place to detect possible virus contamination?

41. What QC lot release tests were employed to detect virus contamination?

42. Were these QC assays conducted in-house, by a contracted testing laboratory, or both?

43. What was the status of the QC assays: R&D only, qualified, or validated?

44. Did the company obtain pre-formulated liquid media or powdered media from a media manufacture?

45. If powdered media, was a heat step used to process the water used for hydration?
    Please describe.

46. List all raw materials used in the cell culture process that were directly sourced from animals.

47. Were animal sourced raw materials tested for virus prior to use?
    List each test for each animal sourced raw material.

48. Did the company know the formulation of cell culture media, or was it proprietary to the media manufacturer?

49. Did the company know the source of each component of the cell culture media?

50. How often was the media manufacturer audited by the company's QA department?

51. Were manufacturers of media components, used by media manufacturers, audited?
    By whom? At what frequency?

52. Have media or media component manufacturers been evaluated for possible cross contamination of raw material contacting equipment?

53. Was the media processed to inactivate or remove viruses prior to use in cell culture?

54. If so, what methods were used to inactivate or remove viruses?

55. Were any special precautions taken by the company to prevent virus contamination of raw materials during sampling and dispensing?

    If so, list the precautions.

56. Was an assessment performed to determine whether any animal-derived materials were used in the cell culture facility that are not product contacting?

    If so, were any identified? Please describe.

57. Were all cell culture systems closed?
    If not, what possible breaches existed that could give rise to virus ingress.

58. Did cell culture operations occur in an environmentally classified area?

59. Was the environment for cell culture operations monitored and trended for microbial load?

Extent of Contamination

60. What methods were used to determine the extent of the contamination within the manufacturing facility?

61. Were the Master Cell Bank and Working Cell Banks re-evaluated with specific tests to determine whether they contained the contaminating virus?

    What were the results?

62. Were retained samples from upstream seed train bioreactors evaluated for virus contamination?
    If any were contaminated, please describe.

63. Were cell culture process units that preceded the contaminated bioreactor during the campaign, tested for the contaminating virus?
    If any were contaminated, please describe.

64. Were other products being manufactured in the cell culture facility during the period of bioreactor contamination?
    Were they tested for virus contamination?
    Were other product cell culture operations contaminated?
    If so, please describe.

65. Were seed trains for future production bioreactors running concurrent with the contaminated vessels?
    Were they tested for contamination?
    Were these seed trains found to be contaminated?
    If so, please describe.

66. Was contaminated cell culture unprocessed bulk processed downstream through product purification?

    If so, answer questions 67-71.

67. Were downstream recovery and purification retains tested for virus contamination?
    Please describe results.

68. Were lots of purified drug substance tested for virus contamination?
    Please describe results.

69. Were lots of drug product tested for virus contamination?
    Please describe results.

70. Was it necessary to recall any drug product lots that had already been distributed?
    If so, please describe.

71. Were downstream purification in-process retained samples evaluated quantitatively to see how effective the process was at manufacturing scale in clearing the contaminated virus?
    If so, please provide clearance data.

72. Did quantitative testing of virus in upstream in-process retains indicate time and place of virus entry?
    Please describe.

73. Was testing conducted for virus outside of closed systems (equipment surfaces, airborne, gas filters, etc.)?
    If so, please describe the method of testing. If virus was detected and identified, please describe whether virus was the same as contaminating virus and how this finding impacted decontamination activities.

Source of Virus Contamination

74. Which sources were evaluated (raw materials, operators, pet animals of operators, pests, air/gas, water, environment, etc.)?

75. How were the sources tested for contamination?

76. Were vendors of raw materials audited in attempt to identify a source? Were these audits instructive?

77. Was the source definitively identified?
    If so, describe source and evidence for source identification.

78. If the source was not definitively identified, what was the likely source considered to be?

    How was this conclusion arrived at?

79. Was the source of the contamination determined to be residual virus from a prior contamination?

Process Breach

80. What possible routes of entry were investigated?

81. Which routes of entry were found to be likely (or unlikely)?

82. Was the breach definitively identified?
    If so, describe the breach and evidence for breach identification.

83. If the breach was not definitively identified, what was considered to be the likely breach?
    Describe your rationale for this conclusion.

Containment

84. What materials were quarantined? In-process materials? Raw materials? Completed lots? QC samples? Maintenance materials?, Tools? Others?

85. What were the criteria for release of materials from quarantine?

86. How was the facility isolated from other neighboring activities?

87. What processes and process flows were restricted?

88. How did you prevent contamination of the testing laboratory?

Investigation Management

89. How was the investigation managed?

90. Was an investigation management team organized?

91. What company department was responsible for leading the management team?
    To whom did the management team report?

92. How was the investigation documented?

93. What specific expertise was represented on the management team?

94. How did the investigation management team communicate with upper management?

95. Was communication controlled carefully within the company?
    Who was responsible for this communication?

96. Were product partners involved in the investigation?
    To what extent were they involved?

    How did the company communicate with the partners?

97. If the contamination occurred at a contract manufacturer's facility, how did your company assure that a thorough investigation and decontamination was conducted at CMO facility? Describe investigation management and the interaction between your company and the CMO during the investigation.

98. Describe company's communication with regulatory agencies. Who (or which group) was responsible for these communications? At what point in time was this communication initiated? What factors were considered in the timing of the initial communication? Was the interaction with regulatory agencies constructive in driving the investigation forward to a satisfactory conclusion? Please explain.

99. Did the company issue a press release about the contamination?

    What factors were considered before a decision was made to make this information public (or not)?

100. Did the company communicate the contamination event and relevant details to the industry (talks at industry meetings, publications, etc)?

What factors were considered in making this decision?

101. Did the management team operate from an SOP or other internal document that had been previously prepared as an emergency plan for virus contaminations?

Was this document adequate to guide the investigation?

102. How were decisions made with regard to all investigation activities and sequence of activities? Were these made by the management team, by function specific sub-teams, by independent standing departments, or in other ways?

103. Did the company have professional virologists on the management team? Were professional virologists from outside the company brought onto the team as consultants? Please describe.

104. Did the company utilize outside contract testing laboratories during the investigation? Did the company seek advice from experienced virologists at contract testing laboratory? Please describe.

105. How was the data generated by the investigation compiled, analyzed and communicated?

106. Was more than one company site involved in the investigation?

107. Did the company seek help and advice from other companies that had prior experience with virus contaminations?
Was this useful?
If yes, in what way?

108. Was an independent GMP compliance review (internal or external) conducted?

Decontamination

109. Did your decontamination procedure follow a written protocol?

110. How were each of the following items decontaminated?

a. Cell cultures within bioreactors

b. Media in hold tanks

c. Empty, used bioreactors

d. Transfer piping

e. Filters

f. Suspect raw materials

g. Elastomers

h. External stainless steel surfaces

i. Resins

j. Chromatography columns

k. Chromatography skids

l. Instruments

m. Carts, tools, etc.

n. HVAC system

o. Other items

111. Were fumigation methods used to decontaminate the affected areas of the manufacturing facility?
If not, what was the rationale for not conducting fumigation?

112. Which fumigant or gas was employed.

What criteria were used to make this selection?

113. How were the areas selected for fumigation?

114. How were the conditions (concentration, temperature, exposure time, etc.) determined for the fumigation?

115. How was the effectiveness of the fumigation monitored?

116. Was the fumigation confirmed to be effective?

117. Which materials used in manufacturing were decontaminated, then discarded (be specific, e.g., equipment, instruments, columns, resins, raw materials, elastomers, filters, etc)?

118. Which materials used in manufacturing were decontaminated, but retained for use in future manufacturing (be specific, e.g., equipment, instruments, columns, resins, raw materials, elastomers, filters, etc)?

Corrective Actions

119. In addition to decontamination activities, what additional corrective actions were taken before manufacturing restart?

120. Were changes implemented in the auditing of media and media component manufacturers?

121. Were new lot release tests added, or current tests modified? If so, please describe.

122. Did the contamination event lead to the development of new testing technologies?
If so please describe.

123. Were new in-process controls or analytical tests instituted?
If so, please describe.

124. Was a suspected process breach modified to prevent virus ingress?

125. If the virus source was identified, what corrective actions were implemented to mitigate future virus contamination?

Discarded Product

126. Describe the quantity of process intermediate, drug substance and drug product that was discarded?

127. Were uncontaminated lots discarded that were made during the campaign either before or after the contaminated lots?

128. Were product lots discarded if they were made concurrently with contaminated lots?

Restart

129. What criteria needed to be met before the manufacturing plant was restarted?

130. Did the restart require approval from regulatory authorities?

131. Did lot release of product made after the restart require regulatory review and approval of the investigation and corrective actions?

132. For how long was the manufacturing plant shut down?

Preventive Actions

133. What process changes were developed and implemented to prevent virus contaminations?

134. Were changes made to facility and operational practices (e.g., raw material operations and handling)?
Please describe.

135. What new test methods were developed and implemented to detect virus contamination?

What were the advantages of any new test methods implemented?

136. Did the company eliminate animal sourced raw materials?

137. Was additional virus testing of raw materials implemented?

138. Were virus tests implemented earlier in the cell culture process?
During seed train production?

139. Was a virus inactivation or removal step implemented for cell culture media?
Did this negatively impact cell culture performance?
Product yield?
Product quality?
Was this step validated for virus clearance?

140. If contamination occurred at a contract manufacturer's facility, was the company satisfied that sufficient preventive actions were implemented by the CMO?
Describe CMO's preventive actions.

141. Describe any other preventive actions that were implemented.

142. Has a sufficient quantity of data been collected by the company since taking the preventive actions to determine whether these actions have reduced virus contamination risks?
Please provide a description of the analysis and the conclusions reached.

Cost of the Event

143. Were patients not able to receive their normal drug supply?
If so, please describe the extent of the problem.

144. What was the cost of discarded product intermediates, drug substance and drug product ($ cost, or number of doses lost)?

145. What was the cost in lost sales?

146. What was the cost of conducting the investigation, including the decontamination activities and restart?

147. What was the cost of replacing raw materials, resins, equipment, etc.?

148. What was the cost of corrective and preventive actions?

149. Were there any costs associated with regulatory actions taken?
If so, please describe.

150. What does the company estimate to be the total cost of the virus contamination?

151. Did the virus contamination result in a product competitive disadvantage?

If so, please describe.

152. Did the virus contamination result in class action lawsuits and legal expenses?
If so, please describe.

153. Did the virus contamination impact company stock value?
If so, please describe.

154. What other costs were associated with this contamination? Please describe.

Lessons Learned

155. Did the company conduct a lessons learned exercise?

156. If so, what were the lessons learned by the company?

Virus Contamination Risk Management

157. Has the company conducted a formal virus risk management exercise?

Is this a regular exercise, or was it a one-time exercise?
Was it related to a contamination event?

Please describe.

158. Did this exercise occur before or after a virus contamination, or both before and after?

159. What did the company estimate to be the risk of having a virus contamination event? (e.g. frequency of occurrence and severity of impact) Were various scenarios evaluated? Please describe.

160. What did the company estimate to be the potential cost of having a virus contamination event including all subsequent direct and indirect costs? Were various scenarios evaluated? Please describe analysis and cost estimates.

161. Has the company developed a decision-making process to determine whether to develop and implement new equipment, manufacturing processes and/or analytical testing methods (e.g., HTST, gamma radiation, UV, nanofiltration, media component changes, PCR), internal expertise, and organizational structure so to mitigate/control virus contaminations?

If so, please describe the process.

162. Has the company developed and implemented plans to mitigate the risk of product stock out in the event of a virus contamination?
If so, please describe.

163. Does the company employ individuals with virus expertise that have overall responsibility to guide the company with regard to virus control systems, risk mitigation, analytical testing, and investigations into virus contaminations?

Does the company rely only on outside expertise of consultants and/or contract testing organizations?

164. Is the company actively engaged in the assessment of virus contamination risks from newly emerging or newly discovered viruses?
If so, please describe.

165. Does the company have a formal “Virus Contamination Preparedness Plan” that describes all investigation activities, organization, management, decision making processes, communication, and responsibilities should a virus contamination occur?

166. What specific new technologies (not currently available) would you like to see developed to detect or prevent virus contamination (e.g. cell line engineering, better process mitigation, detection and identification methods, etc.)?