



Risk Mitigation for Adventitious Agent Contamination of Biotech Products: Consideration of New Industry Standards

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Risk of Adventitious Agent Contamination in Biotech Products is Complex

- **Risk to patients/personnel from direct infection**
 - Known human pathogens
 - Pathogens with potential to cross species boundaries:
 - >60% of human pathogens are zoonotic: may not be detected by human cell line culture
 - >175 pathogenic species associated with emerging infectious disease
 - XMRV a recent potential example
- **Risk to product availability for patients with life-threatening illness**
 - Lifesaving products for unmet medical needs
 - Sole source providers
- **Risk to other products in the facility**
- **Risk to product quality**
 - Infected/stressed cells:
 - Types and levels of post-translational modifications may be altered by cellular stress/infection.
 - assays must be suitably comprehensive and sensitive to detect variants or impurities that might have clinical consequences



Sources of Infection in Fermentation Process

- Cell banks
- ***Naturally sourced raw materials: predominant source of adventitious agent contamination***
- Human error
- Environmental



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Livestock plagues are spreading

As farming intensifies, researchers warn that the developing world is "dangerously behind" on controlling animal diseases.

A new infectious disease emerges every four months, and 75% of them originate in animals, according to ILRI figures. They can have severe socio-economic, health and environmental impacts: some of the most damaging diseases are Rift Valley fever (Phlebovirus), which can sometimes cause a haemorrhagic fever, and Bluetongue disease (Orbivirus).



- “The difficulties inherent in detecting low levels of viral contaminants and thus, the potential to unknowingly contaminate a whole manufacturing facility lie at the centre of the concerns about viral contamination.”
 - RL Garnick 1998

Issues with Detection Assays

(Adapted from K. Brorson, DMA, OBP)

You only find what you are looking for...

- Screening Assays: specific assessment of known/past pathogens
 - Source animal surveillance and testing of animal materials by vendor limited.
 - Screening by sponsor for specific current/past pathogens:
 - requires assumptions about the type and strain of the infectious agent, limiting detection to a small number of known pathogens
 - ignores emerging, novel viruses
 - Infectivity- cell line panel may not be permissive for novel virus

You need to routinely update for detection of prevalent infections or use broad based screen methods

- Must be current on surveillance and literature reviews to target known pathogens
 - Vesivirus identified in 2003 as bovine contaminant; found to be widespread in cattle in USA in 2006.



You may *not* find what is truly there....

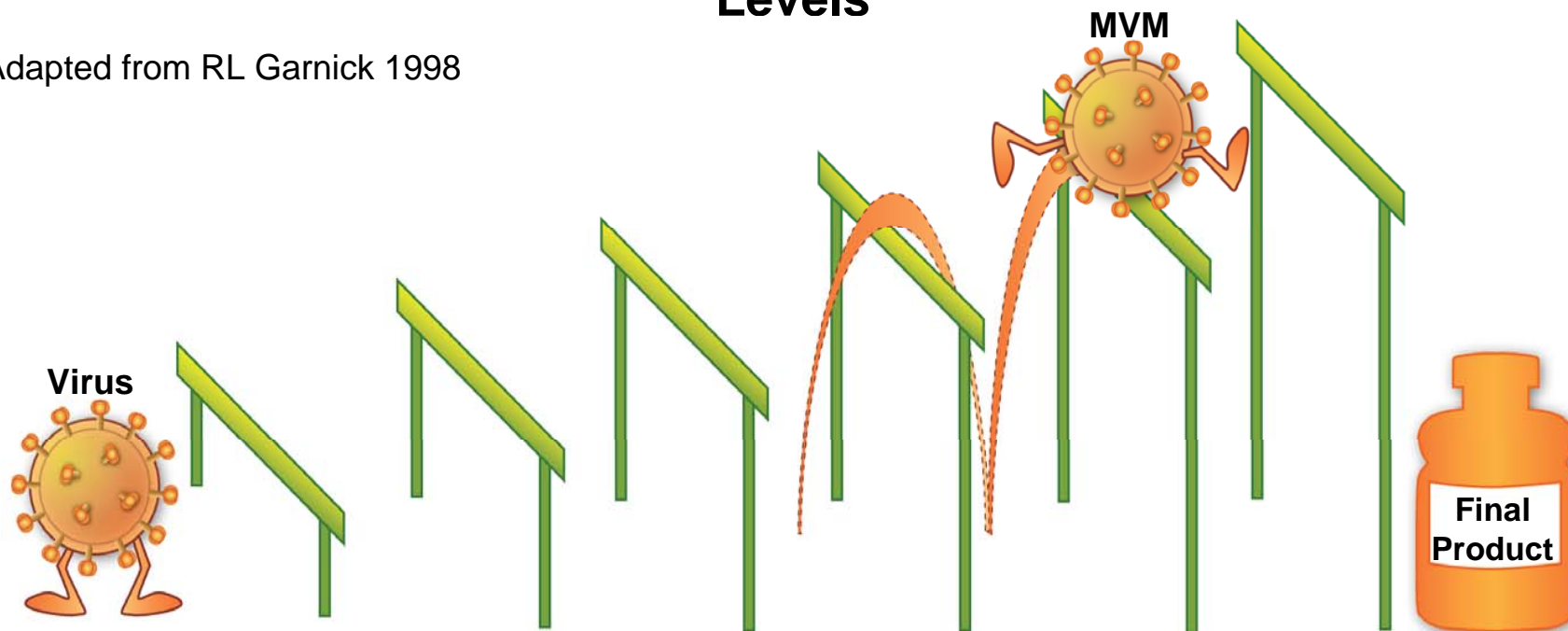
(K. Brorson, DMA, OBP)

- Sensitivity of assay limits detection
 - All assays have a LOD
 - Sample volume limitations
 - Cell lines may not be permissive for some known or novel viruses
- Interference/matrix effects
 - Anti-virus antibodies in FCS used in in vitro assays
 - Cytotoxicity of indicator cells
 - Inhibition of PCR assay enzymes



Viral Control Strategy for Raw Materials: Emphasis on Multiple Levels

Adapted from RL Garnick 1998



Raw materials
• Source
• Type

Testing of selected high risk raw materials

Processing of raw materials: should include a specific inactivation step

Storage of raw materials

Does virus propagate in the cell line?

Amplification->testing

Testing at production stage for virus
• General screen
• Specific assays

Validated inactivation/removal of virus in recovery process





Pillars of Risk Mitigation for Adventitious Agents in Biotech Products

- Remove/Replace when possible, naturally sourced raw materials from cell culture
- Know your source materials: current knowledge of prevalent and emerging infections of source animals or associated with plants
- Use the most sensitive tests to screen raw materials for known potential contaminants: use amplification steps
- Inactivate/remove adventitious agents present in raw materials:
 - Irradiation: UV, γ ,
 - Heat inactivation: HT-ST
 - Viral filters
 - Others?



Pillars of Risk Mitigation for Adventitious Agents in Biotech Products

- Evaluate production culture for adventitious agents **early** in production cycle to mitigate product loss and spread to facility
- Incorporate robust viral inactivation steps in product purification
- Use advanced techniques (e.g. universal biosensor, massively parallel sequencing, viral chip) to assess contamination in raw materials/production culture especially when inactivation is not an option
- Develop new biomarkers of infected cultures



The Most Important Agency Expectation: *Adaptation to Changing Paradigms and Technologies*

- “Since the most appropriate techniques may change with scientific progress, proposals for alternative techniques, when accompanied by adequate supporting data, may be acceptable”

ICHQ5a



Agency Responsibility

- Reevaluate and update current standards of industry with regard to manufacturing practices
- Provide more guidance on CGMP expectations where indicated
- Retain the scientific expertise to evaluate novel technologies and their ability to better ensure product safety



Industry Responsibility

- all firms need to meet CGMP and we will be inspecting to ensure firms meet contemporary standards for viral clearance

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