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Considerations for the Follow-Up of Putative Adventitious Virus Signals Detected by HTS

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BACKGROUND – High-throughput sequencing (HTS) has demonstrated capabilities for the broad and sensitive detection of known and novel adventitious viruses that could be inadvertently introduced during manufacturing of a biological product from raw materials, handling, or facilities and equipment.

CHALLENGES – All nucleic acids present in the sample can be potentially sequenced including adventitious viruses but also sequences from host, vector, sequencing adapters, etc. Additionally, nucleic acids can be introduced in a sample from various reagents, water, kits, and even exposed skin during the various sample handling, processing, and preparation steps in the HTS workflow.
The taxonomy assignment of sequences resulting from HTS is based on a comparison to viral sequence databases. Therefore, using a high-quality and well-characterized database is important for accurate identification of a signal due to an adventitious virus. The presence of misannotated and nonviral sequences in a database may result in extensive follow-up to verify the identity of the signal as an adventitious virus or a nonviral sequence. Additionally, sequencing errors or natural variations in viral genomes may lead to the misidentification of multiple related or unrelated viruses.

PROPOSED APPROACH – The breadth and sensitivity of HTS necessitates thoughtful follow-up strategies for assuring the absence of an adventitious virus in biological products without delaying their release.
In this presentation, we will review potential sources of false-positive signals and sample variability and explore considerations for viral reference database selection, criteria for actionable signals, and bioinformatic and laboratory follow-up of identified hits.