Dealing with Post-market Issues: PCV Case Study
CASE STUDY: Adventitious agent in raw material

ISSUE:

- Presence of porcine circovirus (PCV-1) DNA detected in marketed rotavirus vaccine by an independent research lab (not as a safety signal). Sponsor confirmed findings and notified Health Canada, US FDA, EMA, WHO, and TGA.

OBJECTIVE:

- Assess potential health risks of impurity to determine whether use of vaccine should be suspended and any marketed product recalled.
BACKGROUND:

- Rotavirus vaccine is an orally administered vaccine for protection against human rotaviruses that cause gastroenteritis (diarrhea) in infants


- NEW technology: use of metagenomics to detect contaminating viruses in live attenuated viral vaccines

- Method: Viral particle purification; Sequence independent amplification with random primers; DNA pooled and sequenced; BLAST genomic searching used to identify sequences other than expected virus; Confirmation with virus specific PCR
ISSUE ANALYSIS

- What questions arise?
- Additional info required?
Source of the contaminating virus?

- manufacturer conducted an investigation
- PCV-1 present in cell bank and rotavirus seeds but not in the original source of Vero cells
- Thus, introduced by manufacturer – likely from porcine-derived trypsin that is used to detach cells from flasks during cell culture
- Trypsin was not irradiated
What is PCV-1?

- Small (17nm), circular, ss, non-env, DNA (1.76kb) virus
- Dependent on S-phase cell cycle
- PCV1 (1974) – highly common & non-pathogenic pig infection transmitted fecal-oral
- PCV2 (1997) – pig pathogen: postweaning multisystemic wasting syndrome (PMWS)
  - 75% homology with PCV1
  - 3 genotypes so far – virus ‘appears’ to be changing
  - Pneumonia, enlarged lymph nodes and kidneys
  - PCV2 vaccines effective at controlling the disease
- Is contaminating virus replicating in host cells?
  - Treatment with DNase – is signal still present? YES

- Is PCR signal associated with intact viral particles?
  - YES

- Is contaminating virus present in final product?
  - Purification and/or lyophilization may remove contaminant
  - Removed by purification for another vaccine made with same cells
  - Even though present in final, lyophilization could impact quality of virus
Manufacturing Process

Vero cell line

Trypsin

Viral seed

Rotavirus Expansion on vero cells

Viral harvest

DNase treatment
Ultrafiltration/Concentration
Sterile Filtration

Purified bulk

Dilution and Filling in Final Container

Rotarix vaccine

PCV1 DNA Q-PCR (copies per ml)

<table>
<thead>
<tr>
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<th>PCV1 DNA</th>
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<tbody>
<tr>
<td>Viral harvest</td>
<td>$10^{10}$</td>
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<tr>
<td>Purified bulk</td>
<td>$10^{9}$</td>
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<tr>
<td>Final Container</td>
<td>$10^{7}$</td>
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PCV1 DNA detected

No PCV2 DNA detected
Is contaminating virus infectious to humans?

- Tissue culture safety studies in human cell lines and human PBMC in vitro
  - Conflicting results on infectivity, but does not replicate so is non-productive infection
- Are there safety signals in clinical trials/PSUR/surveillance databases? NO
- Is there seroconversion in vaccinated individuals against contaminant? NO
- Is there proviral integration into human chromosomes? NO
Manufacturer Investigations

- Can PCV1 viral particles cause infection in human infants? NO
- 69 million doses worldwide, 2.5 million US
- No new safety concerns or signals
- 11 clinical studies over 8 yrs – 75000 subjects incl lrg safety trial with 60 000 subjects
  - Retrospective analysis of placebo controlled studies with pre and post vaccination (min 2 timepoints) sera and stool samples
  - 80 subjects from 4 trials (1 with HIV infants)
  - Q-PCR to detect PCV1 in stool, ImmunoPeroxydase Monolayer Assay to detect anti-PCV1 in sera
  - Adverse event profile similar to placebo
Main conclusions

- PCV1 not infectious in humans, does not cause disease in humans or any other animal
- No safety concerns identified
- Rotavirus is leading cause of childhood diarrhea and vaccination only effective preventative strategy
- Rotavirus vaccine prevents:
  - Severe RV GE disease (96% Europe; 85% Latin America)
  - RV GE hospitalizations (100% EUR: 85% LA)
  - 60% reduction in rotavirus disease in US
  - could prevent 2 million deaths in next decade
- **Benefits outweigh theoretical risks**
- **New technologies may reveal new impurities but does not necessarily imply a risk**
What are the Options???
Options

A. Recall product – no doses on the market so not required

B. Suspend further production until change in manufacturing process – alternative product on the market, however no safety concern based on available data

C. Status quo – continue production as is

D. Continue release of vaccine & use in current on-going clinical trials, but with commitment from manufacturer to generate PCV-free cell and virus banks in a timely manner
What would you Recommend???
Considerations

- Research paper by E. Delwart – contacted manufacturer
- March 19: manuf notified HC of PCV1 DNA in rotavirus vaccine
- March 22: FDA temporary suspension of rotavirus vaccine use
- March 24: EMA Vaccine Working Party
  - TGA and EMA no regulatory action
  - WHO prequalification status unchanged
- March 26: HC statement – no safety concern
- May 7: US FDA - Vaccines and Related Biological Products Advisory Committee (VRBPAC)
- May 7: Manufacturer of other product finds PCV1 & 2 (low levels)
- May 10: HC requests labelling update to include PCV
- May 16: FDA advised to resume use of rotavirus vaccine
Recommendations

- BGTD recommended D
- Alert Public Health Agency of Canada
- Health Canada statement to public
- Dear Investigator letter and revised informed consent submitted by manufacturer to inform participants of presence of PCV-1 and safety assessment
- Director of Center approves the decision
Implementation and Evaluation Plan

- Continue to review manufacturer’s ongoing investigation results
- Monitor commitment made by manufacturer to change process within a specified timeline
- Pharmacovigilance increased to scan for potential adverse events that could be linked to PCV
Reference and Attachments

- Delwart published paper
- Additional published papers on PCV infectivity
- Adverse events database listings
- Manufacturer’s investigation reports
- Minutes from EMA Vaccine Working Party meeting
- Consultations with WHO, EMA, and FDA
- Dear Investigator letter and revised informed consent