Dealing with Post-market Issues: OOS Case Study
CASE STUDY: Potency Out of Specification Result

ISSUE:

- 3 lots of DTwP-HB (diptheria-tetanus-whole cell pertussis-hepatitis B) combination vaccine failed the Kendrick potency test (used to assess the potency of the pertussis component) when performed by the NCL but not by the manufacturer

OBJECTIVE:

- Do you release the lots?
BACKGROUND:

- DTwP-HB is indicated against diptheria-tetanus-whole cell pertussis-hepatitis B in infants from 6 weeks onwards
- If rejected, there will be a vaccine shortage resulting in a delay of immunization for thousands of infants to 4 infectious diseases
- There has been a recent outbreak of pertussis in country
- Kendrick test is variable and involves a lethal challenge; alternate serological methods (Pertussis Serological Potency Test or PSPT) used to address 3Rs
ISSUE ANALYSIS

- What questions arise?
- What additional information do you require to make a decision?
- Comparison to historical results (Trend analyses)
- Review of Batch records – were there any deviations in manufacturing process?
- What do the rest of the in-process and release test results look like? Normal? Borderline?
- Was the result valid? Was it confirmed with a repeat test?
- Investigation of OOS – was it a true OOS or a problem with the test?
- Is the test validated and reliable?
Review of Product Quality

- Vaccine has over 15 years of safety
- Manufacturer has demonstrated consistency of production
- No deviations during manufacturing of this lot
- All in-process tests within specifications
- Same lots tested with alternate PSPT met specs
- Another lot was released with same bulk and met specifications for Kendrick potency test
Animals
- Source
- Quality
- Facility

Manufacturer
- Trending
- Batch records (deviations)
- Product history

Method
- SOP
- Validation
- Suitable for purpose

Documentation
- Worksheets
- Traceability of results

Staff
- Training
- Qualifications
- Number
Review of Test

- NCL has limited experience with test
- Validity of test? Yes, controls performed as expected
- Re-test – invalid, problems with supply of animals to conduct additional tests

Quality management system assessment

- Lack of traceability with how animals handled
- No records of calibration dates of pipettes and equipment used
- Lack of training of new personnel (technician performing assay was a summer student)
Manufacturing Results vs National Control Laboratory Results

Manufacturer

NCL
What are the Options???
Things to consider

- Are alternative products available
- Mortality/morbidity of disease
- Time to re-test
  - Immunization program schedule
  - Are there current outbreaks? Is disease seasonal?
  - How long is vaccination schedule for protection: ie. 3-dose
  - Shelf-life shortens and potency further reduces
Options

A. Reject lots: 10 months for alternative product or new lots
   - Delay immunization, expose thousands of susceptible infants to disease including pertussis given recent outbreaks

B. Perform 2nd retest: 8 months for backordered mice & new test
   - Delay immunization with infectious disease risk as above

C. Release the 3 lots:
   - Avoid shortage, ensure protection of infants based on supportive evidence from alternate test
   - Poor QMS likely root cause of OOS, test vs product quality
What would you Recommend???
Options

A. Reject lots: 10 months for alternative product or new lots
   ▪ Delay immunization, expose thousands of susceptible infants to disease including pertussis given recent outbreaks

B. Perform 2nd retest: 8 months for backordered mice & new test
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Considerations

- Analysis prepared and documented in an Issue Analysis Summary by Chief of Bacterial and Combination Vaccines Division
- Consultations with Product experts within Division
- Additional information obtained from another NCL and manufacturer
Option C recommended by Division Chief to release these lots and advise the Public Health Agency to increase the surveillance to monitor adverse events following immunization as a precautionary measure.

Director of Center approves the decision.
Implementation and Evaluation Plan

- Public Health Agency alerted
- Manufacturer informed of decision to release lots
- Conduct review of QMS in laboratory to determine the financial and human resources needed to ensure reliability of key assays used for release
Reference and Attachments

- Lot Release Protocols for the 3 lots of DwPT-HB vaccines
- Additional information on batch records
- Information provided by the other NCL
- Publications on PSTP
- Minutes of teleconference with the manufacturer