Report on the ICCVAM/NICEATM International Workshop on Alternatives to the HIST for Acellular Pertussis Vaccines

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SACATM Meeting
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Etiologic Agent of Whooping Cough

(B. pertussis)

• Highly contagious disease caused by the bacterium *Bordetella pertussis* and characterized by violent coughing

• Whole cell vaccine introduced in the 1940s
  – Replaced by an acellular vaccine over the last 20 years

• Periodic epidemics every 3 to 5 years and frequent outbreaks
  – During past 5 years, 10,000 to 27,000 cases reported annually in the US
Current *In Vivo* Pertussis Vaccine Safety Testing

- Murine HIST is a key safety test performed to assay for residual active pertussis toxin prior to vaccine release
  - Based on the sensitization to histamine induced by active pertussis toxin
  - Requires large numbers of laboratory animals (mice) that experience unrelieved pain and distress
Alternatives to HIST Vaccine Safety Testing Workshops\textsuperscript{1,2}

- Paul Ehrlich Institute workshop (2011) established an International Working Group on Alternatives to HIST for testing alternative \textit{in vitro} methods using standardized acellular pertussis vaccines and pertussis toxin

- Satellite Meeting on Alternative Testing Strategies at 8\textsuperscript{th} World Congress, Montreal (2011)

\textsuperscript{1}Workshop on Animal-Free Detection of PTx in Vaccines - Alternatives to HIST, PEI, Langen, Germany, June 9-10, 2011.
\textsuperscript{2}Alternative Safety Testing Strategies for Acellular Pertussis Vaccines (8\textsuperscript{th} World Congress Satellite meeting), Montreal, Canada, August 21, 2011.
Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines

- Reviewed alternatives that could replace the current in vivo HIST
- Discussed application of in vitro assays for monitoring consistency of vaccine manufacture as alternatives to the HIST
- Established a framework for international collaboration to validate in vitro assay(s) for acellular pertussis vaccine testing
- Identified regulatory acceptance requirements for in vitro assays as alternatives to the HIST
- Reviewed in vitro protocols and data generated by participants of the International Working Group on Alternatives to HIST
- Recommended an international collaborative study

Further information is available at: http://ntp.niehs.nih.gov/?objectid=857B5F04-F413-8E68-E8640C04B788BB4
Satellite Meeting to WC9
Prague, Czech Republic, August 24, 2014

- International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines: Progress and Challenges in the Replacement of HIST
  
  - Discussed the implementation of in vitro assays to replace HIST for acellular pertussis (aP) vaccines on the basis of the consistency approach:

  - Discussed the necessary framework for regulatory acceptance of a harmonized approach that uses in vitro assays instead of the HIST.

  - Discussed recent international efforts towards the development of in vitro assays to replace the HIST.
Challenges to Regulatory Acceptance of HIST Alternative

- Differing regulatory requirements among international authorities
- Critical that there is harmonization during the process of identifying a replacement method
- HIST version used (quantitative, based on temperature decrease) is not included in all licenses/registrations
- Biochemical alternatives proposed do not completely address cell intoxication
Challenges to Regulatory Acceptance of HIST Alternative

- Historical clinical lots can’t be compared with production lots using the biochemical alternatives without parallel testing, because of inconsistent IU.

- Discordant interpretations of the consistency approach (safety vs consistency):
  - Manufacturing consistency should yield new lots that display consistency in testing outcomes.
  - New tests (alternatives to HIST) should be shown to be consistent in performance to HIST.
Next Steps: Completion of International Collaborative Study

- Assessing use of Chinese Hamster Ovary (CHO) cell assay for calibration of PTx international reference standard BRP relative to JNIH-5

- Current CHO assay must be modified to address adjuvant and excipient interference to be successful in vaccine release testing

- Harmonized CHO cell assay protocol

- Study results anticipated in early 2015

- Consistent results in CHO collaborative study and inclusion in monographs or other requirements would increase the willingness of manufacturers to implement
Next Meeting

• International Working Group on Alternatives to HIST meeting
• London, England; March 4-5, 2015
• Organized by National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs)
  – Meeting support from NICEATM
• Will review data from international collaborative study
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