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

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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[1,2]

- Paul Ehrlich Institute workshop (2011) established an International Working Group on Alternatives to HIST for testing alternative *in vitro* methods using standardized acellular pertussis vaccines and pertussis toxin
- Satellite Meeting on Alternative Testing Strategies at 8th Word Congress, Montreal (2011)

[1]Workshop on Animal-Free Detection of PTx in Vaccines - Alternatives to HIST, PEI, Langen, Germany, June 9-10, 2011.
[2]Alternative Safety Testing Strategies for Acellular Pertussis Vaccines (8th 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-E8640C0A4B788BB4*

# 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

# Acknowledgements: Pertussis HIST Organizing Committee


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