Introduction

- Vaccines improve animal and human health and welfare by preventing and controlling infectious diseases
- In the U.S. alone, the childhood vaccine series (Table 1):
  - Prevents an estimated 14 million infections
  - Avoids 33,000 premature deaths
- Saves $30 billion in direct medical costs and $23 billion in indirect costs for each U.S. birth cohort fully vaccinated
- NIEATM and ICCVM have identified vaccine priority and safety testing areas of the four highest priorities for reduction, refinement, and replacement of animal testing (ICCVAM 2008)
- Priority based on the large numbers of animals and significant pain and distress that can occur for potency and safety testing of many human and veterinary vaccines
- NIEATM, ICCVM, and their ICAT partners organized an international workshop held on September 14–16, 2010, to promote and advance the development and use of scientifically valid alternative methods for human and veterinary vaccine testing

Workshop Goals
- Review the state of the science of alternative methods that reduce, refine, and replace the use of animals in vaccine potency and safety testing, and discuss ways to promote their implementation
- Identify knowledge and data gaps that must be addressed through research, development, and validation efforts
- Identify and prioritize efforts needed to address these knowledge and data gaps

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National Workshop in Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Human Vaccine Potency and Safety Testing

1U.S. FDA, Rockville, MD, USA; 2USDA, Riverdale, MD, USA; 3Health Canada, Ottawa, Canada; 4European Commission, ECVM, Ispra, Italy;
5JaCVM, Tokyo, Japan; 6IIS, Inc., RTP, NC, USA; NICEATM/NIEHS/NIH/HHS, RTP, NC, USA

Workshop Sessions

Session 1: Overview of Public Health Needs and Regulatory Requirements for Vaccine Safety and Potency Testing
- Summarized public health needs for vaccines in the U.S., Europe, and developing countries, as well as to identify requirements and rationale for determining potency and safety of vaccine products

- Reviewed currently accepted replacement alternatives (i.e., antigen quantification), knowledge gaps associated with test methods not currently accepted, and areas that should be emphasized as targets for future development

Session 2A: Animal Pain and Distress in Vaccine Potency Testing: Refinement and Reduction Alternatives
- Provided an overview of alternative methods and approaches that could (1) refine current vaccine potency testing methods to reduce or eliminate animal pain and distress associated with current vaccine potency testing procedures and (2) reduce the number of animals used for specific vaccine potency testing procedures

Session 2B: Refinement Alternatives: Using Serialological Methods to Avoid Challenge Testing
- Multi-parametric approaches to replace lethality testing

Session 2C: Refinement Alternatives: Using Earlier Human Endpoints to Avoid or Minimize Animal Pain and Distress in Vaccine Potency Testing
- High throughput approaches to refine or eliminate animal testing

Session 3: Animal Use for Vaccine Potency Testing: Priority Vaccines
- Vaccines that require the largest number of animals
- Vaccines that use in vivo tests that are highly variable and require repeated testing
- Vaccines that are most commonly used

Session 3A: Vaccine Replacement Alternatives
- Discuss challenges associated with antigens and replacement approaches

Session 3B: Refinement Alternatives: Using Earlier Human Endpoints to Avoid or Minimize Animal Pain and Distress in Vaccine Potency Testing
- High throughput approaches to refine or eliminate animal testing

Session 4: Vaccine Post-Licensing Safety Testing: Reduction, Refinement, and Replacement Methods and Strategies
- Focused on current regulatory requirements and rationale for post-licensure safety testing (e.g., general safety, neurovirulence test, pyrogen test) for both human and veterinary vaccines

Poster Session 1: Thirteen poster presentations of ongoing research, development, and validation activities focused on reducing, refining, and replacing animal use for vaccine potency and safety testing

Detailed information on the workshop, including all poster presentations, can be obtained on the NICEATM/ICCVAM Web site at: http://niches.nih.gov/meetings/Biology2010/Biology2010.htm

General Recommendations

Priority Vaccines
- Diphtheria and tetanus toxoid
- Pertussis vaccines (whole cell and acellular)
- Polioviruses
- Anthrax vaccines
- Candidate combination vaccines such as diphtheria/tetanus/pertussis vaccines
- Inactivated polio vaccines

Criteria for Prioritization
- Vaccines which alternative methods are already developed, but not validated
- Vaccines that require the largest number of animals
- Vaccines that use in vivo tests that are highly variable and require repeated testing
- Vaccines that are most commonly used
- Vaccines which have a well defined and understood mode of action or known target

Achieving Broader Acceptance and Use of Alternative Methods
- Broader access to information
- Increased interaction and communication between regulatory agencies, research institutions, and vaccine manufacturers
- Harmonization of requirements, methods, and specifications
- Readily available and/or nonproprietary reference standards

Post-Licensing Human Vaccine Safety Testing: Replacement, Refinement, and Reduction Methods

State of the Science
- In some cases, safety testing in animals has been reduced, refined, and replaced with alternative assays (e.g., diphtheria and one polio vaccine)

Priority Research Needs and Recommendations
- Refine the acellular pertussis lethal endotoxin hemolysis assay (HET) by including a dermal temperature endpoint
- Safety tests commonly used in vivo as replacement alternatives to HET (i.e., carbohydrate binding and enzyme-linked HFC assays)
- Use the Vero cell assay to monitor diphtheria toxoid
- Develop a fully functional in vivo assay for tetanus toxin
- Continue research to allow expanded use of this trypsin mouse model for oral polio vaccine
- Continue research required for validation of the sequence-based approach to oral polio virus neurovirulence testing
- Develop alternatives to the monkey neurovirulence test for preclinical safety and lot release neurovirulence testing of mumps (and possibly measles) vaccines

Eliminate the general safety test for vaccines where consistency of manufacture can be demonstrated

Conclusions

- This was the first international workshop convened in the U.S. to bring together international stakeholders with the human and veterinary vaccine communities to discuss opportunities to reduce, refine, and replace animal use for potency and safety testing
- The workshop reviewed the state of the science for existing alternative methods and approaches that could be used to reduce, refine, and replace animal use for potency and safety testing
- Alternative methods have been incorporated into the regulatory acceptance of the potency and safety testing of several human and veterinary vaccines
- The workshop identified knowledge and data gaps, as well as research, development, and validation activities needed to address these gaps and to advance alternative methods for vaccine potency and safety testing
- Advances in science and technology that can and should be applied to these gaps were highlighted and identified as priorities for future initiatives
- The workshop emphasized the value and role of international cooperation, collaboration, and harmonization in advancing alternative methods for vaccine potency and safety testing
- Increased international cooperation is essential to maximize the impact of new methods and to accelerate their implementation globally
- Implementation of the workshop recommendations is necessary to facilitate the development of alternative methods that will benefit animal welfare and ensure continued protection of human and animal health

References


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