Update on Activities Toward Alternatives to murine HIST test, and General Safety Test

SACATM

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Objectives

- Describe the history and current status of efforts of *The International Working Group for Alternatives to HIST*
- Describe the history and current status of the animal-based General Safety Test (GST) in the United States Code of Federal Regulations for human biologics 21 CFR 610.11

The Murine HIST test

The Murine HIST (an animal-based challenge test) is a key safety test performed to assay for residual active pertussis toxin (PTx) prior to vaccine release

- Based on the sensitization to histamine induced by active PTx
- Requires large numbers of laboratory animals (mice) that experience unrelieved pain and distress

ICCVAM/NICEATM Vaccine Potency and Safety Testing 2010 Workshop

HIST was identified as one of the highest priorities for human vaccines for future research, development, and validation efforts because:

- Many lots of pertussis vaccine are produced annually
- HIST use large numbers of laboratory animals
- HIST involves significant unrelieved pain and distress in mice
- HIST is highly variable, often requiring frequent retests

International Working Group on Alternatives to HIST

- Paul Ehrlich Institute (PEI) workshop, Langen (2011)
  - established an International Working Group on Alternatives to HIST
- Satellite Meeting at 8th Word Congress, Montreal (2011)
- ICCVAM/NICEATM Workshop, Bethesda (2012)
  - evaluated data from first collaborative study (several alternatives)
- Satellite Meeting at 9th Word Congress, Prague (2014)
- NC3Rs Workshop, London (2015)
  - evaluated data from second collaborative study (one alternative)

London Workshop Recommendations:

- The CHO cell assay is a suitable alternative to HIST – Measures PTx whole function
- The CHO cell assay is reasonably well developed to be considered suitable for regulatory purposes (protocol transferability demonstrated)
- Each manufacturer will have to optimize the method for their specific product & regulatory requirements

London Workshop Recommendations (cont'd):

- Implementation of the CHO cell assay - Stepwise approach, initially used for release, then extend to stability testing after a period of demonstrated performance
- In certain cases, waiving of the HIST altogether is an option (based on science & manufacturing history)
- Other *in vitro* assays (i.e. measuring PTx binding & enzymatic activity) have utility as supplemental manufacturing control information, but not for final lot release on their own
- Publication of the collaborative study results should facilitate international regulatory acceptance

Participants in Alternatives to HIST Effort

(non-exhaustive list)

- NICEATM
- JacVAM
- EURL/ECVAM
- NIBSC
- NVL
- EDQM
- Health Canada
- FDA
- PEI
- Sanofi Pasteur
- GSK

(General) Safety Test History

- 1901-Tetanus contamination of diphtheria antitoxin
- 1901- Tetanus contamination of smallpox vaccine
- 1902- Biologics Control Act

General Safety Test History

- 1938 – First CFR published, Safety Test (along with Identity Test) mentioned in 42 CFR 22.110
- 1947 – Proposed rule published in the Federal Register to amend the CFR with a description of the Safety Test [12 Fed. Reg. 6769, 1947]
- 1948 – Minimum Requirements
  - "The Biologics Control Laboratory prepares and issues monographs, known as "Minimum Requirements," on individual biologics

General Safety Test History

- 1974 – Proposed Revision of General Safety Test 39 F.R. 11301, March 27, 1974.
  - The General Safety Test "**has been part of the biologics regulation since their original adoption.**"
- 1998 – Revisions to the General Safety Requirements for Biological Products – exempted products, 63 F.R. 19399, April 20,1998
- 1998 - part of the rule withdrawn, 63 FR 41718, August 5, 1998
- 2003 – Exemptions from GST, 68 F.R. 10157, March 4, 2003
- 2014 - Proposed Rule -Revocation of General Safety Test Regulations That Are Duplicative of Requirements in Biological License Applications, 79 F.R. 49727, August 22, 2014

General Safety Test is History

- 2015 - Final Rule - Revocation of General Safety Test Regulations That Are Duplicative of Requirements in Biological License Applications, 80 F.R. 37971, July 02, 2014
  - Effective Aug 3, 2015