

SEROLOGICAL POTENCY TESTS FOR DIPHTHERIA AND OTHER VACCINES

International Symposium, Budapest, 6-7 October 2004

**SEROLOGICAL DIPHThERIA
POTENCY TESTS
CONCLUSIONS &
ACTION PLAN**

**EDQM
Budapest 6-7/10/2004**

**SEROLOGICAL DIPHThERIA POTENCY TESTS
CONCLUSIONS
Epidemiology & vaccination**

- **Corynebacterium diphtheriae is still around (eg Russia)**
- **Vaccination is effective if:**
 - Vaccination compliance is good
 - Vaccine is of adequate quality
 - Adequate schedule (booster)
- **Clinical and experimental data in support of guinea-pig animal model**

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**SEROLOGICAL DIPHThERIA POTENCY TESTS
CONCLUSIONS
Results of EDQM BSP Collaborative Study**

- **Guinea-pig Serology (ELISA & Vero) is valid alternative for challenge**
- **Single dilution serological model is feasible (vs. Ref vaccine in IU)**
- **D & T in same g-p serum is feasible**

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SEROLOGICAL DIPHTHERIA POTENCY TESTS
CONCLUSIONS
PhEur Monograph Implementation

- **Following Tetanus example**
 - Detailed description of assay method
 - Guideline for replacing challenge by serology & validation of single dilution model (statistics?)

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SEROLOGICAL DIPHTHERIA POTENCY TESTS
CONCLUSIONS
OMCL IMPLEMENTATION

- Reduction (~75%) of animal use already implemented for challenge tests (reduced testing & single dilution after suitable experience & validation)
- Advantages:
 - Further reduction (Te + Di)
 - Reduction variability
 - Existing ELISA can be used
- Disadvantages:
 - Increased duration
 - Supply & handling of animals
 - Cost (x10 vs mice)
 - Challenge know-how should be maintained
- **SINGLE DILUTION & COMBINED ANTIGEN ASSAY ARE ESSENTIAL**

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SEROLOGICAL DIPHTHERIA POTENCY TESTS
CONCLUSIONS
INDUSTRY QC IMPLEMENTATION

- Ethics, performance & cost are main parameters in acceptability of alternative to challenge
- Reduction can already be achieved through use of single dilution challenge (for some vaccines)
- Serology part adds complexity & delay
- **SINGLE DILUTION & COMBINED ANTIGEN ASSAY ARE ESSENTIAL** for adequate performance/cost ratio
- Future:
 - *in-vitro* antigen characterisation (conformation)?
 - Further study of inter-method correlation (4 weeks not valid?)
 - Reference vaccine choice
 - New specs?

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SEROLOGICAL DIPHThERIA POTENCY TESTS
CONCLUSIONS
INDUSTRY QC IMPLEMENTATION

- **Serological alternative will have acceptable performance/cost ratio**
 - single dilution model
 - multiple antigen assay
 - global harmonisation
 - Serum (cross)-sharing with OMCL?

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SEROLOGICAL DIPHThERIA POTENCY TESTS
CONCLUSIONS
COMBINED MULTIPLE ANTIGEN ASSAY

- Current status: eg. PhEur Hexavalent: n.l.t. 400 animals (different animals/routes of immunisation)
- D & T: feasible in multiple dilution/parallel line model
- D, T, Pa, IPV, HepB, Hib antigens in combos: should be feasible (vaccine doses to be optimised for different vaccines)
- Model for routine testing/vaccine characterisation (eg. Interference)

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SEROLOGICAL DIPHThERIA POTENCY TESTS
ACTION PLAN

- Further guidance on what is needed for product specific validation for shift challenge/serology and multiple dilution/single dilution (incl. Statistical)
- Implicate national and EU licensing authorities (data requirements, taking into account publication in PhEur)
- Further investigation of multiple antigen assays feasibility
- Further investigation into *in-vitro* antigen characterisation

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SEROLOGICAL DIPHTHERIA POTENCY TESTS
CONCLUSIONS
OTHER REGIONS

- WHO serology
 - approach is fully compatible with PhEur (fine-tuning possible; guidelines on methods and validation would be welcomed)
 - Encourage further investigations into multiple antigen assays and *in-vitro* antigen characterisation.
- FDA/CEBR
 - Words should be more clearly defined: potency, validation, correlation
 - Developing countries can not use full-blown challenge/US method is simpler and used
 - Major difference is specification in antitoxin IU
 - Compared to US method any change increases complexity including regulatory complexity (variations)
- Australia
 - Basis is BP/PhEur
- Canada
 - Use US serological model but 3 dilution model (+ euthanasia as humane endpoint)
 - Eg Infanrix Hexa: batch released by US method)
