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

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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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

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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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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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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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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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)

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