New Cells for New Vaccines II
Focus on Respiratory Virus Diseases

Regulatory View From the European Medicines Agency

Dr. Michael Pfleiderer, Paul-Ehrlich-Institut, German Federal Agency for Sera and Vaccines
The Safety of Cell Substrates

►► A wide range of aspects
  ▪ Historic
  ▪ Cultural
  ▪ Academic
    ▷ An intellectual challenge
      ▪ Evolutionary epistemology = “the theory of learning” (Sir Karl R. Popper)
      ▪ Will hardly provide solutions for medicinal products
  ▪ Scientific
    ▷ Will provide solutions for medicinal products
  ▪ Regulatory
    ▷ Risk management considering all aspects
The Safety of Cell Substrates – Historic and Present EU Priorities

► Virus safety
  ▪ Defined test procedures (e.g. viral seeds, cell stocks, control cells)
    ► In vivo
    ► In vitro
    ► PCR

► Minimizing the risk of transmitting TSE
  ▪ Defined starting and raw materials
    ► The region
    ► The source
    ► The manufacturing
    ► The impact on the product

Although the extent of all possible risks remains unknown, neither viruses nor the TSE agent are currently transmitted via medicinal products.
The Safety of Cell Substrates – Further Acceptance Criteria or a Risk Minimization Strategy

- Identity and purity (pass)
- Bacterial and fungal contamination (pass)
- Mycoplasmas (pass)
- Chromosomal characterization (pass)
- Substances of human and animal origin (to be certified)
- (Endogenous) Retroviruses (pass)
- Tumorigenicity (pass or fail but how to deal with the result?)
EU Guidance on Tumorigenicity Issues

► European Pharmakopoea

- General text 5.2.3. Cell substrates for production of vaccines for human use
  - Tumorigenic cell lines are not acceptable for live vaccines
  - For other types of vaccines residual DNA should be less than 10 ng per single human dose
  - Cells of known tumorigenic potential do not have to be tested again
  - A cell line of unknown tumorigenic potential is considered to be tumorigenic as long as there is no acceptable negative test result at the level of the maximum doubling level used for production
ICH Topic Q 5 D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products

- For products that are highly purified and that contain no cells, karyology and tumorigenicity testing are generally not considered necessary, provided that appropriate limits for residual host cell DNA are shown to be consistently met by either process validation studies or by lot release testing.
WHO Guidance on Tumorigenicity Issues

- Continuous consultations over decades
- Systematic approach to calculate the risk
  - Tumorigenicity concerns based on experimental data
- Over time issues related to the manufacturing process were included in the evaluation of potential tumorigenicity risks
- Likewise, product specific considerations became relevant
- Focus on safety records
Issues Common to All These Guidance Documents

► No cell line is currently disqualified for production of biologicals for human use
► In fact, the more recent the guidance on cell substrates the less stringent the focus on specific cell substrates with a historically proven safety record, i.e. primary and diploid cells
► Growing interest in any new cell line that might be useful for manufacturing processes for biologicals
► Generic concerns are replaced by appropriate risk assessments with regard to tumorigenicity
Assessing the Risk of Tumorigenicity - What Does This Mean for Vaccines?

- Product specific issues
- Process specific issues
- The therapeutic indication
  - Prophylactic vaccines
  - Therapeutic vaccines
- The route of administration
- The number of doses needed
Assessing the Risk of Tumorigenicity – Product Specific Issues

► Pivotal considerations
  - Unmet medical need versus availability of established products
    - The public pressure
  - Live attenuated versus inactivated vaccines
  - The age of the target group
  - DNA vaccines
  - New vaccine classes
    - Immune stimulatory
    - Anti fertility
    - Anti addictive
    - .......
Assessing the Risk of Tumorigenicity – Process Specific Issues

► From a tumorigenic cell line to a safe product
  ▪ Validation of virus removal capacity
  ▪ Validation of removal of host cell and media derived impurities
    ➤ Proteins
    ➤ Nucleic acid
      ▪ Amount
      ▪ Fragment size
      ▪ Functionality of fragmentized DNA
  ➤ Validation of inactivation processes
  ➤ Validation of splitting processes

► Calculating the individual and collective capacity of process steps to remove and destroy residual DNA
Assessing the Risk of Tumorigenicity – The Therapeutic Indication

► Prophylactic vaccines
  - Best possible risk minimization desirable
    - Depends on the indication

► Therapeutic vaccines
  - Remaining risk might be acceptable under certain circumstances
    - No such vaccines available
    - Consider public health perspective
    - Consider view of patient organizations
    - Compare risk-benefit evaluation with “high risk” products from other therapeutic areas (“Tysabri”)
Assessing the Risk of Tumorigenicity – The Route of Administration

- Oral
- Transdermal
  - Hypothetical risk
- Intramuscular
- Intra-/Subcutaneous
  - Theoretical risk
Assessing the Risk of Tumorigenicity – The Number of Doses

► Prophylactic vaccines
  - 2 – 4 doses for primary immunization
  - Single booster dose in regular intervals

► Therapeutic vaccines
  - More doses required
  - Higher dosage
  - Repeated or life long administration
New Cell Substrates for New Vaccines – EU Experiences

Licensed products based on new cell substrates

- Cervarix, GSK
  - Prevention of cervix carcinoma induced by HPV 16/18
    - Recombinant HPV L1 produced by recombinant baculovirus replicating in Hi-5 insect cells

- Optaflu, Novartis
  - Immunization against seasonal influenza virus strains
    - Vaccine viruses grown in MDCK cells
Cervarix and Optaflu – Issues Related to the Suitability of the Cell Substrate

► Cervarix
  - Hi-5 cells as used in the Cervarix production process were shown to be non-tumorigenic in an athymic (nu/nu) mouse model
  - Efficient elimination of host cell derived impurities

Conclusion: Acceptable cell substrate, no tumorigenic potential conveyed to the finished product
Cervarix and Optaflu – Issues Related to the Suitability of the Cell Substrate

► Optaflu
  - Intact MDCK cells are tumorigenic but not lysed cells
  - No intact cells in the finished product
  - Robust process capable to eliminate, destroy and inactivate host cell DNA
    - BPL inactivation
    - Detergent splitting

Conclusion: MDCK cells are an acceptable cell substrate for the production of Optaflu and do not convey a tumorigenic potential to the finished product
Cervarix and Optaflu – Issues Related to the Suitability of the Cell Substrate

► Scientific discussion on the cell substrates
  ▪ Main points raised during the evaluation process
    ► Viral safety of cell substrates
    ► Potential adventitious agents in viral seeds that could multiply in the Hi-5 or MDCK cells
      ▪ Particularly complex issue for Optaflu and the annual updates

► Tumorigenicity has only been of marginal importance during the EU-licensing procedures for both vaccines
EU-Strategies to Implement New Cell Substrates

- Generic acceptance or rejection of new cell substrates not possible
- Rather unspecific guidance
- No generic recommendation or position statement available nor desirable
- Case by case approach requiring early contact between manufacturers and authorities
  - National scientific advice
  - EMEA scientific advice
    - Follow-up advices at critical points of the pharmaceutical development process
      - Development of a commonly agreeable scientific position within the EU through the involvement of BWP, VWP, SAWP and CHMP

Paul-Ehrlich-Institut
Thank you for your attention