Human papillomavirus vaccines Quality Evaluation

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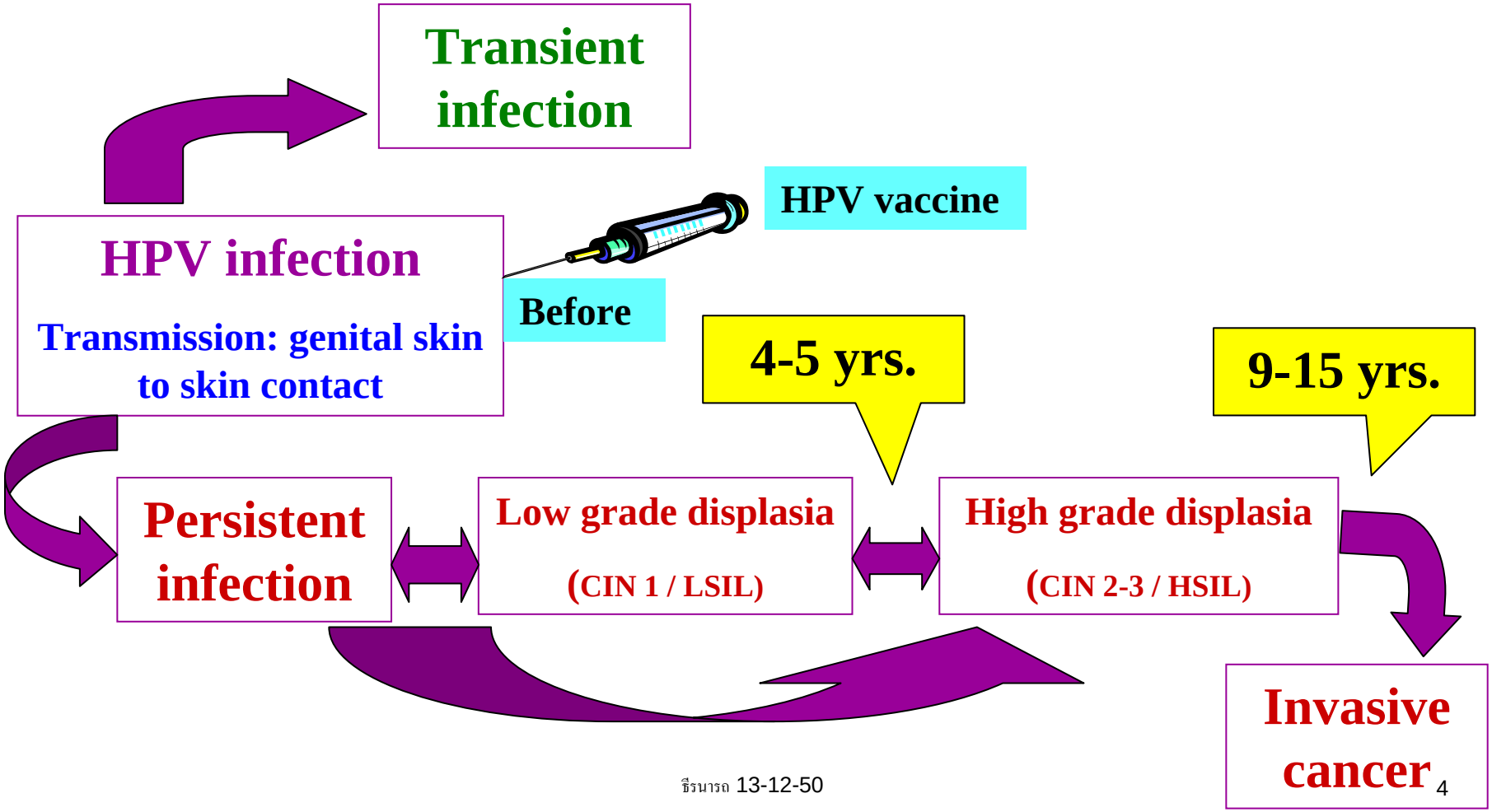
Cervical Cancer

- **The leading cause of cancer mortality among women in developing countries.**
- **Approx. 500 000 new cases and 239 000 deaths each year. (80% occur in developing countries)**
- **Over 99% of cervical cancer are linked to genital infection with human papillomavirus (HPV).**
- **Peak incidence of HPV infection occurs in adolescents and young women under 25 year old.**

Etiologic model of Human papillomavirus

- **More than 100 genotypes exist.**
- **Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 have compelling evidences for the carcinogenicity (high-risk types)**
- **The most common genotypes in cervical cancer are 16 and 18. (about 73.5% of cervical cancer in Asia)**
- **The second common genotypes are 31, 33, 45,52 and 58, with some regional/country variation.(In Thailand found 16, 18, 33, 52)**

Steps of carcinoma development & Prevention concept



Current HPV vaccines

- **Recombinant products**
- **Prophylactic vaccines**
- **DNA-free virus like particle (L1 proteins self-assemble into VLP)**
- **Genotypes specific**
  - **16 and 18**
  - **16 and18 + 6 and 11 (cause genital warts in males and females)**

Clinical trials

- **Recommendation for surrogate endpoints for HPV vaccine efficacy**
  - **CIN 2-3 + virological data are used as primary endpoint**
  - **Cancer is used as secondary endpoint**
- **NT Ab is also used for long term follow up**

Clinical trial conclusion

- **Safety and immunogenicity profile of HPV vaccine candidates appears satisfactory.**
- **None of vaccinees found CN 2-3 caused by HPV types 16 and 18**
- **Three doses administration are recommended.**
- **Target group for vaccination should be considered:**
  - **Female 15-25 years**
  - **Female 9 years and upwards**
  - **Male**

Continuing work done

- **Vaccine R&D**
  - **Cross prevention to other types**
    - **Types 31, 52** ⟷ **Type 16**
    - **Type 45** ⟷ **Type 18**
  - **Vaccine for male.**
- **Activities in a post vaccination era**
  - **Monitoring vaccine performance**
  - **Surveillance of the epidemiology of HPV and cancer**

Vaccine regulatory process

Applicants Dossier
(manufacturer or distributor)

Pre-marketing phase
Licensing/Registration= evaluation process

Post Marketing phase
Market distribution

Product Evaluation

Dossier

Quality

Safety

Efficacy

Licensing facility

Laboratory testing

GMP Compliance

Lot release

Post marketing AEFI surveillance

Regulatory inspections

Clinical trials
(Ethical review process, compliance against GLP,GMP,GCP)

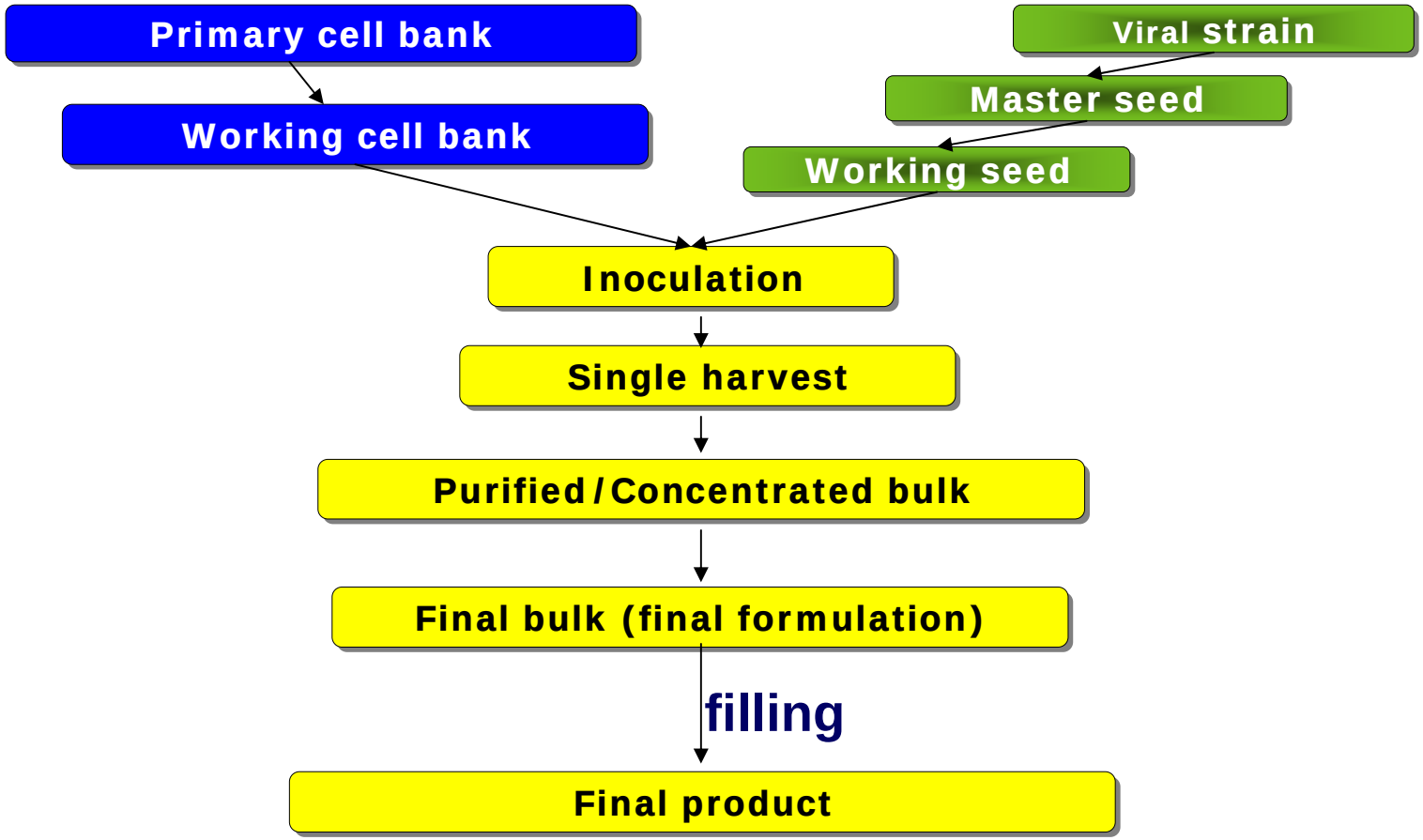
Marketing Authorization (M.A.)

Vaccine Quality assessment

- Manufacturing process & Quality control testing
- Product characterization
- Stability evaluation

To assure that the commercial lots have the consistent quality to the lots found efficacious and safe in clinical trial and maintain its quality until the expiration date.

Diagram of the production of a vaccine



Control of source materials

- **Seed lot system**
- **Cell banking system**
  - **Identity test**
    - **biochemical tests (e.g. isoenzyme analyses)**
    - **immunological tests (e.g. human leukocyte antigen, HLA assays)**
    - **cytogenetic tests (e.g. for chromosomal markers)**
    - **Tests for genetic markers (e.g. DNA fingerprinting).**
- **Control passage number (virus seed & cell)**
- **Safety**
  - **Contaminants from the source of origin (cell substrates)**
    - **Test for adventitious viruses (test for cytopathic change by baculovirus, test for haemadsorbing viruses)**
    - **Other possible adventitious agents.**
  - **Tumorigenicity of cell line**
- **Genetic stability**

Manufacturing process & QC tests & Process Validation

Sufficient information on validation to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps

- **Culturing**
- **Harvesting**
- **Inactivation**
- **Purification**
- **Formulation**

Product characterization

- **Dosage form and description:**
  - **A sterile liquid vaccine preparation which contains purified VLPs composed of the recombinant major capsid (L1) protein of one or more HPV genotypes. The VLPs may be formulated with a suitable adjuvant. The vaccines are for prophylactic use.**

Product characterization

- **Active ingredients (HPV like particle: A non-infectious and non-oncogenic, non-enveloped, icosahedral capsid particle composed of regular arrays of L1pentameric capsomers.)**
  - **Identification:**
    - **Immunological assay or by a molecular biology-based assay, e.g. hybridization or PCR can be used for each monovalent type**
    - **Potency test may be used**

Product characterization

- **Potency**
  - **Immunogenicity (Titration of Ab induced in suitable animal model)**
    - **Pseudovirion (of homologous type) neutralization assay**
    - **ELISA**
  - **Antigen content**
    - **ELISA**
    - **SDA-PAGE**
- **Impurities should be characterized and quantitated**
  - **product related impurities (variants or alteration of antigen occurring during processing or storage)**
  - **process related impurities**
  - **Media components**
  - **Cell substrate proteins or nucleic acids or process reagents which have not been removed by the purification process**
  - **Compatibility of each component if it is combined products**

Product characterization

- **Adjuvants: Test for content and degree of adsorption**
  - **Aluminium hydroxide (the content of aluminium should not be greater than 1.25 mg per single human dose)**
  - **AS04 (Aluminium hydroxide + monophosphoryl lipid A --MPL)**

Safety

- **Free from contaminants and control of chemicals**
  - **Sterility test (Bacterial, Fungi, Mycoplasma)**
  - **Test for adventitious viruses**
  - **Test for viral clearance (if Baculovirus is used)**
  - **Tests for residuals derived from the antigen expression system (host cell DNA)**
  - **Tests for agents used during purification or other phases of manufacture**
  - **Test for free from toxic substances**
    - **Abnormal toxicity (test in mice & Guinea-pigs)**
    - **Bacterial endotoxin contents**

Stability

- **The proposed shelf-life, expiry date and storage conditions should be determined on the basis of the results of real-time/ real-condition stability studies.**
- **The criteria for justification**
  - **The vaccine shall have the quality meeting all specifications until the end of expiry date**

References

- **WHO GUIDELINES TO ASSURE THE QUALITY, SAFETY AND EFFICACY OF RECOMBINANT HUMAN PAPILLOMAVIRUS VIRUS-LIKE PARTICLE VACCINES (WHO/BS/06.2050)**
- **WHO GUIDELINES ON STABILITY EVALUATION OF VACCINES (WHO/BS/06.2049)**
- **Vaccine Journal**


THANK YOU