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# Vaccine Development for Developing Countries – Regulatory Approach in the European Union

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# Regulation (EC) No 726/2004

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- **REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**
- *of 31 March 2004*
- **laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use –and–**
- **establishing a European Medicines Agency**



## Article 58 of Regulation (EC) No 726/2004

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- Allows the EMEAs Committee for Medicinal Products for Human Use (CHMP) to give scientific opinions/advice on medicinal products that are intended exclusively for markets outside of the EU
- Procedure in cooperation with the World Health Organization (WHO) only
- Key philosophy – assist developing countries
- Same data requirements, procedure and overall benefit / risk ratio as for EU medicines



## Article 58 of Regulation (EC) No 726/2004

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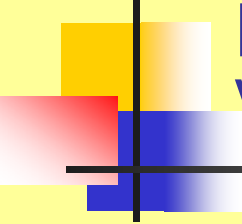
- Responds to the need of non-EU-member countries to
  - Protect public health
  - Give scientific assistance
- Allows rapid access to non-EU-member countries for important new medicinal products
- New vaccines may be licensed first in developing countries and not in the producing country
- Does not exclude future application for MA in the Community



## Guideline EMEA/CHMP/5579/04 on Article 58

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- GUIDELINE ON PROCEDURAL ASPECTS REGARDING A CHMP SCIENTIFIC OPINION IN THE CONTEXT OF COOPERATION WITH THE WORLD HEALTH ORGANISATION (WHO) FOR THE EVALUATION OF MEDICINAL PRODUCTS INTENDED EXCLUSIVELY FOR MARKETS OUTSIDE THE COMMUNITY
  - *mirrors the centralised procedure for initial assessment of the dossier*



## EMA should provide advice for vaccines/medicines of major public interest

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- Vaccines for (possible) use in the WHO Expanded Programme on Immunization (EPI)
- Vaccines for protection against a WHO public health priority disease
- Vaccines that are part of a WHO stockpile for emergency response
- Medicines for WHO target diseases such as HIV/AIDS, malaria, or tuberculosis.



# Growing Need for new vaccines in Developing Countries recognised worldwide

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- Malaria and Schistosomiasis
- Cholera and Shigellosis
- Tuberculosis
- Dengue fever
- ETEC diarrhea
- Typhoid fever

Vaccines industry faces a number of serious problems and needs supportive action by all interested parties



# Different vaccines for different reasons needed in Developing Countries

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- Combined vaccines with whole-cell pertussis
- Combined vaccines with mening. A/C component
- Combined vaccines with fewer components
- Oral Polio Vaccine and BCG Vaccine
- Multidose vaccines with thiomersal
- Monovalent Measles Vaccine





# ELIGIBILITY FOR A CHMP SCIENTIFIC OPINION

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- Evidence of the applicant or a contact point in EEA
- SPC or draft product profile
- Justification for product's eligibility
- Statement: product not intended to be marketed in the EC
- Consultation with WHO
- Decision on eligibility



## SCIENTIFIC ADVICE (SA)

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- Article 58(2) makes provision for scientific advice
  - During development
  - Before an application
  - Post opinion
- Existing procedural guidance for SA applies
  - See EMEA Website “Scientific Advice”
- Same fee applies
  - Total or partial fee exemptions may be granted



# Summary of procedural aspects (1)

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- Detailed description of procedure for submission in guideline
- Pre-Opinion inspections: GMP, GCP and GLP
- CHMP carries out a scientific assessment of applications submitted under Article 58 and adopts a scientific opinion
- No marketing authorisation granted in Europe (i.e., No Commission Decision according to article 10)
- A summary of opinion is published at the time of adoption of the opinion



## Summary of procedural aspects (2)

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- Evaluation procedure is an EMEA/WHO partnership
- Opinion adopted after consultation with the WHO
- Observers/experts from WHO and authorities of developing countries may attend CHMP meetings
  - Provided they complete and sign DoI and Confidentiality Undertaking form
- Experts and observers have no voting rights



## Summary of procedural aspects (3)

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- For all positive opinions adopted under Article 58 the EMEA prepares and publishes a European Public Assessment Report (EPAR)
  - EPAR reflects the scientific conclusions on the Quality, Efficacy and Safety reached at the end of the evaluation process
  - Post-opinion follow-up measures are included in the EPAR



# Summary of procedural aspects (4)

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- Steps following the CHMP Scientific Opinion
  - Updating the CHMP scientific opinion
  - Pharmacovigilance
  - Batch control
  - Product defects
  - Product recalls



Most countries of the industrialized world have established competent national control authorities

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- European Medicines Agency (EMA), EU/London
- Center for Biologics Evaluation and Research (CBER), FDA/USA
- Paul-Ehrlich-Institut (PEI), Germany
- Medicines and Healthcare products Regulatory Agency (MHRA), UK

**NCA's take very efficiently care for Regulation and Testing of Vaccines**

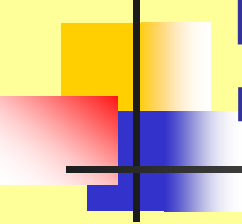


## Many developing countries have still not established competent national control authorities for vaccines

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- WHO and EC should consider increasing funding for capacity building of national drug regulatory authorities
  - autonomous decisions on product registration are desirable
- A careful dialogue is needed with the target users of the Article 58 mechanism
- EU awareness of specific problems due to differences between the EU and developing countries

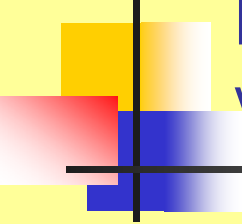




## Most developing countries have still no domestic vaccine manufacturing capability

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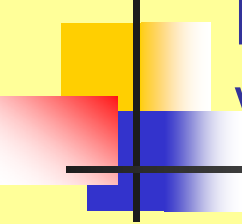
- Research, development work, manufacturing and clinical trials primarily in industrialised nations
- The vast majority of Vaccine Doses are produced in Europe, according to EVM:
  - About 90% of the production from Europe
  - About 10% from North America
  - Less than 1% from rest of the world
- Existing production sites in non-EU-countries should be maintained and improved, e.g. in India, Brazil, Indonesia and Cuba



## First application for a scientific opinion for a combo vaccine ends with withdrawal (1)

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- 2007, a European vaccine manufacturer submitted the first application file to the EMEA under Article 58
- Combined vaccine against diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b, *Neisseria meningitidis* serogroups A and C
- Indication: primary immunisation of infants in the first year of life and booster immunisation of young children during the second year of life
- Vaccine was to be used exclusively in markets outside the EU, primarily in Sub-Saharan Africa



## First application for a scientific opinion for a combo vaccine ends with withdrawal (2)

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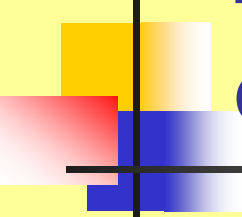
- In October 2007 applicant withdrew application
- Reasoning: Combo does not fit with the current WHO vaccination strategy, i.e.
  - to built upon existing EPI vaccination schedule + monovalent meningitis A mass vaccination in children older than one year
- At the time of withdrawal CHMP had in addition a few concerns



## Successful applications for a scientific opinion

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- For all positive opinions adopted under Article 58 the EMEA prepares and publishes a European Public Assessment Report (EPAR), which reflects the scientific conclusions reached at the end of the evaluation process
  - **Aluvia** *Common name: lopinavir / ritonavir* Rev. 2  
29/11/07
  - **Lamivudine GSK** *Common name: Lamivudine GSK* Rev. 4  
18/03/08
  - **Lamivudine/Zidovudine GSK** *Common name:  
Lamivudine/zidovudine GSK* Rev. 3  
18/03/08
- Indicated for the treatment of HIV-1 infected adults and children in combination with other antiretroviral agents

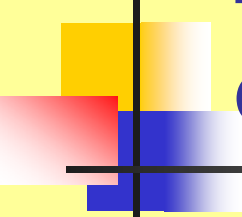


# The Role of the CHMP in Vaccine MA Procedures

## Centrally Authorised Vaccines (1)

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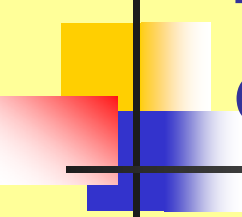
| <b><i>Vaccine</i></b> | <b><i>INN</i></b>   | <b><i>MAH</i></b>                 |
|-----------------------|---|-----------------------------------|
| <b>Ambirix</b>        | Inactivated hepatitis A virus, hepatitis B surface antigen    | GlaxoSmithKline Biologicals       |
| <b>Cervarix</b>       | Human Papillomavirus Vaccine Types 16&18 recombinant          | GlaxoSmithKline Biologicals       |
| <b>Daronrix</b>       | A/ Vietnam/1194/2004 (H5N1) flu whole virus (inactivated)     | GlaxoSmithKline Biologicals       |
| <b>Dukoral</b>        | Vibrio cholerae and recombinant cholera toxin B-subunit       | SBL Vaccin AB                     |
| <b>Fendrix</b>        | Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed)             | GlaxoSmithKline Biologicals       |
| <b>Focetria</b>       | Flu virus surface antigens strain A/ Vietnam/1194/2004 (H5N1) | Novartis Vaccines and Diagnostics |
| <b>Gardasil</b>       | Human papillomavirus vaccine (Types 6,11,16,18) rec. adsorbed | Sanofi Pasteur MSD                |
| <b>HBVAXPRO</b>       | Hepatitis B surface antigen (HbsAg) + Hib                     | Sanofi Pasteur MSD                |



## The Role of the CHMP in Vaccine MA Procedures Centrally Authorised Vaccines (2)

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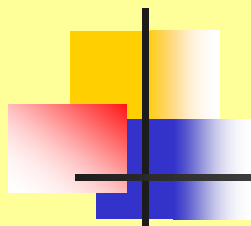
| <b><i>Vaccine</i></b> | <b><i>INN</i></b>   | <b><i>MAH</i></b>                  |
|-----------------------|---|------------------------------------|
| <b>Infanrix hexa</b>  | <b>Comb. vaccine (DTPa-HBV-IPV-HIB vaccine)</b>   | <b>GlaxoSmithKlineBiologicals</b>  |
| <b>Infanrix penta</b> | <b>Comb. vaccine (DTPa-HBV-IPV vaccine)</b>   | <b>GlaxoSmithKline Biologicals</b> |
| <b>MMR-VaxPro</b>     | <b>Measles, mumps and rubella vaccine (live)</b>  | <b>Sanofi Pasteur MSD</b>          |
| <b>Prevenar</b>       | <b>Pneumococcal conjugate vaccine</b>   | <b>Wyeth-Lederle Vaccines S.A.</b> |
| <b>Procomvax</b>      | <b>Haemophilus b conjugated and hepatitis B vaccine</b>                                   | <b>Sanofi Pasteur MSD</b>          |
| <b>Proquad</b>        | <b>Measles, mumps, rubella and varicella vaccine (live)</b>                               | <b>Sanofi Pasteur MSD</b>          |
| <b>Quintanrix</b>     | <b>Comb. Vaccine (DTPw-HBV(rDNA) and Haemophilus type b conjugate vaccine (adsorbed))</b> | <b>GlaxoSmithKline Biologicals</b> |



## The Role of the CHMP in Vaccine MA Procedures Centrally Authorised Vaccines (3)

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| <b><i>Vaccine</i></b>     | <b><i>INN</i></b>  | <b><i>MAH</i></b>           |
|---------------------------|--|-----------------------------|
| <b>Rotarix</b>            | Human rotavirus, live attenuated                               | GlaxoSmithKline Biologicals |
| <b>Rotateq</b>            | Rotavirus vaccine, live, oral                                  | Sanofi Pasteur MSD          |
| <b>Silgard</b>            | Human papillomavirus vaccine (Types 6,11,16,18), rec. adsorbed | Merck, Sharp & Dohme        |
| <b>Tritanrix-HepB</b>     | Comb. vaccine (DTPw-HBV vaccine)                               | GlaxoSmithKline Biologicals |
| <b>Twinrix adult</b>      | Comb. Hep A and B vaccine                                      | GlaxoSmithKline Biologicals |
| <b>Twinrix paediatric</b> | Comb. Hep A and B vaccine                                      | GlaxoSmithKline Biologicals |
| <b>Zostavax</b>           | Zoster vaccine (live)  | Sanofi Pasteur MSD          |



Thank you for your attention

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