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

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Regulation (EC) No 726/2004

- **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

- 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

- 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

- 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*

EMEA should provide advice for vaccines/medicines of major public interest

- 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

- 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

- 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

- 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)

- 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)

- 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)

- 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)

- 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)

- 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

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

NCAs take very efficiently care for Regulation and Testing of Vaccines

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

- 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

- 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)

- 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)

- 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

- 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)

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

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

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

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

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

Thank you for your attention

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