Overview of the Regulatory Environment for Developing New Vaccines Including the Specific Smallpox Vaccine and Pandemic Influenza Virus Vaccines.

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1 List of Abbreviations

BWP	Biotechnology Working Party
CBER	Center of Biologics Evaluation and Research
CDC	Centre for Disease Control
CEFs	Chick Embryo Fibroblast Cells
CFR	Code of Federal Regulations
CHMP/CPMP	Committee for Medicinal Products for Human Use, the former 'Committee for Proprietary Medicinal Products'
CMC	Chemistry, Manufacturing and Control
CP	Centralized Procedure
DNA	Deoxyribonucleic Acid
EASAC	European Academies Science Advisory Council
EDQM	European Directorate for the Quality of Medicines
EMEA	European Agency for the Evaluation of Medicinal Products
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HHS	Department of Health and Human Service, USA
HIV	Human Immunodeficiency Virus
IASG	MVA Interagency Study Group
ICH	International Conference on Harmonization
IND	Investigational New Drug
MA	Marketing Authorization
MVA	Modified Vaccinia Ankara
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health, USA
NOAEL	No Observed Adverse Effect Level
OMCL	Official Medicines Control Laboratories
Ph.Eur	European Pharmacopoeia
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SPF	Specific Pathogen Free
VAMF	Vaccine Antigen Master File
VWP	Vaccine Working Party
WHO	World Health Organization

2 Preface

The purpose of a vaccine is to induce a specific and active immunity against an infecting agent and to create a memory within the immune system so that exposure to the active disease agent will stimulate an already primed immune system to fight the disease. Hence, all approaches to vaccine development focus on the immune system and the body's natural defences against foreign invaders. In most cases, vaccines are administered prophylactically. Vaccines are therefore generally administered to healthy individuals, including small children. Examples of standard childhood vaccines include Diphtheria, Tetanus, and Acellular Pertussis, Inactivated Polio Vaccine, Haemophilus influenzae type b, Hepatitis B, and Measles, Mumps, and Rubella. Vaccines may also be administered to individuals who have been exposed to a particular infectious agent, in an attempt to prevent the individual from developing the disease. Other vaccines may be administered to alter the course of a non-infectious disease, such as Bacillus Calmette Guerin for the treatment of bladder cancer and are therefore often used as therapeutic vaccines.

Vaccines are biologics, their basic components begin as living material. Vaccines for human use may contain chemical or physically inactivated organisms that maintain adequate immunogenic properties, living organism that are naturally avirulent or that have been treated to attenuate their virulence whilst retaining immunogenic properties or antigens extracted from organisms secreted by them or produced by recombinant DNA technology. Bacterial vaccines contain living or inactivated bacteria whereas bacterial toxoids are prepared from toxins by diminishing their toxicity to a non-detectable level or by completely eliminating it by physical or chemical procedures whilst remaining adequate immunogenic properties. Viral vaccines are prepared from viruses grown in animals, fertilised eggs or in suitable cell cultures or tissues.

Infectious diseases pose a major threat in the world. Therefore vaccines have and will have also in the future a very considerable impact on public health. The European Academies Science Advisory Council (EASAC) stressed the importance of a co-ordinated, EU-wide response (EASC 2006). This is reflected in the fact that with effect from 20 May 2008 medicinal products for viral diseases and for human use containing new active substance are mandatory for the centralised procedure.

The European Pharmacopoeia (Ph.Eur) established 1964 by the eight founder countries of the European Directorate for the Quality of Medicines (EDQM) comprises beside the monographs of drugs of chemical origin and special forms thereof and chapters concerning methods of analysis, materials and containers, reagents and dosage forms, several vaccine monographs. A general monograph concerning vaccines for human use contains information about production, test, storage and labelling. The special monographs give detailed advice for specific vaccines like cholera, diphtheria, haemophilus, influenza, measles and smallpox. The purpose of the established European Pharmacopoeia (Ph.Eur) is to promote public health by the provision of recognised common standards for use by health-care professionals and others concerned with the quality of medicines. Such standards are to be of appropriate quality as a basis for the safe use of medicines by patients and consumers.

Beside these special monographs for vaccines in the Ph.Eur. which are not discussed in the following, several guidelines covering quality, preclinical and clinical development for new vaccines has been issued by the European Agency for the Evaluation of Medicinal

Products (EMEA) as well as by the US Food and Drug administration (FDA). The Ph.Eur in addition gives a good clue what is essential during development of a new but comparable vaccine which is not described in a monograph.

In the following the major guidelines released by the EMEA and the FDA for the development of new vaccines concerning manufacturing, non-clinical and clinical evaluation, special approval forms and pharmacovigilance will be discussed. No national guidelines from different member states of the EU will be considered for the reasons mentioned above. If a vaccine will be developed for world wide marketing, and that will be the case for most vaccines due to low return on investment, manufacturer must use the most stringent common denominator of EU and FDA requirements. Therefore a strict separation of the guideline recommendations makes no sense.

Special guidelines exist for the development of influenza vaccine and vaccines against rare or eliminated diseases like Anthrax or smallpox. Pandemic influenza virus as well as bioterrorism agents like the smallpox virus cause both diseases which should be treated as fast as possible. The EMEA as well as the FDA have reacted by streamlining some of the guidelines and procedures in order to shorten the normal approval process. Two chapters describe the particularities in developing a vaccine against an eradicated organism (smallpox) and a vaccine where the pathogenic organism is not present at the moment (pandemic influenza vaccine).

Combined vaccines, recombinant vaccines as well as therapeutic vaccines where again special characteristics have to be considered will not be addressed in this thesis. Nevertheless, all guidelines mentioned apply to these vaccines, too. For therapeutic vaccines that are often in addition biotech derived or gene transfer products and recombinant vaccines (these are so called “advanced therapy medicinal products” as described in Annex I of Commission Directive 2003/63/EC), the following additional guidelines have to be considered: ICH Topics Q5A-Q5E, Quality of biotechnological products (viral safety, stability, cell banking, comparability etc.); Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products, CPMP/BWP/3088/99, Points to consider on the manufacture and quality control of human somatic cell therapy medicinal products CPMP/BWP/41450/98; Note for guidance on specifications, CPMP/ICH/365/96(ICH Q6B)).

3 Manufacturing of New Vaccines (Quality)

3.1 Introduction

The most important aspect during manufacturing development of vaccines is the comparability of the test material during a development program. Parts of the toxicology program as well as the formulations for different phases of clinical trials are often performed with charges produced by different manufacturing processes due to the proceeding development from laboratory to final manufacturing processes and in order to improve product quality and yields. Therefore the comparability should be demonstrated when a modified manufacturing process or other significant changes in the product or formulation are made. Comparability can be evaluated on the basis of biochemical and biological characterization (i.e., identity, purity, stability, and potency). However, sometimes an effect on efficacy and/or safety can be expected or cannot be ruled out. Then the need for preclinical and/or clinical testing should be reconsidered (pharmacokinetics, pharmacodynamics and/or safety).

In general a discussion of any differences in formulation, manufacturing process, or site between the clinical trial materials and commercial production batches of drug substances and drug product should be done. Differences should be completely described. The FDA CMC guideline recommended also a detailed description of the water system, computer systems, and the possibility of cross contamination.

The “Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning medicinal products in clinical trials” should be followed as well as the “Guideline on pharmaceutical aspects of the product information for human vaccines”. In addition the standards and principles contained in the “Guide to good manufacturing, practice for medicinal products of the pharmaceutical inspection convention” (PIC) intended to serve as a reference for the preparation of information on manufacturing practice. The “Guideline on the scientific data requirements for a Vaccine Antigen Masterfile (VAMF)” describes the procedure and briefly only in headings the content of the VAMF. The “Guideline on pharmaceutical aspects of the product information for human vaccines” provides guidance on the content of the SmPC. The CMC requirements for vaccines in the USA are described in a special guideline (Guidance for Industry: Content and format of chemistry, manufacturing and controls Information and establishment description information for a vaccine or related product. CBER, 1999).
If the vaccine is a gene transfer medicinal product the “Note for guidance on the quality, preclinical aspects for gene transfer medicinal products” is also of relevance.
In addition all ICH guidelines dealing with pharmaceutical development should be considered. These guidelines are not described in detail here e.g. M4: CTD for the registration of pharmaceuticals for human use; Q1A-1F: Stability testing guidelines; Q6 A/B: Specification guidelines; Q7A: GMP guidance; Q8: Pharmaceutical development.
The European Pharmacopoeia should also be considered if applicable in case of specific vaccines as well as the general aspects documented in the chapter Vaccines for Human Use.

3.2 Specific Regulatory Documents

In addition to the ICH guidances related to CMC topics, the Ph.Eur. and the PIC recommendations the following guidelines are of special importance:

Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning medicinal products in clinical trials, CHMP/QWP/185401/2004

Guideline on pharmaceutical aspects of the product information for human vaccines. EMEA/CPMP/BWP/2758/02

Note for guidance on biotechnology/biological products subject to changes in their manufacturing process, CPMP/ICH/5721/03, 2004

Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance, CPMP/3087/02

Guideline on the scientific data requirements for a vaccine antigen master file (VAMF). EMEA/CPMP/BWP/3734/03

Concept paper on the development of a guideline on viral safety evaluation of biotechnological products to be used in clinical trial. EMEA/CHMP/BWP/124447/2004

Guidance for Industry: Content and format of chemistry, manufacturing and controls Information and establishment description information for a vaccine or related product. CBER, 1999

3.3 Chemistry, Manufacturing and Controls

The quality control of vaccines relied on the control of the starting material, the control and validation of the production process, demonstration of consistency of production and the control of the final product. When a marketing authorization is obtained an independent lot release by national authorities guarantees the manufacturer's performance. These tests are conducted in the EU by Official Medicines Control Laboratories (OMCLs). The activities of the OMCLs are coordinated by the European Pharmacopoeia Secretariat, the European Directorate for Quality of Medicines (EDQM) which also has the responsibility for developing binding vaccine monographs to ensure appropriate quality control and quality assurance for pharmaceutical products.

Vaccines are produced using a seed lot system where successive batches of a product are derived from the same master seed lot. The strain of bacterium or viruses used in the master seed lot must be appropriate identified including the origin of the strain and its subsequent manipulations. For routine production, a working seed lot may be prepared from the master seed lot. It is recommended that in the production of the final lot of vaccine, the number of virus, or the number of subcultures of a bacterium, from the master seed lot shall not exceed that used for production of the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy (Ph.Eur).

The production system of a vaccine itself consists of several steps which should be adequately monitored. The different topics are described briefly as follows (CBER, Compliance Program Guidance Manual, Chapter – 45 Biological Drug Products):

Cell Culture: Includes inoculation of the initial vessel with the adequately characterized starting materials and scale up. Characterization of the cell substrates includes genealogy, genetic markers, tumorigenicity, viability during storage, growth characteristics at passage levels, absence of contamination with other cell lines, for diploid cells the demonstration of diploidy, and the absence of detectable contaminates. If cell cultures are derived from eggs they must be produced by chicken flocks free from specified pathogens (SPF). Recommendations for quality control of SPF flocks and cell substrates (diploid cell lines, continuous cell lines) are given in the Ph.Eur.

Disruption and Harvest: Disruption (when appropriate) and harvesting of the product is performed using chemical, physical, or enzymatic means. All process parameters should be specified and documented in the batch production records.

Adventitious Agent Removal: For products derived from cells of human or animal origin, viral removal must be performed in accordance with the process described in the approved license application. In some manufacturing operations there may be a specific viral removal step. In other operations, viral removal may be accomplished by a step or series of steps in the manufacturing process, which are not specifically considered to be for viral removal, e.g., chromatography.

Purification: Purification of vaccine bulks may include one or more of the following methods:
Column or batch chromatography, Centrifugation, Filtration, Precipitation followed by filtration or centrifugation.

Adsorption: Adsorption is the process of adding an aluminum adjuvant to a vaccine antigen in order to increase its immunogenicity. Aluminum adjuvants of various formulations are used in vaccine production. The vaccine manufacturer should specify the quality attributes of the adjuvant, including percent purity, particle size, and protein binding capacity. Quality attributes are generally specified on Certificates of Analysis (COA) provided by the adjuvant manufacturer. Batch records must specify the type of adjuvant used. Aluminum adsorption may be performed on intermediates, bulks, or both. Two general procedures are used for aluminum adsorption: (1) addition of pre-formed aluminum adjuvant to vaccine antigens, and (2) on-site formulation of an aluminum adjuvant. For some vaccines, conditions for binding the aluminum adjuvant to the antigen may be known, and specifications will be established for this process. However, for many products, the scientific mechanism for binding the aluminum adjuvant to the antigen has not been determined, and therefore, no binding specifications will be established. The extent of adsorption of an aluminum adjuvant to an antigen may be affected by production process parameters such as pH, phosphate concentration, and adequate mixing. These adsorption process parameters should be specified by the manufacture, in order to promote consistency in manufacturing. Products containing aluminum adjuvant are formulated aseptically because once they are alum adsorbed they cannot be sterile-filtered.

Inactivation: If the active ingredient of the vaccine is a killed or inactivated version of a live bacteria or virus, the methods for inactivation will have been established by the manufacturer and reviewed during product approval. Either heat or chemical treatment

may be used for inactivation. All process parameters should be monitored and appropriate testing performed to demonstrate inactivation. Appropriate containment procedures should be established for the agent being inactivated.
If the active ingredient of the vaccine is a bacterial toxin, methods of toxin inactivation will also have been established by the manufacturer and reviewed during product approval. Treatment with formaldehyde is an example of toxin inactivation. All process parameters should be monitored, and appropriate testing performed to demonstrate inactivation of the toxin.

Conjugation: The chemical linkage of a polysaccharide immunogens to a carrier protein generally forms conjugate vaccines. Polysaccharide immunogens are extracted from bacterial cells. Carrier proteins are usually derived from bacterial cells that are different from those used to produce the polysaccharide. The polysaccharide immunogens and the carrier proteins are purified using a variety of methods including; centrifugation, buffer exchange, diafiltration, and chromatography. The purification process should be monitored through in process testing in order to assure the purity of the polysaccharide and carrier protein, and to assure removal of product and process related impurities. Specifications for in-process testing should be specified and results documented in the batch production records.
After purification of the polysaccharide and carrier protein, a chemical reaction(s) is (are) used to covalently link the two molecules together. The reaction should be monitored in order to determine completion of the conjugation reaction, amount of impurities, yield, and purity of the final conjugate product. Additional purification steps may be employed to remove excess reagents and reaction by-products. In addition, post-purification steps may be performed to produce a stabilized conjugate.

Endotoxin Levels: Some bacterial vaccines are manufactured from gram-negative organisms, which produce endotoxin. In these types of vaccines, the endotoxin is often the immunizing agent of interest, and the manufacturer will have defined specifications for endotoxin levels in the final product. The production and testing records should be routinely reviewed to assure that the final product meets the pre-defined endotoxin specifications.

Finished Products: For vaccines and related products, the biological drug substance may be diluted, adsorbed with adjuvant, mixed with stabilizers, mixed with preservative, and/or lyophilized to become the final finished product. In addition, more than one vaccine can be formulated together to produce a combination vaccine product. There are several different final container/ closure systems for vaccine products. Examples include capsules (blister packed), sachets, oral solutions, sealed glass ampules, single-dose syringes, single-dose and multi-dose vials (solutions or lyophilized), and multiple puncture devices pre-loaded with antigen.

Cross-contamination is a significant concern in facilities that manufacture more than one product. There are specific regulatory requirements aimed at preventing cross-contamination with regard to spore-forming organisms and live vaccines. The regulations, found in 21 CFR 600.10 and 600.11, require that personnel, buildings, and equipment used for processing spore-forming organisms and live vaccines be isolated from other processes, so as to prevent contamination and cross-contamination.

3.3.1 Drug Substance

In general the description requirements of vaccines concerning drug substance and drug product are similar to other drugs. Therefore only additional features will be mentioned here which based basically on the FDA CMC vaccine guideline and the Ph.Eur. The Ph.Eur. gives general advice in a general monograph for developing vaccines and detailed advice for special vaccines in the named monographs. In the Vaccine antigen master file (VAMF) guideline the requirements for the CMC part of vaccines are described only rudimentarily.

The description of the drug substance should in detail include the source of the cells, the active component and a list of any inactive substance which might be present.

The characterization of the drug substance should also include a physicochemical characterization concerning amino acids, sequencing, peptide mapping etc. as well as a biological activity testing (Western blot, ELISA, cytometric analysis, neutralization assays etc.). The drug substance specification section includes in addition to identity, purity, the potency, physiochemical measurements which predict potency and stability.

The manufacturer section should include a Floor diagram, which should be sufficiently clear to enable visualisation of the production flow and to identify adjacent operations that may influence the production. Also information about other products manufactured in the same area used to produce the drug substance should be provided. This includes a detailed description of the type and development status of the other products and indicates the area into these products will be introduced. In addition a description of the equipment used for both and information about the cleaning procedure should be provided as well as all precautions taken to prevent contamination or cross-contamination (air classification, control procedures, general equipment design etc.). The narrative text should provide information about personnel, equipment, waste and air flow.

The method of manufacture includes in addition to the description of the raw material and flow charts of manufacturing process a detailed description of the animal sources, virus sources, cellular sources, microbial cells, animal cells, genetic constructs and recombinant cell lines, cell bank system with master cell bank and working cell bank, cell growth and harvesting, purification and downstream processing, inactivation (if appropriate), stability processing and detoxification in case of toxoid or toxoid-containing vaccines. If animal cells are used, adventitious agent testing and other in vivo and in vitro assays conducted to assess product safety should be described.

The requirements for viral safety of products derived from cell lines of human or animal origins is described in ICH Q5A for marketing authorization. The requirements for the products for clinical trials are described in the concept paper mentioned above. The criteria for the design of viral safety evaluation includes the nature of the cell line and its history, use or non-use of raw material of human or animal origin, exposure to adventitious contamination, prior data on viral inactivation or removal steps and published data.

In the process control section all in-process controls including sampling procedure should be described in detail. The process validation report should document the variability in each process (propagation, virus harvest, inactivation, purification, and microbiology) as it relates to final specification and quality.

The manufacturing consistency for each vaccine should be demonstrated by manufacturing of at least three, preferably consecutive batches of drug substances. A description of the preparation, characterization and stability of primary and working reference standards should be provided. The release testing with results for each batch should be submitted.

For each intermediates during the production of vaccines a period of validity applicable for the intended storage conditions must be established.

3.3.2 Drug Product

This section should contains information on the final drug product including all drug substances and exipients, manufacturing details, release testing and so on similar to the data presented in the drug substance part. The information provided for an IND in the USA should include certificates of analysis, results of analytical testing for raw material as well as for the final product.
The release and stability protocol provides data concerning potency, moisture if the product is lyophilised, pH, sterility and control of bioburden, viability of the cells if frozen and thawed, pyrogenicity and general safety.
An environmental assessment should address all the components involved in the manufacture and disposal of the product.

4 Pre-clinical Evaluation of New Vaccines

4.1 Introduction

The Pre-clinical testing as product characterisation provides the proof of concept and shows the immunogenicity and safety in animals prior to clinical testing in humans. The aim of the non-clinical regulations and guidances is to protect clinical trial participants and vaccinees from potential adverse effects. Potential safety concern associated with vaccines include general systemic toxicity, enhancement of the intended disease, induction or local toxicity, pyrogenicity, adverse immunological effects such as autoimmunity or sensitisation, and in some cases teratogenic/reproductive effects. The availability of neurological events should be considered.
The biological activity together with species specificity of many vaccines often preclude standard toxicity testing designs in commonly used species like rats and dogs. In general it exists not always a suitable animal model. And the animal model itself varies depending on the tested vaccine. Therefore a general recommendation in the guideline is not given. The selection of the animal species should be made on a case by case basis and scientifically justified. The route of administration should be as close as possible to the proposed clinical route. If this is for practical reasons not possible, another route could be used but this should be justified, too.
The non-clinical Lot(s) used in toxicity study should be in compliance with GMP and ideally the same lot as used in clinical study. If this is not feasible, then the preclinical batch should be comparable to the clinical material with respect to physico-chemical data, stability, formulation, etc and the lot release protocol. The need for preclinical testing should be reconsidered when a change in the manufacture during the development of the vaccine from laboratory to final manufacturing process is being made.
Attention should be paid to additives including adjuvants, preservatives, and excipients.

Performing pre-clinical safety testing on material that is not sufficiently well characterized may result in invalid studies.

4.2 Specific Regulatory Documents

In addition to the ICH Note for guidances M3(M) and other ICH guidances (e.g. ICH S6 (pre-clinical safety evaluation of Biotechnology-derived pharmaceuticals), S5a) related to pre-clinical development several guidances for vaccines or subclasses of vaccines has been issued. These guidances focus on the development of new vaccines whose antigen is not yet described in the European Pharmacopoeia monographs or in WHO requirements.

“Note for guidance on preclinical pharmacological and toxicological testing of vaccines. CPMP/SWP/465/95”
This Note for guidance does not describe test procedure for the yearly update of influenza virus. For this type a particular guideline exists (see above). Also DNA-vaccines, gene therapy or genetically altered somatic cell therapy are not addressed.

“Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications. (FDA, CBER, 2006)”

"Concept paper on the development of a committee for proprietary medicinal Product (CPMP), Note for guidance on requirements for the evaluation of new adjuvants in vaccines"

"Note for guidance on the development of vaccinia based vaccines against smallpox. CPMP/1100/02"

WHO Guidelines on Non-clinical Evaluation of Vaccines (TRS 927, 2005)

4.3 Animal Studies for Pre-clinical Documentation

4.3.1 Pharmacodynamics (Immunogenicity and Protection)

The evaluation of the immune function should involve the proof of concept, immunological characteristics and interactions between vaccine components. The choice of the appropriate animal model should be done with respect to the antigen-protective response. The endpoint in the study should be the protection against a challenge from the pathogenic organism. The model should reflect the infections in humans. The quantification of the immunological response only, is in most cases not a sufficient indication of protection. In addition the formation of neutralizing antibodies, immune complex formation, interactions with immune cells and the release of other molecules that affect the immune system should be investigated. Immunogenicity studies should also assess the humoral and cell-mediated immune response and the duration of response.
Also interactions with other vaccines that could be probably given at the same time should be evaluated.
The limitations of animal studies are that the pathogenesis and immune response is often species specific and that safety concerns identified during animal testing may not necessarily indicate a problem in humans.

4.3.2 Secondary Pharmacodynamics (Safety Pharmacology)

The evaluation of potential undesirable effects of the vaccine on the circulatory and respiratory system as well as on CNS parameters might be incorporated in toxicity studies. In general repeat dose toxicity studies reveal the effects better than a single administration.

4.3.3 Pharmacokinetics

Pharmacokinetic studies are normally not needed. However, they should be considered in case of new formulations, novel adjuvants or when alternative routes of administration are intended to be used.
Distribution studies are highly recommended for nucleic-acid and some virus-vector based vaccines (non GLP). The most sensitive method to detect the virus in a variety of tissues (injection site muscle and skin, lymphatic tissues, other highly perfused organs, body fluids, reproductive tissues etc) should be used. If the vaccine signal persists in tissues then integration studies should be performed.

4.3.4 Single Dose Toxicity

Single dose toxicity should be performed in at least one animal species with adequate safety margin in relation to the human dose. If toxic findings are seen, the dose relationship should be further characterized. The data could be collected as part of animal immunogenicity or safety pharmacology studies.

4.3.5 Repeat Dose Toxicity

A study on repeat dose toxicity should be performed if multiple doses in clinical settings will be used (but also for single dose appropriate). Normally one animal species is sufficient. For vaccines, repeat dose toxicity is not the same as chronic or sub-chronic dosing of drugs. Dose and regimen should reflect the intended clinical use with the inclusion of one additional dose beyond that proposed clinically. In addition the time schedule can be compressed. Safety pharmacology endpoints can be included as well as immunogenicity data.

The following points should be considered on a case by case basis:

- immunological aspects of toxicity (complexes with host immunoglobulins, release of immunofunctional molecules (cytokines) affecting functions of the immune system.
- Hypersensitivity reactions, induced by the antigen itself, degradation products, additives etc.
- In rare cases: induction of antibodies that can cross react with human tissue

4.3.5.1 Protocol Design for Repeat Dose and Local Toxicity

Some general recommendations are (according to the guidelines and Chang et al. (NIAID/NIH):

- The choice of the animal model should be appropriate for the product and clinical indication. Often rabbits are used for parenteral vaccines because their muscle mass can receive a volume equivalent to a full human clinical dose (e.g. 0.5-1 mL)
- The high dose should be 1-10 times the actual highest planned clinical dose not scaled on weight or body area.
- To determine the NOAEL and potential dose-related toxicity, 2 or 3 concentrations in addition to a vehicle or adjuvant control should be used. At a minimum, the highest proposed human does should be tested.
- Treatment number should be the proposed clinical inoculations plus one.
- The period of the study varies depending on the frequency of dose administration to the proposed clinical dosing schedule. Tissue samples should be processed and data analyzed after intermediate and terminal sacrifice.
- The time point for sacrifice is 1-3 days post-last inoculation and 2-4 weeks post-last inoculation for the recovery period.
- The minimum number of animal per gender is 5 per dose for each time point of sacrifice.
- The same route of administration as proposed for clinical use should be used.
- The minimal endpoints examined should include:
    - Clinical observations (daily)

- Physical examinations (weekly)
- Evaluation of injection site(s) for irritation and histopathology
- body weights (weekly)
- Food and water consumption, body temperatures (daily in week following inoculations)
- Ophthalmologic observations
- Clinical pathology at regular intervals for haematology, serum chemistry, serology, urinalysis measurements (not possible for mice)
- Gross observations and organ weights at necropsy
- Histopathology evaluation to include a select tissue list, especially the immune function organs (e.g., lymph nodes), other highly perfused organs, and the genital organs in the control and high-dose animals and target tissues in the remaining groups. Depending on the route of inoculation, additional organs may need to be examined. (Full tissue collection and preservation should be performed even when only a select list are examined histopathologically),
- Relevant immunogenicity (Humoral and CMI) studies.

Additional endpoints may be included to address therapeutic-specific concerns.

4.3.6 Reproductive Functions

In the ICH guideline S5a reproductive toxicology studies are described. The aim of reproduction toxicology studies is to reveal any effect of the active substance on mammalian reproduction. This guideline is valid for all medicinal products and should therefore also be followed for vaccine development. Three kinds of studies are described in detail: Pre- and postnatal development, Embryo-foetal development in two species and Fertility and Early Embryonic Development.

Since in most cases vaccination occurs during childhood, embryo/foetal and perinatal toxicity studies are not necessary. The integrity of the reproductive organs could be evaluated in histopathology examinations in toxicity studies.
Is the vaccine intended for use in women of childbearing potential or during pregnancy or is the vaccine for general emergency use also in adults such studies become necessary.

A new guidance for industry (FDA) was issued in February 2006 concerning development toxicity potential of vaccines for infectious diseases indicated for females of childbearing potential and pregnant women. Hereafter the timing of these toxicology studies depends on the target group. For maternal immunization it is recommended that the data from non-clinical development studies are available prior to the initiation of a clinical study enrolling pregnant women. For females of childbearing potential these data could be included in the initial MA submission, if it is ensured that during clinical studies appropriate precautions are taken to avoid vaccination during pregnancy (pregnancy testing and use of birth control). Currently, including of males in clinical trials is possible without recommendations for male fertility studies.

4.3.6.1 Design of Developmental Toxicity Studies

In the following only the particulars of development toxicities studies for vaccines described in the FDA guidance are mentioned. In general one should keep in mind that lack of adverse events in animal studies not necessarily implies absence of risk in humans. This is because of species-specific differences in the immune response, different developmental time lines, and differences in placentation.
The vaccine formulation should be the same lot proposed for clinical trial that enrolled pregnant women. The formulation should be a final formulation in order to avoid duplication of this study due to formulation changes during development. That means on the other hand that such development studies take place at a later stage of formulation development and that phase I and II trials are conducted in non-pregnant subjects. The FDA guideline specifies the development studies for vaccines: Concerning the animal model it is recommended that the species of choice is able to develop an immune response to the vaccine antigen, even though may be quantitative and qualitative differences in immune responses. In addition it must be verified that the fetus is exposed to maternal antibodies. In most cases it is sufficient to conduct development toxicity studies only in one species. The number of animals per group should at least 40. These animals can be further allocated to the Caesarean and littering subgroup using 20 animals each. The guideline recommended that the female be exposed to the vaccine during the interval from implantation through closure of the hard palate and also at later stages of pregnancy. The offspring should be followed to weaning and observed for normal growth and development. The dose administered should be when possible the maximum human dose regardless of body weight. Timing and number of doses will depend on the onset and duration of the immune response of the vaccine. Because daily dosing could potentially induce immune tolerance the guideline recommends episodic dosing and in particular cases also administration several days prior mating. Control groups could be placebo, other components of the vaccines like adjuvants, exipients or preservatives. The endpoints are in general the same as those recommended in the ICH S5A document. In addition immunological endpoints should be considered e.g. exposure of the embryo/foetus to maternal antibodies.

4.3.7 Genotoxicity and Carcinogenicity

Genotoxicity and carcinogenicity studies are normally not needed. Damage of DNA in form of gene mutations, larger scale chromosomal damage or genotoxic events caused by interactions with non-DNA targets (spindle apparatus of cell division leading to aneuploidy, topoisomerase inhibition, inhibition of DNA synthesis etc.) are unlikely since vaccines consist of proteins and/or DNA/RNA. In case for concerns about the product, for example when an organic linker is introduced, those studies become relevant.

4.3.8 Local Tolerance

Local tolerance should be evaluated in either case due to intramuscular, subcutaneously or intracutaneously administration of the vaccine. This study may be part of toxicity studies. Ideally the formulation intended for clinical use should be tested.

4.4 Additives (Adjuvants/Excipients/Preservatives)

Since modern vaccines must give maximum efficacy, require the minimum of doses and should be delivered safely novel adjuvants will be developed. Adjuvants may exert their activities by their impact on the presentation of the antigen to the immune system (e.g. adsorbents, particles, and emulsions), the antigen/adjuvant uptake (e.g. emulsions), the distribution (targeting to specific cells), the immune potentiation/modulation (e.g.microbial, synthetic & endogeneous adjuvants) or the protection of the antigen from degradation and elimination.
The "Note for guidance on requirements for the evaluation of new adjuvants in vaccines" proposes documents that give appropriate guidance on pharmaceutical/biological and pre-clinical aspects of novel adjuvants. The quality part should include information on the adjuvant alone (description, manufacturing, characterisation, routine testing, and stability) as well as information on the adjuvant/antigen combination. The non-clinical part is also divided in toxicity studies without (local toxicity, induction of hypersensitivity and anaphylaxis, pyrogenicity, systemic toxicity to tissues/organs, reproduction toxicity, genotoxicity) and in combination with the antigen (local toxicity, characterisation of immune response). In the clinical part it must be demonstrated that the amount of adjuvant is appropriate to enhance the immune response to the antigen(s), to further direct the immune response towards the intended effect, or to improve the safety profile. The safety of new additives could be tested by preparation of mock vaccines (vaccine formulation without antigen). In principle, no pharmacokinetic studies on adjuvant alone except in case that accumulation of adjuvant is expected are necessary.

If preservatives are used, the safety has to be documented and discussed. When a new preservative is used, documentation should be provided to support the safety and it should be treated as a new pharmaceutical excipient.

5 Clinical Evaluation of New Vaccines

5.1 Introduction

As usually clinical evaluation of vaccines are designated in different phases. Phase I trials seek to determine if the vaccine is safe. Phase II trials examine the effect of increasing dose on safety and immunogenicity of a vaccine. Phase III trials evaluate the efficacy of a vaccine. Phase IV trials are usually configured as large scale post-marketing surveillance of those who have received the vaccine to determine if use of the vaccine is associated with adverse effects that occur with a low frequency.

The clinical testing program should generate data concerning appropriate route of administration, dose schedules, and age categories of exposed subjects in relation to efficacy of the vaccine. The Immunogenicity (humoral and/or cell-mediated immune response) and efficacy of the new vaccine should be appropriate studied. The primary endpoint in trials is the protection against clinical disease unless an immunological correlate for protection is fully validated. Special attention should be paid to the ethical considerations if special groups such as children are included in trials. In addition the use of placebo control and challenge tests should be carefully balanced.

The clinical protocol should in detail describe the study design, samples size, statistical criteria, and duration of follow-up and assessment of outcome. All other relevant data, like in other clinical trials should be reported according to the relevant guidelines.

The vaccine lot used in clinical trials should be representative of the formulation intended for marketing authorization. In general any change in the composition of a vaccine during development should be evaluated as to the need to additional clinical evaluation.

5.2 Specific Regulatory Documents

In general the design and conduct of vaccine trials based on the ethical considerations described in GCP (Good Clinical Practice) guidelines and the ICH guidelines.

The clinical development of new vaccines is described in:
Note for guidance on clinical evaluation of new vaccines. CHMP/VWP/164653/2005 (Revision of the Note for guidance on clinical evaluation of new vaccines. CPMP/EWP/463/97)

5.3 Immunogenicity

Immunogenicity data are usually generated during all phases of clinical development. Primary pharmacodynamic data received from animal models can be used to determine the doses, schedules and route of administration. Early clinical studies should generate data concerning safety and immunogenicity of the antigenic components of the vaccine.
The characterisation of the immune response should include information about level, class, sub-class and function of specific antibody produced, the lag-time of appearance and duration of adequate antibody titres, the cell-mediated immunity (with monitoring quantity and quality of T-cell response), formation of neutralizing antibodies, cross-reactive

antibodies, or interactions which might affect the immune system. The kinetic of the immune response concerning onset of protection, antibody persistence, seroconversion and induction of immune memory should be evaluated. An exploration of immunological factors which might be influence the humoral response such as pre-existing antibodies should be given. Immunological interference with other vaccines which are expected to be administered simultaneously in the same time period as well as dose response relationship should be evaluated.
When the induction of humoral immune response is hypothesized to correlate with vaccine efficacy, this should be appropriate confirmed by qualitative and quantitative considerations. It is desirable, that one or more immunological correlate(s) of protection should be defined for short and long term protection. The immunological correlate will be based in most cases on the measurements of functional antibodies. Otherwise it must be well described. Established animal challenge models may help to support a putative immunological correlate for protection in humans. In this case applicant should as early as possible seek advice from the competent authority.
Comparative immunogenicity studies are commonly performed to explore immune response. That includes comparison of the antigen to a similar antigen in a licensed comparator, in different subgroups, concomitantly given with other vaccines or in different formulations.

5.3.1 Essential Immunogenicity Studies

Dose finding studies which my also incorporate exploration of schedules may be performed in healthy adults, but dose-response data should be obtained as early as possible in the target population. The lowest amount of antigen for protection should be explored. That is also important for the determination of the appropriate shelf-life of the vaccine.
For the determination of the primary vaccine schedule (one or more doses) sufficient data from immunogenicity and efficacy studies must be generated. It is essential to prove the schedule in the specific target group. It is not necessary to study every possible schedule in use. The demonstration of satisfactory immunological response at the most challenging schedules could be extrapolated to less condensed schedules. Special considerations should be focus on the schedules of vaccines administered in infants and travellers.
The persistence of protection and the need for and timing of booster doses should be ideally determined before authorization. When those data are not available at the time of marketing authorization, plans for appropriate post-marketing studies should be in place.

Pharmacokinetic studies are generally not required, but should be considered in case of other route of administration than injections e.g. for oral vaccines.

5.4 Efficacy

If an appropriate challenge system exists and is ethically justified, this may be used to demonstrate protection. Protective efficacy studies are not necessary, if there is a well established immunological correlate for protection against a specific infection (e.g. diphtheria, tetanus). They are not feasible, if the potentially preventable infectious disease does not occur (e.g. smallpox) or occurs at too low rates for a study to be performed in a reasonable period of time. In these cases the applicant should discuss the basis for authorization with the competent authority. In some cases, relevant data on protective efficacy from challenge studies in animal models may be obtained. If the authorization

based on this limited data, it may be not possible to estimate vaccine effectiveness in the post-authorization period unless a substantial natural epidemic or deliberate release occurs. Therefore a close contact to health authorities to develop plans for collecting data on safety and efficacy should be given.
If the disease is rare a possible alternative may be to use estimates of effectiveness from prospective studies conducted during vaccination campaigns after authorization.

Special care should be taken establishing the primary endpoint since this may have a major influence of the selection of the study design. The endpoint for determination of efficacy may be disease incidence or an immunological surrogate marker for protection, if it exists. For determination of the efficacy of the vaccine the validity of diagnosis of infection is one of the most vital aspects. Infections in vaccinated subjects should be identified as true vaccine failures. A clear case definition and methods for case detection should be established.

5.4.1 Clinical Efficacy Studies

The pivotal studies for establishing vaccine efficacy are randomised controlled studies. Pre-exposure studies are preferred for establishing vaccine efficacy in outbreak investigations in populations. The efficacy assessment is always dependent upon the appropriate control. This may be an adequate comparator, placebo, and/or adjuvant. If an active comparator is used the study should show that the new vaccine is superior to the licensed product.

Secondary attack rate studies are useful in infections with relatively high secondary cases and in outbreak situations. The bias of these studies should be minimized and should be adequately described in the protocol.

If it was not feasible to estimate the protective efficacy of a vaccine pre authorization it may be possible and highly desirable to assess the protective effectiveness during the post authorization period. This may be in observational cohort studies or by phased introduction of the vaccine into the target population.

5.5 Special Consideration in Clinical Vaccine Development

If a vaccine contains more than one antigen there is a potential for each antigen to interfere with the immune response to one or more other antigens in the same product. An adequate exploration of the effects is required. In most cases the assessment of immune interference will be based on serological data.

If a cross-reacting immune response is anticipated very special considerations are needed for post-marketing safety studies.

At the time of marketing authorization of a novel vaccine, there should be safety and immunogenicity data concerning concomitant administration with at least one type of licensed vaccine that would be very likely be given at the same time. Special care should be taken for vaccines intended for vaccination of infants.

For interchange of vaccines within a schedule, safety and immunogenicity data should be provided.

Ideally, vaccines from several lots of the final formulation intended for marketing should be tested during the clinical development programme. The need for lot-to-lot consistency studies might be important when there is an inherent and unavoidable variability in the final formulation. The design should be discussed in advance with the competent authority.

Bridging studies generate immunogenicity data to support the extrapolation of data on safety and protective efficacy obtained under specific circumstances of use to other situations. This may be the case between data from premature infants compared to full term infants, immunosuppressed compared to healthy individuals or between different formulations of a vaccine.

5.6 Safety

In the pharmacodynamic studies safety data should be collected with regard to local and systemic reactions. As a minimum, the total data at the time of approval should be sufficient to reliably determine the nature and frequency of adverse events occurring at a frequency > 1/1,000. Any rare and or unusual adverse events must be thorough causally assessed. Detailed information is given concerning the methodological considerations e.g. time frame for collecting data, details of collection (route of administration, batch number, co-administered vaccines, patient diaries and information for the investigators). An indepedent Data Safety Monitoring Board during the clinical development programme is appreciated.

5.6.1 Post Marketing Surveillance

Until a vaccine is given to the general population, all potential adverse events cannot be anticipated. Thus, many vaccines undergo Phase 4 studies once it is on the market. Since vaccines are almost always administered to healthy individuals a continued re-assessment of the overall risk-benefit relationship is necessary. In addition, as mentioned earlier, the estimation of vaccine effectiveness is a subject in the post-authorization period. General considerations for post marketing surveillance are similar to other medicinal products.

6 Development of New Smallpox Vaccine

6.1 Introduction

Smallpox is a viral disease characterized by a skin rash and a high death rate caused by Variola virus. Smallpox has two forms: Variola major, which is a serious illness with a mortality rate according to the CDC of 30% or more, in unvaccinated people, and Variola minor, a milder infection with a mortality rate of less than 1%. The incubation period for smallpox is approximately 12-14 days. A massive program by the World Health Organization (WHO) eradicated all known smallpox viruses from the world in 1977, except for samples that were saved by various governments for research purposes. The vaccination was discontinued in the United States in 1972. In 1980, WHO recommended that all countries stop vaccinating for smallpox (Medical Encyclopedia). Therefore a large proportion of the population has no immunity.

The only commercially approved smallpox vaccine available for limited use is Wyeth Dryvax (in the United States). This vaccine is a lyophilized preparation of live Vaccinia virus, prepared from live calves. Vaccine prepared by this traditional manufacturing technique of harvesting vaccinia virus from the skin of cows or sheep was used in most regions of the world during the smallpox eradication campaign. The facilities, expertise, and infrastructure required for producing the virus in this way are no longer available. Wyeth Laboratories discontinued distribution of smallpox vaccine to civilians in 1983 (CDC 1983.) This live-virus vaccine also caused rare but serious adverse reactions and common local reactions. Dermatologic and central nervous system disorders were the most frequently recognized adverse events. A survey conducted by WHO in 2001 found that only small amounts of stockpiled smallpox vaccines still existed (WHO, web-page). These stocks are distributed quite unevenly around the world and are accessible to only a very selected part of the global population. Additional production would be needed to meet any major demand on vaccine supply such as might follow an intentional release of smallpox vaccine for example in case of a bioterrorism act.
Bioterrorism is the use of bacteria or viruses with the deliberate intent of making people ill or causing death in order to achieve certain goals. Variola major is a particularly dangerous biological weapon threat because of its clinical and epidemiologic properties. This virus can be manufactured in large quantities, stored for an extended period of time, and delivered as an infectious aerosol.

New smallpox vaccines were developed using modern cell-culture manufacturing methods. These pock forming 2nd generation smallpox vaccines derived from NYCBH vaccines strain may cause serious adverse reactions similar to historical vaccines. Highly attenuated strains like Modified Vaccinia Ankara (MVA) strains were developed and used during the eradication program. However, its effectiveness against smallpox is unknown. The evaluation of an effective vaccine, especially ones that do not induce a vaccine take (formation of pustular lesions 6 to 20 days after vaccination) and induce an immune response that substantially differs from that induced by the currently licensed vaccine, may pose problems. Specifically, the usual measures of efficacy that require exposure to natural disease currently are not possible because the disease has been globally eradicated. In addition, definitive human challenge and protection studies with Variola would not be possible for ethical reasons.

6.2 Specific Regulatory documents

Note for guidance on the development of vaccinia based vaccines against smallpox. CPMP/1100/02

Recommendations for the production and quality control of smallpox vaccine, revised 2003 WHO Technical Report Series. No 926, 2004, Annex 1

EMEA/CPMP Guidance document on use of medicinal products for treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism. CPMP/4048/01.

Control authority batch release of vaccines. EDQM 2004

Emergency Use Authorization: MVA Interagency Study Group (IASG) Current Thinking Regarding the Information Needed to Use Modified Vaccinia Ankara (MVA) Vaccines for Pre-exposure Prophylaxis in a Setting of Known Smallpox Virus Release – Including Prophylaxis of Individuals when Dryvax® is Contraindicated. DRAFT: Revised April 18, 2005

6.3 Manufacturing

The smallpox vaccine monograph in the Ph.Eur. (not discussed here) applies to second generation smallpox vaccines and does not apply to non-replicative strains such as Modified Virus Ankara (MVA), the strain used for developing 3rd generation smallpox vaccines. Nevertheless, this monograph demonstrates what is essential in developing a smallpox vaccine. Also the recommendation of the WHO and a guidance document of EMEA are applicable for 2nd generation smallpox vaccines.

Recommendations published by WHO are intended to be scientific and advisory and cover only vaccinia strains that do induce pock formation (2nd generation). In addition only smallpox vaccines produced on animal skin, embryonated eggs and chick embryo fibroblast cells (CEFs) are considered. A section covers the production and control of cell substrates. An important parameter to establish is that the cell substrate does not have a negative effect on the safety and/or efficacy of the vaccine virus. Another important point is the adventitious agent testing for viruses in the vaccines virus seeds and product intermediates which is complicated because complete neutralization of vaccinia virus is difficult to achieve. Since removal or inactivation of such agents is unlikely to be possible at any level of the production process of a live smallpox vaccine, the presence of extraneous agents in the seed lots is not acceptable. The recommendation gives detailed information concerning the production control including control of source materials (virus strains, virus seed lot system, test on virus seed lots), cell seed and manufacturer's working cell bank, identity tests, control of vaccine production (bacterial and fungal sterility, mycoplasma test, test of haemadsorbing viruses, adventitious agent testing, virus titration, endotoxin test, test for pH, protein and DNA content, residual moisture if freeze-dried).

The guidance document CPMP/1100/02 for developing second generation smallpox virus which does even not include non-replicative vaccines like modified Virus Ankara (MVA) strains, focus in the quality part on the different steps during production from vaccine seed lots (cell bank or primary cells), production, to the final vaccine product, and the relevant

controls. If primary cells are used special care should be taken to the avoidance of adventitious agent contamination. Only primary cultures from closed, specified pathogen free (SPF) healthy flocks should be used. Such flocks must be stringently controlled for the presence and maintenance of the SPF status at regular intervals in accordance with Ph.Eur. requirements. The production is likely to follow that of other live viral vaccines. Therefore the basic requirements for manufacture and control will be essentially the same.

6.4 Efficacy

Licensing of a new vaccine usually requires the demonstration of its efficacy against the natural infection in a clinical trial. This is not possible in the case of new smallpox vaccines because the natural infection has been eradicated. One approach that has been taken is to develop a new vaccine that is phenotypically similar to a vaccine known to be successful in the eradication initiative. Immunological correlates of protection are not defined for vaccinia virus. However pock formation in humans after smallpox vaccination is a marker of vaccine effectiveness. If highly attenuated vaccinia virus strains or inactivated vaccines are used alternative markers to pock formation are needed. Other parameters such as levels of neutralizing antibodies or haemagglutination inhibiting anti-vaccinia virus antibodies can presently be considered only as supportive information. Challenge studies in a relevant animal model (e.g. mouse/vaccinia virus and monkey/monkeypox virus) may provide additional evidence on the protective efficacy of new smallpox vaccines.

The guidance document CPMP/1100/02 for developing second generation smallpox virus recommended animal studies where the primary endpoint should be the protection by the candidate vaccine in comparison with an original vaccine against the challenge with a relevant pathogenic orthopox virus. An animal model to be used should be as close as possible to the human setting. Cross protection should be demonstrated against two different pathogenic orthopox viruses in two different mammalian species, normally BALB/c mouse as a non-primate model and a monkey model (cynomolgus macaques) as primate model. Beside the primary endpoint, protection against lethal respiratory infectious dose of challenge other data could be collected. This include antibody response (neutralising antibody titres) and cell-mediated immune response (specific CD4 and CD8 subset activities e.g. by IFN-gamma ELISPOT assay). The viral load can be assessed by cell titration or genomic quantification. The effects on respiratory and cardiovascular systems will also be investigated in monkeys whereas neurovirulence must be tested in appropriate models. For emergency situations reproductive studies in mice or rabbits must be performed.

In the USA a draft paper from the MVA Interagency Study Group (IASG) considering aspects concerning the emergency use authorization of smallpox vaccines based on the Modified Vaccinia Ankara strain (3rd generation) was issued. This paper focuses on the pre-exposure prophylaxis in a setting of known smallpox virus release and covers animal efficacy data, human immunogenicity data and data for humans for whom Dryvax is contraindicated (see below). The animal models (cynomolgus macaque and BALB/c mouse) are described in detail including selection of the challenge dose and the appropriate challenge route. The suggested definitive animal study for Emergency Use Authorization (EUA) is described with case definition of mild and severe infections. For licensure in immunocompromised people safety and efficacy studies must be performed in immunocompromised animal models. This procedure is based on the “animal rule” laid

down in the US law. The regulatory issues are described in detail in section 8 (8.4.1). The demonstration of efficacy via the animal rule means an additional development program to be conducted in parallel to the clinical and manufacturing programs (Clifford 2000). The identification of the appropriate animal species includes the evaluation of the experimental infection as well as the pathophysiology of the disease. Beside the time to onset of the symptoms, the nature of the symptoms and the time to death, the effects of agent challenge dose and route of exposure on morbidity and mortality must be evaluated. In addition the immune response to the candidate vaccine must be considered. Proof of concept studies will give results on dose ranging, administration schedules and will initially demonstrate a protective level of response or the threshold of protection. Efficacy studies then optimize the dose and schedule by means of immunogenicity endpoints (assays, kinetics, duration) as well as efficacy endpoints like morbidity and mortality. The extrapolation of the animal model protective level as a predictor of human protection will be done by correlation of the animal with clinical immunogenicty data.

6.5 Clinical Trials

Under normal circumstances, the clinical assessment of a novel vaccine should include the assessment of the immune response to the major antigen, protective efficacy trials, and the documentation of the safety profile. Since smallpox does not currently exist in the population trials of protective efficacy are not feasible. Therefore the likely protective efficacy must be inferred from other parameters.

In the guidance document CPMP/1100/02 for developing second generation smallpox virus it is recommended that the pock formation (take rate) and the assessment of serological and cell-mediated immune responses should be correlated. The endpoints of clinical studies are therefore the pock formation, time to crusting and crust fall which should be carefully documented. The immunological responses should include the detection and titration of neutralising antibodies against an appropriate reference material calibrated against a suitable standard. Assessment of the cell-mediated component of the immune response should include the evaluation of CD8 T-cell activity. Uncontrolled pharmacology trial should be performed in healthy adult with no history of smallpox vaccination. Confirmatory Immunogenicity trials should be randomised and double blind in order to demonstrate non-inferiority between the novel and a licensed vaccine. In the absence of a vaccine that meets current production standards a comparative trial would not be mandatory. In general children and elderly subjects would be eligible in clinical trials. Concerning duration of follow-up immunity the guideline stated that an initial application for marketing authorization may well occur when less than one year has elapsed since the majority of subjects were exposed to the new vaccine. Laboratory test of immune responses should be repeated over a long time in at least one cohort. The assessment of safety should consider the various types of adverse reactions described in the literature. The duration of follow up should at least 3 months at the time of initially application for marketing authorization, in order to detect late development of neurotoxicity and any case of progressive vaccinia.

For 3rd generation smallpox vaccines a draft paper from the MVA Interagency Study Group (IASG), USA, which considers smallpox vaccines on the bases of live attenuated strains was published. A key point is human imunogenicity data in comparison to Dryvax as an important surrogate measurement despite the fact that the exact immune response for protection is unknown. A comparison of the immune response between humans and those

animals protected from challenge will help to establish efficacy. Immunogenicity data should also be obtained in people for whom Dryvax is contraindicated (HIV infected and immunocompromised people). A detailed list considering the different CD4 counts is given in the document. In general all data must be obtained with vaccinia naïve people but vaccinia experienced human subjects data will also be helpful.

7 Development of Pandemic Influenza Virus Vaccine

7.1 Introduction

An influenza pandemic is a global outbreak of disease that occurs when a new influenza A virus appears or "emerges" in the human population, causes serious illness, and then spreads easily from person to person worldwide. Pandemics are different from seasonal outbreaks or epidemics of influenza. Seasonal outbreaks are caused by subtypes of influenza viruses that already circulate among people, whereas pandemic outbreaks are caused by new subtypes, by subtypes that have never circulated among people, or by subtypes that have not circulated among people for a long time. Pandemic Influenza can occur at any time of the year and may spread rapidly throughout the world.

Prevention and control of pandemic influenza will depend on the rapid production and worldwide distribution of specific pandemic vaccines. A vaccine probably would not be available in the early stages of a pandemic. After selection of the virus strain that will offer the best protection against that virus, manufacturers then use the selected strain to develop a vaccine. Once a potential pandemic strain of influenza virus is identified, it takes several months before a vaccine will be widely available. Therefore the interpandemic period must be used to explore the optimal scientific, manufacturing, regulatory and clinical research strategies for developing vaccines that are effective against pandemic influenza so that the vaccine will be available as soon as possible in the event of pandemic.

Because of the expected size of an influenza pandemic, the governments in USA and Europe plan preparedness activities that will permit a prompt and effective public health response. The EMEA and the U.S. Department of Health and Human Services (HHS) supports pandemic influenza activities in the areas of surveillance (detection), vaccine development and production, strategic stockpiling of antiviral medications, research, and risk communications. Both have developed a comprehensive Pandemic Influenza Plan for a potential pandemic which urged a long-term commitment between the industry and the authorities to make sure answers available before the threat becomes a problem.

7.2 Specific Regulatory Documents

Harmonisation of requirements for influenza vaccines, Directive 75/318/EEC as amended

Guideline on dossier structure and content for pandemic influenza vaccine marketing authorization application. CPMP/VEG/4717/03.

Guideline on submission of marketing authorization applications for pandemic influenza vaccines through the centralised procedure. EMEA/CPMP/VEG/4986/03.

Concept paper on guideline on dossier structure and content of marketing authorization applications for influenza vaccines with avian strains with a pandemic potential for use outside of the core dossier context. EMEA/CHMP/VWP/171037/2006

The EMEA Pandemic Influenza Crisis Management Plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals (Draft Doc.Ref. EMEA/397403/2005)

Point to consider on the development of live attenuated influenza vaccines EMEA/CPMP/BWP/2289/01

Draft Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines

Draft Guidance for Industry: Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines.

U.S. Department of Health and Human Services (HHS): Pandemic Influenza Plan, 2005

7.3 Situation in Europe

The key objectives in case of crisis are to initiate the pandemic plan, to activate all parts of the network and to coordinate the different activities between the parties as described in the pandemic plan. The WHO will identify the start of the influenza pandemic. This information will be provided to the Commission who will notify the EMEA. The EMEA (different crisis teams are established) is responsible for fast track approval of pandemic influenza vaccines via the centralized procedure, the post-authorization follow-up of centrally authorised pandemic influenza vaccines and antivirals and to react to any safety signals arising from the use of non-centrally authorised antivirals or from the use of bulk active substance of centrally authorised antivirals.

To speed up the development in case of a pandemic situation the EMEA has established the core pandemic dossier which has to be submitted and approved during the interpandemic period, followed by a fast track approval of the pandemic vaccine, based on the submission of a pandemic variation. This procedure is laid down in the “Guideline on dossier structure and content for pandemic influenza vaccine marketing authorization application”. The “Guideline on submission of marketing authorization applications for pandemic influenza vaccines through the centralised procedure” gives advice in a pandemic situation for the time between the authorization of the core pandemic dossier and initiation of the fast track pandemic influenza variation.

The core pandemic dossier includes the description of the development strategy and the validation of the production processes and analytical methods, and reports the findings from preclinical and clinical trials. This information should support a vaccination strategy. To achieve this, a “mock-up” vaccine should be produced in the same way, having the same antigen content and same adjuvant system, if used and the same route of administration. The antigens in the mock-up vaccine should be different from those currently circulating in order to simulate a situation where the target population for vaccination is immunological naïve. The reference viruses suitable for use as mock-up strains are described in detail in the guideline mentioned above. The guideline gives detailed advice concerning quality, pre-clinical and clinical development which is summarized in the following.
Concerning quality the vaccine production of the mock-up and the pandemic vaccine should be identical concerning vaccines seeds, testing procedures, formulation, adjuvants and stability.
Non-clinical data need to be submitted only in the core dossier of the mock-up vaccine except non-clinical data concerning immunogenicity for the first three batches to document

consistency of production. Further exceptions for e.g. non-clinical safety studies in case of an already authorized manufacturing process are also described in the guideline. Challenge studies contingently in dedicated facilities, should be conducted.
Clinical efficacy and safety data should be included in pandemic core dossier and should be obtained with viral antigen to which humans are immunological naïve. It is recommended that beside data in healthy adults, data in healthy children should also be obtained. Since the immune response in different age groups of the population differs depending on previous influenza vaccination a critical review of the literature and a close contact with the authority is essential. Clinical data concerning efficacy of the mock-up vaccine can of course not be performed. Concerning safety the safety database should be sufficient to detect adverse events at a frequency of approximately 1%. Follow-up for the evaluation of safety should be at least 6 months.
Most if not all people will never have been infected with an influenza virus like the pandemic virus. As they will be immunological naïve, they will require two doses of vaccine to be fully protected.

If the final pandemic vaccine is of similar nature and produced in the same way as the mock-up vaccine, the clinical data can be extrapolated. In addition the final pandemic vaccine will have to be approved without immunogenicity data. Therefore the marketing authorization holder has to prove immunogenicity, effectiveness and safety during the use as post-approval commitments.

The actions of the EMEA, consisting of different task forces and the applicant/manufacturer are described in detail in the guideline "Guideline on submission of marketing authorization applications for pandemic influenza vaccines through the centralised procedure".

Some EU governments are considering using avian influenza vaccines outside of the context of a core dossier. Therefore, the EMEA prepared a concept paper that addresses the content of an application for marketing authorization for an avian influenza vaccine for human use. In contrast with the principles of the core pandemic dossier, where the dossier can in principle be based on any influenza virus strain to which the study population is immunologically naïve, the data presented in a dossier for avian influenza vaccines for human use in the Pandemic alert period should all be derived from a vaccine prepared with the strain(s) against which protection is claimed. The vaccine reference virus shall be derived from a circulating avian strain with pandemic potential. Alternatively, manufacturers might develop vaccines on basis of library strains or seeds of avian or other animal or human influenza strains, provided that a high degree of cross-reactivity with circulating avian strains has been shown. In general the requirements concerning quality, pre-clinical and clinical development as identified for core pandemic dossier are applicable. The guideline provides a comprehensive table concerning immunogenicity and safety studies by population group. The SmPC of the vaccine should strictly reflect the characteristics (e.g. age range and/or immunocompetence) of the population(s) in which it is considered that sufficient data are available to support a dose regimen that is potentially protective. As with all vaccines, variations to the SmPC that extend the population in which dose recommendations have been established may be approved if suitable data are provided. For each population group a targeted Risk Management Plan should be prepared. In the post-authorisation period there will be a need to follow up cohorts of each type of vaccinee studied for antibody persistence and the need for booster doses as well as for cross reactivity with other circulating avian viruses.

7.4 Situation in the USA

The US Food and Drug Administration (FDA) has released two draft guidance documents aimed at helping companies speed up their development of influenza vaccines. One guideline addresses seasonal flu vaccines and the other pandemic flu vaccines. The documents give sponsors advice on developing and submitting clinical data to demonstrate the safety and effectiveness of new vaccines for human use. They are consistent with the FDA's critical path initiative to get products to market more quickly and to advance the development and use of new technologies.

The guidance entitled “Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines” covers new split virus trivalent inactivated influenza vaccines. The guidance “Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines” addresses split virus and whole virus inactivated pandemic vaccines propagated in embryonated chicken eggs and also cell-culture derived, recombinant haemagglutinin-based protein and adjuvated pandemic influenza vaccines. The guideline points out that, once a pandemic influenza vaccine against a new subtype has been licensed, further clinical data with a variant of that subtype is unlikely to be needed to gain a licence. Information to support a change in the viral subtype variant included in the vaccine should be submitted as a manufacturing supplement to the existing biologics licence application.

The documents describe the process for changing rapidly from the currently-licensed seasonal vaccine to a new pandemic vaccine by supplementing the existing licence. For new vaccines, the pathways for both traditional and accelerated approval approaches are described. Accelerated approval allows for the evaluation of a vaccine to be based on biological indicators, such as immune response to the vaccine, to demonstrate effectiveness.

The draft guidelines address new approaches to developing and evaluating vaccines using new technologies, such as cell culture and recombinant manufacturing. They also highlight potential ways to stretch limited pandemic vaccine supplies, such as the use of adjuvants to improve the immune response the vaccine triggers.

The documents do not address the nonclinical development of investigational vaccines. Nor do they address the chemistry, manufacturing, control or inspection of the facility needed for licensure.

8 Approval

8.1 Introduction

Vaccines must be approved in the EU by the centralised procedure if it is developed by biotechnological processes according to the annex of regulation 726/2004. Otherwise vaccines may be approved by the decentralised procedure but also by national authorities. With effect from 20 May 2008 medicinal products for viral diseases and for human use containing a new active substance which were not authorised in the Community are mandatory for the centralised procedure.
Beside these general approval possibilities (centralised procedure, decentralised procedure and national authorizations) in the European Union and the New Drug Application (NDA) in the United States there are several other approval forms for exceptional cases.

Procedures for granting approval under accelerated approval in the EMEA and FDA were designed to increase the speed at which therapeutically important products reach the relevant patient populations.

According to article 14 (9) of 726/2004 a centralised accelerated procedure in the EU is possible: "when an application is submitted for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. The request shall be duly substantiated." This accelerated assessment procedure reduces the time for review from 210 days to 150 days.

In the United States exists beside the accelerated approval, the priority review and the rolling NDA. Accelerated Approval (CFR 314.500 Subpart H) is part of the FDA's fast track initiative and is given on surrogate end-points with an expedite review process and restrictions to assure safe use.
The priority review is for a product that would be a significant improvement compared to marketed products or existing therapies like increased effectiveness in treatment, prevention or diagnosis, substantial reduction of a treatment-limiting drug reaction, enhancement of patient compliance, safety and effectiveness in a new subpopulation. The decision is made at the date of submission for every application submitted, regardless of applicant request. Priority Review, therefore, does not alter the steps taken in a drug's development or testing for safety and effectiveness. The time for priority applications is 6 months versus 10 months for standard applications.

A rolling NDA is a process used by the FDA to expedite the review of a drug intended for the treatment of a serious or life threatening condition and that demonstrates the potential to address an unmet medical need. This allows the FDA to begin to review sections of the NDA as they are submitted, as opposed to the normal approval process, which requires the entire NDA to be submitted at once. In order to be eligible to submit a rolling NDA, a company will usually have been granted Fast Track designation by the FDA which means early consultations during drug development with a fast track procedure for whole development process.
After licensure, monitoring of the product and of production activities, including periodic facility inspections, must continue as long as the manufacturer holds a license for the product. If requested by the FDA, manufacturers are required to submit to the FDA the

results of their own tests for potency, safety, and purity for each vaccine lot. They may also require submitting samples of each vaccine lot to the FDA for testing. However, if the sponsor describes and alternative procedure which provides continued assurance of safety, purity and potency, CBER may determine that routine submission of lot release protocols (showing results of applicable tests) and samples is not necessary.

8.2 Specific Regulatory Documents

Guideline on procedures for the granting of a marketing authorization under exceptional circumstances of 15 Dec 2005.EMEA/357981/2005.

Draft commission regulation on the conditional marketing authorisation for medicinal products falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004

Guideline on the scientific data requirements for a Vaccine Antigen Masterfile. EMEA/CPMP/BWP/3734/03

Guideline on requirements for vaccine antigen Masterfile (VAMF) Certification. EMEA/CPMP/4548/03

Draft guidance: Emergency Use Authorization of medicinal products FDA, Jun 2005

8.3 Specific Approval Forms in Europe

As outlined in the Regulation No 726/2004 of the European Parliament and of the council of 31 March 2004 there are some other possibilities of approval listed in article 14 (7) for conditional approval, 14 (8) exceptional circumstances approval and 14 (9) for accelerated approval (see above).
The Commission Directive 2003/63/EC amending Directive 2001/83/EC introduces the concept of the Vaccine Antigen Masterfile. The use of the VAMF certification system is optional.

8.3.1 Approval Under Exceptional Circumstances

Article 14(8) of Regulation (EC) 726/2004, states that “in exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC, as amended. Continuation of the authorisation shall be linked to the annual reassessment of these conditions.”

The CHMP released the corresponding guideline on procedures for the granting of a marketing authorization under exceptional circumstances 15 Dec 2005. The conditions for marketing authorization under exceptional circumstances are 1) that the indications is so rarely, that the applicant cannot provide comprehensive evidence 2) in the present state of

scientific knowledge, comprehensive data cannot be provide because of e.g. diagnostic tools have not been developed in order to specifically study defined patient populations and 3) inability to collect efficacy and safety data because it would be contrary to medical ethics. The applicant should give in each case a detailed justification. In addition a proposal for detailed information on the specific procedures/obligations to be conducted must be given. This includes an EU risk assessment plan, a pharmacovigilance plan, the program of studies which may be the basis for future reassessment of the benefit/risk profile, conditions for use and the product information (SmPC). The CHMP then will prepare an assessment report. The continuation of the authorization depends on an annual risk/benefit assessment.
The marketing authorization under exceptional circumstances will normally not lead to the completion to a full dossier. Therefore a clear discrimination to the conditional marketing authorization must be performed.

8.3.2 Conditional Marketing Authorization

The European Union has introduced a new procedure for awarding conditional marketing authorizations to certain products for seriously life-threatening and rare diseases, as well as in public health emergencies. The aim of the new approval form is to get products through the centralised procedure as quickly as possible when the data that would normally be needed for approval are not available. Conditional approval addresses situations where an urgent public health need exists, and a drug in development promises significant health benefits, but full safety or efficacy testing has not been completed. The new procedure was implemented by regulation (EC) No507/2006, which came into effect at the beginning of April 2006.
A conditional approval can be granted on the basis of a data package that is less complete than it normally would be. However, it is important that the product's risk/benefit profile should be positive, and the public health benefits of making it available more quickly should overweight the risk inherent in the fact that additional data are required. Generally, the system should be limited to cases where only the clinical data are less complete than normal, but in case of a product for emergency use, the pre-clinical or pharmaceutical data can also be incomplete.
The conditional marketing authorization is a temporary authorization and not intended to remain conditional. Clear information on the conditional nature of the MA must be given in the SmPC and on the package leaflet. This information must include the date on which the authorization is due to renewal. The conditional MA is reviewed once a year and the manufacturer, or "marketing authorisation holder" is committed to fulfil post-marketing obligations to obtain a definitive authorisation, based on full safety research and testing, or the product may be withdrawn from the market.

8.3.3 Vaccine Antigen Master File

Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC introduces the concept of the Vaccine Antigen Master File (VAMF). The use of the VAMF certification system is optional. The VAMF is a stand-alone part of the marketing authorisation application dossier for a vaccine. One given VAMF contains all relevant information of biological, pharmaceutical and chemical nature for one given vaccine antigen, which is common to several vaccines from the same applicant or marketing authorization holder. The aim of the VAMF is reducing the number of dossier submissions

and data evaluations carried out for the same vaccine antigen, harmonising the data for a given antigen present in several vaccines and ensuring consistency throughout the European Community. The VAMF certification consists of a centralised assessment of the VAMF application dossier submitted by the Applicant, which results in a certificate of compliance to the Community legislation, issued by the EMEA. This certificate shall be valid throughout the European Community. The detail procedure consisting of pre-submission activities (information of the relevant authority that they intend to use the Community VAMF certification system), submitting a letter of intent to EMEA, the appointment of co-ordinator(s), submission, validation and evaluation as well as inspections are described in the guideline mentioned above. Variation submission, data requirements and evaluation will follow the current established procedure for variations to centralised marketing authorizations. The dossier requirements for initial application for certification consist of administrative information, expert statements and scientific data. The requirements for the scientific data are described in the "Guideline on the scientific data requirements for a Vaccine Antigen Masterfile" but should in principle follow the NtA volume 2B and the guidelines published for vaccines development.

8.4 Specific Approval Forms in USA

8.4.1 Animal Rule

In the case that human clinical trials to establish efficacy of a drug, are not feasible like for a vaccine against smallpox, the companies may develop the vaccine based on the "animal rule". The FDA has published and requested comments on a proposed rule intended to address certain efficacy issues for new agents to be used against lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances (FDA 1999). The proposed rule attempts to define standards so that new drug and biological products developed to prevent serious or life-threatening conditions could be approved for marketing on the basis of evidence of effectiveness derived from appropriate studies in animals, without adequate and well-controlled efficacy studies in humans (21 CFR 601.90-95 (biologics) and 314.600-650 (drugs)). FDA may approve a product for which safety has been established and requirements of Sec. 601.90 (314.600) met based on adequate and well controlled animal trials when the results of those animal studies establish that the product reasonably likely to provide clinical benefit in humans. The FDA rely on evidence from animal studies only where the mechanism of toxicity of agent is well understood, and where the effect independently substantiated in >1 species (some exceptions), including species expected to react with a response predictive for humans. The animal study endpoint must clearly relate to the desired benefit in humans. The approval depends on three additional requirements which are a) postmarketing studies to verify and describe the product's clinical benefit when feasible and ethical, b) postmarketing restrictions as needed to assure safe use and c) specific labelling requirements, which clearly explain amongst others that product's approval is based on efficacy studies conducted in animals alone. The animal rule does not apply if product approval can be based on standards described elsewhere in FDA's regulations e.g., accelerated approval based on human surrogate markers or clinical endpoints other than survival or irreversible morbidity. The animal rule does not address safety evaluation of products to which it applies.

8.4.2 Emergency Use Authorization of Medical Product

This draft guideline explains FDA's policies for authorizing the emergency use of medicinal products under section 564 of the Federal Food, Drug, and Cosmetic Act, which was amended by the Project BioShield Act of 2004. Section 564 permits the FDA Commissioner to authorize the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency. The purpose of the Emergency Use Authorization (EUA) is to ensure that people at risk, including members of the Armed Forces, have the benefit of the best available medical countermeasures to protect them against biological, chemical, and radiological threats.

For Emergency Use Authorization the Secretary of Homeland Security must determine a case of emergency that is defined as heightened risk of attack with a biological, chemical, radiological, or nuclear agent. This may be a domestic emergency as well as a military emergency or an emergency case concerning the national security. The authorization of the product will be given by the FDA after consultation between the EUA working group (EUA WG) and the directors of NIH and CDC. The declaration ends normally after one year, after consultation with the Secretary of Homeland Security and the Secretary of Defense (if appropriate), but may be also renewed.

The FDA commissioner may issue an EUA only if the following three points are fulfilled. First the agent must cause a serious or life-threatening disease or condition. Further on it must be due to the presented data reasonable believable that the product may be effective in diagnosing, treating or preventing the disease caused by the agent specified in the declaration of emergency. At last the known and potential benefits must outweigh the known and potential risks of the product and it is no adequate, approved, and available alternative to the product on-hand.
The range of potential EUA products includes drugs, biological products (e.g., vaccine, blood products, and biological therapeutics), and devices (e.g., in vitro diagnostics).

Concerning effectiveness of a drug the FDA will decide by a case-by case basis and use lower level of evidence. Normally it is sufficient that the drug may be effective. That means if, based on the totality of the scientific evidence available, including adequate and well-controlled clinical trials, if they are available, it is reasonable to believe that the product may be effective for the specified use, the FDA Commissioner may authorize its emergency use--provided that other statutory criteria (e.g., relating to the risk-benefit analysis and alternatives) are also met. The known and potential benefits of the product must outweigh the known and potential risks. For this overall risk-benefit determination the FDA will review and consider all evidence, including results of domestic and foreign clinical trial, animal data, and in vitro data. The agency will consult also the Director of NIH and the director of CDC.

The authority strongly encourages the applicant to contact the authority before determination of emergency due to time limits during submission and review. Although the length of time required by the authority for review will vary, a request for consideration for an EUA will be acted upon within a matter of hours and days.

The authority may establish conditions on an EUA authorization to protect the public health. Such conditions may include: requirements for information dissemination to health care providers and product recipients; adverse event monitoring and reporting; data collection and analysis; restriction on product advertising, distribution, and administration.

Some conditions may apply to the manufacturer, while other conditions may apply to any person who carries out any activity for which the authorization is issued.

The appropriateness of an EUA will be periodically reviewed for e.g. significant adverse inspectional findings, reports of adverse events, product failure, product ineffectiveness, and availability of a preferred product. After termination an authorization only shall continue to be effective to provide for continued use in any patient who began treatment before termination.

9 Pharmacovigilance

9.1 Introduction

Pharmacovigilance of vaccines after their marketing is essential because they are generally administered to wide and healthy populations, so naturally a very high standard of safety is to be expected. Normally, prior to its availability on the market, the size of clinical trials is insufficient to identify rare or deferred adverse effects. Therefore anything must be done to ensure adequate protection of public health, especially because vaccines are often administered to small children. Whereas even common and potentially life-threatening side effects of an anti-cancer therapy are considered to be acceptable, adverse reactions in the case of vaccines are less tolerated, especially if the incidence of the infectious disease in the target population is low or is reduced as a result of a successful vaccination campaign. Therefore a Risk Management Plan (RMP) for vaccines is essential. Article 8 (3) (ia) of directive 2001/83EC, as amended, requires the applicant to submit "a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce". The pharmacovigilance plan includes investigation of rare, unexpected long-term AEs and increase of AEs, follow-up of pre-approval safety signals, investigation of potential toxicity of stabilizers, preservatives and adjuvants, subgroups not investigated (e.g. immunocompromised, pregnant women, premature infants), changes of the manufacturing process and possible implications on safety and efficacy, new important safety information post-marketing and surveillance for strain replacement. The EU-RMP is a living document, that should be updated throughout the lifecycle of the product because safety specification will change over time, results from other clinical trials and from the pharmacovigilance plan will be available, and because of spontaneous reports and literature news. A description of how the marketing authorization holder will implement the pharmacovigilance requirements is given in regulation (EC) No 726/2004, and directive 2001/83EC as amended.

9.2 Specific Regulatory Documents

Beside the universally valid pharmacovigilance and ICH guidelines and the NtA Volume 9 which are not discussed in detail here, the EMEA published a concept paper for a guideline on pharmacovigilance of vaccines and the FDA a draft guideline:

Concept paper for a guideline on the product of pharmacovigilance for vaccines. Doc. Ref. EMEA/CHMP/PhVWP/372004/2005

Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines. FDA. 2001.

9.3 Pharmacovigilance for Vaccines

The concept paper mentioned above focuses on vaccines used for prophylaxis against infectious diseases. Therapeutic vaccines (e.g. viral-vector based gene therapy, tumour vaccines and anti-idiotypic vaccines such as monoclonal antibodies used as immunogens) will not be considered. Since the acceptance and trust of vaccination in the public is reduced the guideline will focus on methods and tools to investigate the tolerability and

safety of vaccines. One of the main topics will be adverse effects especially the intensive investigation of rare suspected adverse reactions, the need for a clear case definition of adverse reactions, the need for long-term follow-up for delayed adverse reactions in a post-marketing setting, the age relatedness of adverse reactions, special risk of live-attenuated vaccines, batch relatedness of adverse reactions and also the implications of changes in the manufacturing process on the safety profile of the vaccine. The guideline will take account of the role of a wide range of stakeholders, ranging from health authorities responsible for vaccination program and for batch release, marketing authorization holders including manufacturer, healthcare professionals and different target groups like infants with a developing immune system, immuno-compromised patients and elderly patients. In addition the safety considerations will include different types of vaccines like live virus and attenuated vaccines, killed vaccines, new vaccines as well as vaccines with new adjuvants or alternative administration routes and combined vaccines.
Pharmacovigilance planning is an important element of the application for marketing authorization and the guideline on "Risk Management for Medicinal Product for Human Use" (EMEA/CHMP/96268/2005) should be considered. However the concept paper focuses on post-authorization concepts linked to the different characteristics of each vaccine, whether it is new or well established. Concerning spontaneous reporting marketing authorization holders and competent authorities should develop a checklist for those reactions which can be anticipated from the experience with comparable vaccines. The causality assessment on established criteria should include "vaccine induced" adverse reactions due to the intrinsic characteristics of the vaccine preparation and the individual response, and "vaccine precipitated", triggered by administration of a vaccine but which may also have occurred later or in other circumstances. Two other aspects of the new guideline will be handling of consumer reports and vaccine failure. In the periodic safety reports specific aspects for vaccines should be addressed. Post-marketing studies should investigate adverse reactions/risks, which are not identified and /or fully characterized prior to authorization. Another topic will be the benefit-risk assessment. The risk-benefit balance for vaccines depends on the incidence of the infectious disease in the target population, the proportion of infected persons with clinical disease, as well as the risk of transmission. The guideline will explain why the benefit-risk assessment of vaccines changes over time and may differ between different target populations.

The above mentioned CBER guideline covers only the following post-marketing reports: 15-Day Reports of Serious, Unexpected Adverse Experiences; Periodic Reports; Follow up Reports; and Distribution Reports for Biological Products Including Vaccines. The focus is here only on administrative aspects.

10 Conclusion and Outlook

Vaccines are biological medicinal products which are effective in providing protection against a large number of infectious diseases. Since vaccines are of major public health interest in the European Union, it is necessary to address these issues in a consolidated approach with the aim to maintain a high level of vaccination compliance. A harmonization between the Member States, EMEA/CHMP and European Commission to all questions related to vaccines was therefore desirable. To achieve this, the CPMP decided in 2002 to set up a specific Working Party, the Vaccines Expert Group. In 2004, the Vaccine Expert Group was transformed into a permanent working party, the Vaccine Working Party (VWP). The task of the working party is among others the preparation, review and update of guidelines, in conjunction with other appropriate working parties, to ensure that vaccine specific issues are fully addressed. The CHMP Biologics Working Party (BWP) shall maintain its responsibility for the quality and safety aspects in relation to the quality of vaccines. For the most section until approval of a vaccine a comprehensive guideline from the EMEA is available. But a detailed guideline of the EMEA for the CMC section of vaccines equivalent to the FDA guideline is missing. The requirements of the authorities concerning special aspects on vaccine quality e.g. potency testing and stability could be described in additional guidelines binding in the entire EU. In general it would be desirable if the guidelines for vaccine development could be harmonized all over the world. This would shorten the time to market as well as the cost for developing vaccines. This is especially of value if the new vaccine is also used in developing countries. Immunization is one of the best ways to improve health there. But there are obviously insufficient commercial incentives for the pharmaceutical industry to invest in research and development for diseases primarily affecting poor countries, such as malaria, tuberculosis, HIV and other tropical diseases (Rappuoli 2002). In the past, vaccines developed against diseases afflicting rich countries, e.g. measles and polio, have been widely and effectively used in developing countries. But there is no commercial rationale to develop vaccines for diseases that occur mainly in the poorest countries and for which there would be only a very small market in rich countries. Though these diseases kill millions of people, the communities affected cannot afford to buy vaccines at a price that would enable developers to recover the research and development costs. Because vaccines are biologics, even routine manufacture involves care, expertise, and expense much beyond that required for pharmaceuticals. Vaccines require dedicated production facilities that include physical and chemical barriers to protect workers from pathogen exposure and finely regulated temperature and ventilation to keep the biologics viable while stored. Also, because the product is injected, the purity standard has to be much higher than for a pill. Although the authorities inspect both drug- and vaccine-production facilities, the authority release every lot of vaccine produced and only a sample of drug production lots. Therefore new approaches for financing in order to stimulate the industry to increase its efforts in vaccine research and development should be created. This can be e.g. public funds or special contracts like the program from the government in the USA established for developing a smallpox vaccine (Rappuoli 2002). A program from the WHO like the orphan drug designation of the EMEA could offer incentives in form of scientific advice, cost reduction or market protection (Lang and Wood 1999). Implementing regulatory and manufacturing reciprocity between the USA and the EU would further diminish the development costs and perhaps also decrease time to market. Additional patent extension could be also an alternative to get a higher return on investment.

The level of trust in immunisation is usually high at the beginning of an immunisation program when the disease is frequent and patients and healthcare providers have personal experience with the disease (e.g. polio, diphtheria). As immunisation programmes successfully reduced the incidence of vaccine-preventable disease the proportion of vaccinees and healthcare providers, who do not have personal experience with the disease, are increasing. They have to rely on historical and other more distant descriptions for their subjective analysis. This situation significantly influences the risk perception. The risk perception may differ between stakeholders (health authorities, industry and public) especially if there is uncertainty of scientific evidence about the scientific evidence of the risk. Both the scientific and regulatory communities must communicate better on the public health benefits and good safety record of vaccines (EASAC 2006). To make a vaccine as safe as possible for all, new pharmacovigilance tools could be established e.g. large scale prospective observational studies using administrative databases and national/international disease and vaccines registries. This and the use of standardised and unified registration of side effects of vaccines would positively influence the acceptance of vaccination into the community.

Since the most vaccines are used in children the new paediatric initiative of the EMEA is of importance for developing vaccines. The new guideline "Testing in juvenile animals for pediatric indications" and the guidelines concerning pharmacovigilance for pediatric populations and pharmacokinetics in pediatric populations will have an impact on testing of vaccines for infants. However, details for developing vaccines are not yet described.

The approval process was reviewed in the new regulation 726/2004 and the conditional MA as well as the approval under exceptional circumstances introduced. To facilitate shorter review times in the EU the possibility of introducing rolling submissions according to the procedure in the USA should be considered, although these are not specifically mentioned in the revised legislative text. By mutual arrangement the applicant could be permitted to submit discrete sections of the dossier as they are completed, while continuing to finalize remaining sections. This would allow the rapporteur/ co-rapporteur to commence their review and would therefore shorten the time taken for them to produce the draft assessment report.

Smallpox vaccines

New smallpox vaccines are required as a contingency for protecting civilian and military personnel against deliberate dissemination of smallpox virus by terrorists. The currently available smallpox vaccine consists of a live animal poxvirus that was grown on the skin of calves that caused rare but serious adverse reactions and common local reactions (Rosenthal 2001). Because of potential issues with controlling this earlier manufacturing process, new vaccines are being developed and manufactured by using viral propagation on well-characterized cell substrates.

Modified Vaccinia Ankara was derived from the Ankara Vaccinia strain and is one of the most highly attenuated strains. With >570 passages in chicken embryo fibroblasts, it is host restricted and unable to replicate in human and other mammalian cells. Pock lesions did not form at the site of inoculation, and no adverse reactions were observed in clinical trials in persons at high risk with skin lesions (Sutter and Moss 1995). The vaccine was safely used to vaccinate >120,000 persons in Turkey and Germany; however, its effectiveness against smallpox is unknown.

One difficulty in evaluating a new smallpox vaccine is demonstrating that the vaccine generates a protective immune response in the recipient. The usual measures of efficacy

that require exposure to natural disease currently are not possible because the disease has been globally eradicated. Therefore the FDA has published and requested comments on a proposed rule intended to address certain efficacy issues for new agents to be used against lethal or permanently disabling toxic substances (Federal Register 1999;64:53960-70). The proposed rule attempts to define standards so that new drug and biological products developed to prevent serious or life-threatening conditions could be approved for marketing on the basis of evidence of effectiveness derived from appropriate studies in animals, without adequate and well-controlled efficacy studies in humans. Such an "animal rule" doesn't exist in the EU. However, this issue is addressed in the "Note for guidance on clinical evaluation of new vaccines" that recommended in these cases where challenge studies are not possible, an early discussion with the competent authority.
In general vaccines are intended for prophylaxis in a pre-exposure setting. From a terrorism perspective, however, both pre-exposure and post-exposure prophylaxis may be desired. Therefore differences in the optimal vaccination schedules may be possible which are addressed neither by the FDA and the EMEA nor by the IASG group draft paper.

Pandemic influenza vaccines

Concerning influenza virus vaccines special items should be considered. If the pandemic virus is entirely new, everyone may need at least 2 doses to ensure protection (Fedson 2005). Once the threat of a pandemic appears, health officials in a large number of countries can be expected to urgently try to negotiate contracts for vaccine supply with several vaccine companies. As a result, several hundred simultaneous negotiations (or attempts at negotiations) will be initiated within a period of a few months. These efforts will be difficult and most likely chaotic. Moreover, they will almost certainly be compromised by the extreme political vulnerability of the vaccine companies themselves.
Studies using inactivated vaccines against H9N2 and H5 subtypes of AI or purified recombinant H5 HA have demonstrated that these vaccines are poorly immunogenic in comparison to epidemic human influenza strains of the H1N1 and H3N2 subtypes. For example, inactivated vaccines against avian influenza subtypes require 2 doses and administration with adjuvant to achieve the desired level of neutralizing antibody (Luke and Subbarao 2006). The precise antigenic properties of a nascent pandemic strain can therefore not be predicted, so available vaccines may be poorly antigenically matched to the pandemic virus. Practical considerations and hurdles for pandemic influenza vaccine development also have to be overcome. Manufacturing capacity, the ability of candidate vaccine strains to grow well in eggs, and biological safety containment of parent strains for vaccine development are all problems to be addressed.
If these obstacles are to be overcome, a new approach to planning the production and distribution of pandemic vaccine must be developed. Planning must be undertaken at the international as well as the national level. EU support concerning development of standardised immunological assays for evaluating pandemic vaccines, exploration of alternative vaccination strategies and fund research to develop new vaccine concepts should be needed.

11 Summary

Vaccines are crucial to maintaining public health: They are a safe, cost-effective, and efficient way to prevent sickness and death from infectious diseases. In most cases, vaccines are administered prophylactically but may also be given to individuals who have been exposed to a disease in an attempt to prevent the progress of the disease. Other vaccines may be given to alter the course of a non-infectious disease like cancer. Vaccines for human use may contain inactivated organisms that maintain their immunogenic properties, living organism that are naturally avirulent or that have been treated to attenuate their virulence. Both bacterial and viral vaccines are manufactured using a seed-lot system with a strict control of the manufacturing process and intermediates. The most important aspect during development is the comparability of the test material. The preclinical evaluation of the vaccine candidate demonstrates the immunogenicity and safety and guarantees the protection of clinical trial participants from potential adverse effects. The clinical testing programme should generate data concerning appropriate route of administration, dose schedules, and age categories of exposed subjects in relation to the efficacy of the vaccine. Special consideration should be taken for vaccines against pathogens that are eradicated but may be used as bio weapons (e.g. smallpox) or for pandemic influenza viruses where the organism still not exists in order to make a vaccine available as soon as possible after a potential outbreak. Beside the general approval possibilities (centralised procedure, mandatory with effect from 20 May 2008 for drugs against viral diseases; decentralised procedure, national authorisations several other forms are possible e.g. accelerated approval, approval under exceptional circumstance or conditional marketing authorization in the EU as well as Emergency Use Authorization and approval under the animal rule in the USA. Pharmacovigilance of vaccines after their marketing authorization is essential because they are generally administered to wide and healthy populations. Therefore anything must be done to ensure adequate protection of public health.
Since vaccines are of major public health interest in the world, it is necessary to address all issues concerning vaccine development in a consolidated approach with the aim to maintain a high level of vaccination compliance. A harmonization between the Member States, EMEA/CHMP and European Commission to all questions related to vaccines was therefore desirable. The EMEA (since 2004 the permanent Vaccine Working Party) as well as the FDA has released a lot of vaccine guidelines covering the different topics in order to ensure the consistency and safety of vaccine development.

12 Literature

The guidelines cited are mentioned in the respective chapters. The following literature and web pages were used to prepare the master thesis.

Autret-Leca E, Bensouda-Grimaldi L, Jonville-Bera AP, Beau-Salinas F. Pharmacovigilance of vaccines. Arch Pediatr. 2006 Feb;13:175-80.

Barder O. Vaccines for development. CGD Brief, Center for global development. Web page: www.cgdev.org. 2006

CBER, Compliance Program Guidance Manual, Chapter – 45 Biological Drug Products

CDC, Center for Disease Control and prevention, webpage www.cdc.gov/

Centers for Disease Control. Smallpox vaccine no longer available for civilians—United States. MMWR Morb Mortal Wkly Rep 1983;32:387.

Chang P.Y., Sheets R, Shapiro S, Hargus S, Gruber M. Vaccine Pre-clinical Toxicology Testing http://www.niaid.nih.gov/hivvaccines/Science/VRTT/00_Main.htm

Clifford, JCM. A regulatory perspective on the development of new vaccines against Bacillus anthracis. Powerpoint presentation from FDA/CBER. 2000

Dellepiane N, Griffiths E, Milstien JB. New challenges in assuring vaccine quality. WHO Bulletin, 2000, 78: 155-162

EASAC, Vaccines: Innovation and human health, May 2006

EMEA/CHMP/VWP/73919/2004 Mandate, objectives and rules of procedure for the CHMP vaccine working party (VWP)

EMEA web page: http://www.emea.eu.int/

Ericson M, Webster C, Cremiers F. Accelerated Assessment and temporary marketing authorization in the European Union. RAJ Pharma. Sept. 2004; 645- 649.

Fedson DS. Preparing for Pandemic Vaccination: An International Policy Agenda for Vaccine Development. J Pub Health Pol 2005; 26:4–29.

Food and Drug Administration. New drug and biological drug products: evidence needed to demonstrate efficacy of new drugs for use against lethal or permanently disabling toxic substances when efficacy studies in humans ethically cannot be conducted. Federal Register 1999;64:53960-70.

FDA web page: www.fda.gov/cber/vaccine/

Healy E.M. and Kaitin K.I. The European agency for the evaluation of medicinal products' centralised procedure for product approval: current status. Drug Information Journal 1999; 33:969–978.

HHS: Department of Health and Human Services web page: http://www.hhs.gov/

ICH web page: http://www.ich.org/cache/compo/276-254-1.html

Influenza vaccine for 2005/6 season: total supply assured but some delivery delays possible compared to 2004. EFPIA/EVM

Lang J and Wood SC. Development of orphan vaccines: and industry perspective. Emerg Infect Dis 1999;5:749-756

Luke C.J. and Subbarao K. Vaccines for Pandemic Influenza. Emerg Infect Dis 2006; 12:66-72.

Medical Encyclopedia: http://www.nlm.nih.gov/medlineplus/ency/article/001356.htm.

National Institute of Allergy and Infectious Diseases (NIAID) web page: http://www3.niaid.nih.gov/research/topics/HIV/vaccines/

O'Donnell P. Two-Timing on Todays's vaccines? 2006 website. Applied Clinical Trials. www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=283026.

PIC, Guide to good manufacturing, practice for medicinal products of the pharmaceutical inspection convention. 1 August 2006 PE 009-5.

Rappuoli R, Miller HI, Falkow S. The intangible value of vaccination. Science 2002; 297: 937-939.

Roland E. AFSSAPS Presentation: FDA review principles.

Rosenthal R, Merchlinsky M, Kleppinger C, and Goldenthal LK. Deveoping New Smallpox Vaccines. Emerg Infect Dis 2001;7:920-925.

Sutter G and Moss B. Novel vaccinia vector derived from the host range restricted and highly attenuated MVA strain of vaccinia virus. Dev Biol Stand 1995;84:195-200.

Slifka M. The Future of smallpox vaccination: Is MVA the key? Med.Immun. 2005;4:2-10.

United Nations. A/60/825. Report of the Secretary-General. Uniting against terrorism: recommendations for a global counter-terrorism strategy

WHO, World Health Organization web page: http://www.who.int/biologicals/areas/vaccines/smallpox/en/

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Windach, den _____

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