The Development of Regulatory Authorities and of the Process of Post Marketing Surveillance in Developing Countries

Fondation Mérieux Conference Centre
‘Les Pensières’
Veyrier-Du-Lac, France

March 29-31, 2010

Steering Committee:

• Nora DELLEPIANE
• Catherine DUTEL
• Bernadette HENDRICKX
• Jacques LOUIS
• Pieter NEELS
• Patrick ZUBER
March 29, 2010

Dear Participant,

It is our pleasure to welcome you to the symposium entitled:

“The Development of Regulatory Authorities and of the Process of Post Marketing Surveillance in Developing Countries”

in Fondation Mérieux’s Conference Center “Les Pensières.” We hope you will enjoy this meeting, which brings together some of the world’s foremost experts.

The format of the discussion is intended to generate discussion and interaction among participants and to foster the dissemination of new information on this topic. The conference will provide an opportunity for specialists to exchange their knowledge and experience through collaboration with researchers from around the world.

Over the next three days, the team at Les Pensières will be on hand to help you with any questions you may have and to make your stay and conference as comfortable and valuable as possible.

Yours sincerely,

Benoît Miribel
Directeur Général
Fondation Mérieux

For more information: www.fondation-merieux.org
Background and rationale

Vaccination is a very powerful public health tool for preventing many infectious diseases. The protection obtained in vaccination programs can be measured both at individual level and community level. As for drugs, the vaccines need to be registered and licensed by regulatory and health authorities before vaccination recommendations.

The evaluation of the vaccine to be licensed is focusing on 4 major aspects: quality, efficacy, safety and post-marketing surveillance. As the last item is implemented since several years in the Western Countries, the Developing Countries are still working on better pharmaco-vigilance systems.

Recently risk management plans have been implemented both in Europe and North America, significantly increasing the safety activities in a pro-active manner. Manufacturers have to meet the requirements set by regulatory agencies for both registration of vaccines and post-marketing surveillance. Although most developed countries have a national regulatory authority, with two forefront agencies (EMEA for EU countries and FDA for the USA), important differences exist between different regions of the world regarding the requirements for registration of vaccines and pharmaco-vigilance. Developing countries have a broad range of regulations regarding both the registration and the pharmaco-vigilance systems.

The objective of this meeting is to bring together experts from the regulatory agencies, the vaccines manufacturers and vaccines program (EPI) from both Developed and Low to Middle Income Countries (LMIC), aiming at:

- presenting status on the role of regulatory agencies in relation to the benefit-risk ratio of vaccines (clinical trials and pharmaco-vigilance) in both western and low to middle income countries; with a discussion on how vaccines are evaluated on the different parts of the dossier: Quality, Non-Clinical, Efficacy, Safety and Risk Management Plan.

- discussing the response of vaccine manufacturers to increasing demands of regulatory agencies in terms of vaccines safety and effectiveness. Indeed once a vaccine is licensed, it is extremely important to measure and follow how the vaccine will behave in real world conditions.

- reviewing the international and regional actions for developing/strengthening regulatory authorities in Low to Middle Income Countries and the involvement of the WHO, western regulatory agencies and the manufacturers.

- trying to identify the gaps in the regulatory systems in low to middle income countries.

- trying to identify further actions to be taken to help filling these gaps.
## Scientific Program

### Monday 29 March 2010

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### Tuesday 30 March 2010

**Session 1**

The role of regulatory agencies in relation to safety in clinical trials and pharmacovigilance in industrialized countries

09.00 - 14.00  

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The registration and post-marketing surveillance in Germany  
Brigitte KELLER-STANISLAWSKI

**11.35 - 11.50**  
Discussion

**11.50 - 12.10**  
The Role of Regulatory Agencies in Vaccine Safety – Perspective from the US FDA  
Robert BALL

**12.10 - 12.25**  
Discussion

**12.30 - 14.00**  
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### Session 2
**14.00 - 18.30**  
The role of regulatory authorities in low to middle income countries  
Chaired by Patrick Caubel & Patrick Zuber

**14.00 - 14.20**  
The registration and post-marketing surveillance in Brazil  
Laura CASTANHEIRA

**14.20 - 14.35**  
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**14.35 - 14.55**  
The registration and post-marketing surveillance in Indonesia  
Antonia RETNO UTAMI

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The registration and post-marketing surveillance in South-Africa  
James SOUTHERN

**15.50 - 16.05**  
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**16.05 - 16.25**  
The role of national control laboratories in Europe in acceptance for vaccines  
Jean-Marc SPIESER

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Discussion

**16.40 - 17.00**  
Evaluation of the performance of the pharmacovigilance systems in developing countries  
Patrick ZUBER

**17.00 - 17.15**  
Discussion
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### Session 4

#### Workshops

Facilitators: Daniel Brasseur & Maria Cortes Castillo

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Keynote Lecture

Adverse Events of Vaccination, with some examples
Adverse Events of Vaccination, with some examples

Neal A. HALSEY
Johns Hopkins Bloomberg School of Public Health - USA

Vaccines and the immunization process can result in adverse events through several different mechanisms. The injection process alone can result in fainting or damage to nerves or joints. Infectious agents that are inadvertent contaminants can cause serious infections. The replication of live infectious agents used as vaccines sometimes trigger adverse events that are mild in the vast majority of recipients, but can be associated with rare complications, especially in individuals with altered immune systems. Vaccine components can induce undesirable immune responses, such as immediate or delayed hypersensitivity reactions. Also, there are rare instances of autoimmune responses such as Guillain-Barré syndrome following the 1976 swine influenza vaccine and idiopathic thrombocytopenia. There have been instances of immunizations altering the host response to the target natural infections many years later, such as with inactivated measles and RSV vaccines. In some instances, the pathogenesis of adverse events that have been shown to be causally associated with vaccines has not been clearly elucidated. Past experiences with serious adverse events that were not detected prior to licensure have resulted in increased scrutiny of vaccine safety after regulatory approval of recently licensed vaccines in order to detect rare adverse events.
Session 1

The role of regulatory agencies in relation to safety in clinical trials and pharmacovigilance in industrial countries
Overview: the Evaluation of the Different Aspects of a Vaccine Dossier

Von NAKAYAMA
Public Health Service - USA

The vaccine dossier is a compilation of documents that comprise a request to market the vaccine. It contains the important information about the applicant and the vaccine that is required to demonstrate that the proposed use of the vaccine is safe and effective.

The objective of this session is to identify and summarize the significant vaccine informational elements of the dossier and provide an understanding of one aspect of the vaccine approval process. This presentation will discuss the purpose of the dossier and the different categories and types of information required to meet regulatory expectations.
The EU view on clinical trials evaluation

Pieter NEELS
Belgian Federal Agency for Medicinal & Health Products
Belgium

The evaluation of Clinical Trial Application (CTA) is regulated via the EU Directive 2001/20 (on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). This directive has been implemented in all the different Member States. The Member States are responsible for the evaluation of the CTA and thus the organisation (Who does what) of this evaluation is different from MS to MS.

However, the data package of the CTA containing information on the Quality, Non-Clinical and Clinical aspects of the new medicinal product have to be evaluated. In Belgium, by example, the tasks have been split: the Q and the NC is evaluated by the competent authority (FAMHP), while the clinical aspects have to be evaluated by an Ethics Committee (EC). There is a single opinion, but all the local Ethics Committees of the hospitals where investigators are working, are implicated in the procedure.

For vaccines the Q part is very important as most vaccines are intended for use in a healthy population and most of the clinical trial subjects are throughout the whole vaccine development healthy volunteers.

The NC part is for vaccines frequently rather meagre: for many infectious diseases, animal models are lacking and thus the proof of concept is rather difficult to perform in an animal model.

The C part is of course extremely important for the evaluation of a CTA for vaccines. All the different aspects have to be taken into account: placebo or active comparison; primary endpoint, immunogenicity or disease prevention; sample size calculation; stratification per age category, per risk group; definition of the target population and special subgroups; inclusion and exclusion criteria; duration of follow-up, etc.
The safety of clinical trials investigating paediatric vaccines, a European perspective

Daniel BRASSEUR
European Medicines Agency - Belgium

The Paediatric Regulation EC 1904/2006 (“Better medicines for the children of Europe”) has created since 2007 a new environment for the development of paediatric medicines, including vaccines. Indeed Industry is now obliged by law to submit to the authorities (EMA) their views on how the paediatric counterpart of any adult medicine will be developed without any undue delay. Companies submit paediatric investigational plans (PIP) as soon as the pharmaco-kinetic data in adults have been generated and comforted their pharmacodynamic concept. For paediatric vaccines some data in adult volunteers can allow drafting a PIP proposed to the PDCO of the European Agency. This plan should contain a comprehensive pharmaceutical part, potentially pre-clinical studies on (juvenile) animal models but surely describe the age-appropriate formulation supposed to reach the market after extensive clinical studies supporting efficacy/immunogenicity and safety of the candidate product has been convincingly demonstrated. A special attention is given to the safety profile before engaging with a new product in children and similarly sufficient follow up is required during the market phase to confirm the initial safety data. In this respect some elements of the future risk management plan as decided by the licensing body at the time of marketing authorization are already envisaged saving time and enriching the safety database with early results generated by the clinical trials. The PDCO discusses with Applicants their strategy having implications on the future use of the candidate vaccine and without saying, its positioning in (official) schedules.
The registration and post-marketing surveillance in Germany

Brigitte KELLER-STANISLAWSKI
Paul Ehrlich Institut - Germany

Abstract not provided
The Role of Regulatory Agencies in Vaccine Safety
Perspective from the US FDA

Robert BALL
Office of Biostatistics and Epidemiology - CBER - FDA - USA

Vaccination is considered one of the most successful public health achievements of the 20th century and has prevented thousands of deaths and illnesses. Nevertheless, vaccines, like all medical products, have some risk of adverse effects. These risks are generally small because of the extensive testing vaccines undergo prior to licensure and stringent controls on vaccine manufacture. This talk will review the history of vaccine safety and the regulatory framework that has been adopted in the US to respond to vaccine safety concerns. Principles will be derived from this examination to suggest a framework for developing a vaccine safety infrastructure in countries with a range of available economic resources.
Session 2

The role of regulatory authorities in low to middle income countries
The registration and post-marketing surveillance in Brazil

Laura CASTANHEIRA
Gerência Geral de Medicamentos - Brazil

Abstract not provided
The registration and post-marketing surveillance in Indonesia

Antonia RETNO UTAMI  
National Agency of Drug and Food Control - Indonesia

NADFC is a functional Regulatory Authority in Indonesia which has responsibilities of controlling pre-market and post market assessment based on safety, efficacy and quality aspect of drug as well as safety of food, marketed in Indonesia. It is stipulated in the current Indonesia Health Act No. 36, 2009, that drug and food products should be safe, efficacious and assured quality. Structure of the organization covering responsible units that comprehensively taking care of pre market and post market control of Therapeutic Product. Those unit covers the functions of Marketing Authorization of Product; laboratory for testing; lot release for vaccines; GMP inspection for production and distribution facilities; Clinical trial authorization; Post market surveillance activities. Pre market evaluation of therapeutic product is done by thorough assessment of pre clinical, clinical and pharmaceutical data. Experts panel and National Committee also involve in the system for the final decision making process of marketing authorization. Clinical trial for registration purposes conduct in Indonesia should have authorization from NADFC. The post market surveillance activities is very much related to the registration unit as primary source of information on the safety and efficacy of the product. However, any new signal or unwanted effect should be reported using adverse drug monitoring report system.

Variation on product information related to safety, efficacy and pharmaceutical or product specification, should be approved prior to implementation.

Special consideration on post marketing activities has been taken for vaccines use in the national immunization program. NADFC strongly supports the Adverse Event Following Immunization (AEFI) system lead by CDC. In this regard NADFC involve in the product quality assessment, causality assessment of AEFI and training program for central and regional committee on AEFI.
The registration and post-marketing surveillance of vaccines in South-Africa

James SOUTHERN
National Regulatory Authority - South Africa

Objective:
Describe the background and structure of the current system for registration of medicines – particularly vaccines in South Africa. The inter-relationships between the various bodies are outlined, and the flow of the regulatory procedures described. Some detail is provided of the composition of the expert committees and their functions and responsibilities.

The Medicines Control Council (MCC) has the responsibility for deciding on the registration of a medicine and the Registrar of Medicines issues the Certificate of Registration. A series of expert committees support the MCC.

The members of the Biological Medicines Committee are responsible for the evaluation of an application and the reports are peer reviewed by the full committee before a recommendation is made to the MCC for registration.

The Clinical Trials Committee reviews applications for clinical trials in parallel with a local Ethics Committee and may recommend approval subject to Ethics Approval. Reports of adverse events during clinical trials are reported to the Clinical Trials Committee.

The Pharmacovigilance Committee and the National Adverse Event Monitoring Centre collect, collate and analyze the spontaneous adverse event reports from all registered medicines, received nationally. There is a link with the PV Centre in Uppsala.

The National Immunization program, EPI(SA), has a monitoring component for adverse events following immunization. The National Anti-retroviral program also has funded two centres to collect and collate reports of adverse reactions. Other special programs, such as the Malaria program and the Tuberculosis program also have a pharmacovigilance component.

Some of the strengths and weaknesses of this regulatory model are discussed and the probable future changes to the system are also noted.
The role of national control laboratories in Europe in acceptance for vaccines

Jean-Marc SPIESER
EDQM - Council of Europe - France

Abstract not provided
Evaluation of the performance of the pharmacovigilance systems in developing countries

Patrick ZUBER
WHO - Switzerland

Vaccine Pharmacovigilance systems from developing countries rely heavily on the collaboration of governmental services involved in vaccine delivery and disease surveillance with their national regulatory authorities (NRAs). Through the process of assessing the functions of national regulatory authorities, a benchmarking system using indicators and sub-indicators has been developed since 1997 and applied to 101 countries with different level of vaccine safety performance and infrastructure. Vaccine pharmacovigilance, as one of the six functions, is currently assessed through 8 indicators and 25 sub-indicators. Those encompass the structural and functional aspects of pharmacovigilance, including the quality management systems, the assessment and monitoring of vaccine performance, the feedback system, the training and feedback, the communication and information to the patient, public and media. Based on the findings from those assessments, it was estimated that as of 2009, at least 71 developing countries encompassing more than 3 billion inhabitants had not implemented all recommended functions for vaccine pharmacovigilance. However, there are also already 33 developing countries encompassing 2.3 billion inhabitants that are estimated to have implemented those functions. Enhancing the performance of national pharmacovigilance systems requires a strong capacity model, continuous quality assessment systems, effective government commitment, and external support mechanisms. WHO has consistently promoted the use of standards guidelines and case definition, improvement of the detection and case investigation, introduction of causality assessment, continuous feedback, as well as keep abreast information and communication with public and media, and increase an environment of transparency about vaccine safety concerns. The past experience has been helpful for WHO, with many partners including regulatory agencies and vaccine manufacturers to open the debate on a worldwide concerted approach that will address new challenges. This discussion will be translated into a global blueprint model that will aim at proposing an improved global, regional and country level vaccine safety assessment and response system.
Current status of the responses of Manufacturers to the demands of Authorities regarding pharmacovigilance, signal detection and Risk Management

Patrick CAUBEL  
Sanofi Pasteur - France

The current limitations of post-marketing vaccine surveillance in developing countries is problematic for all stakeholders in the Immunization Community, particularly for vaccine manufacturers. They can be summarized as (1) lack of safety data due to inadequate safety collection systems, (2) insufficient availability of vaccine post-marketing surveillance systems to manufacturers and (3) poor flow of information between manufacturers and regulatory authorities. Improving data collection as well as information sharing is considered as critical by vaccine manufacturers in order to meet their ethical and regulatory obligations. New safety issues may emerge with legacy products that require access to large populations for full investigation (i.e. yellow fever vaccine and viscerotropic and neurotropic syndromes). Re-introduction of vaccine with established risk-benefit ratios may require extensive post-launch safety monitoring (i.e. rotavirus vaccine and intussusception). Introduction of vaccines based on new technologies (i.e. chimeric vaccines) will necessitate careful safety assessment large populations not achievable during clinical development. At a time when proactive safety Risk-Management is becoming both an internal and a regulatory standard for vaccine manufacturers, regardless of the country of distribution, vaccine manufacturers would like to contribute to a continuous improvement pharmacovigilance, signal detection and Risk Management in developing countries. Vaccines manufacturers have high expectations regarding their role in a global vaccine safety partnership.
Yellow Fever Vaccine Pharmacovigilance at Bio-Manguinhos/Fiocruz

Reinaldo DE MENEZES MARTINS
Bio-Manguinhos/Fiocruz - Brazil

Objective:
To assess the risk-benefit of yellow fever vaccine in Brazil, according to risk of disease and risk of serious adverse events.

Methods:
Brazil has a system for Surveillance of Adverse Events Following Immunization, implemented in 1998. There is a Manual with definitions of adverse events, and a form for reporting them. The basic source of information are the more than 30,000 Health Centers spread all over Brazil. Cases are identified locally, consolidated at state level and final classification is done at central level (Ministry of Health). Other sources of information are sentinel hospitals, for reporting of ictero-hemorrhagic syndromes, active surveillance during campaigns, and complaints of customers to Bio-Manguinhos through the Customer Service and Post-Marketing Division of Bio-Manguinhos. A Pharmacovigilance Unit has been established in Bio-Manguinhos/Fiocruz, connected to the MoH and the Brazilian Regulatory Agency. A Guideline for Investigation of Serious Adverse Events has been developed and distributed, as well as a simple flowchart, explaining how to collect, transport and deliver samples from patients to laboratories. A network of laboratories at state and national level gives support to the surveillance system. The Ministry of Health provides information on the number of doses of vaccine administered by age groups, so rates of adverse events may be estimated according to age.

Results:
Since 1999, more than 100 million YFV doses have been administered in Brazil. Hypersensitivity events (total) have been detected at a frequency of 0.9/100,000 doses, of which anaphylactic shock in 0.023/100,000 doses. YFV-AVD (total) has been detected at a frequency of 0.084/100,000 doses. We have data on 26 AVD cases with Bio-Manguinhos YFV, 21 from Brazil and 5 from other countries, of which 19 are confirmed, 4 probable and 3 suspect cases. Of these, 10 are male, 15 female and 1 unknown sex, a 1975 case. Letality has been very high: 24/26 cases (92.3%). There are no clear differences of risks of adverse events according to age.
During recent YFV campaigns in São Paulo and Rio Grande do Sul, rates of serious adverse events have been much higher, probably due to better system alertness. The number of cases of wild yellow fever in Brazil remains low, despite increasing dissemination of the virus to almost all parts of the country. YF vaccine is recommended for regions were the risk of the disease justifies it or for travelers to these regions.

Conclusions:
Risk assessment is basic for rational recommendations regarding yellow fever vaccine and other immunizations. This evaluation should be permanent and recommendations must be changed according to the information available. Pharmacovigilance is an important tool for public health decisions.
Session 3

International and regional status and possible actions for developing regulatory authorities in low to middle income countries
Developing Country Vaccine Regulators’ Network

James SOUTHERN
DCVRN - South Africa

The DCVRN comprises representatives from the National regulatory authorities (NRA) of developing countries that have achieved a degree of medicine regulatory competence as assessed by the WHO. The member countries are Brazil, China, Cuba, India, Indonesia, South Korea, Russia, South Africa and Thailand.

These representatives have met twice a year, starting in September 2004, to discuss a defined agenda and propose actions for the future. In practice representatives from other regulatory authorities that have a specific and urgent interest in the agenda topics have been invited as observers. Experts from other more-developed regulatory authorities, and the WHO have acted as presenters, advisors and facilitators at meetings.

The focus of activities has been to support and promote the strengthening of the regulatory capacity for evaluation of clinical trial proposals including pre-clinical data, product development processes and clinical trial data for registration of new vaccines.

The DCVRN has been active in providing an annual list of items for consideration by the WHO Expert Committee on Biological Standardization that relate to the concerns of developing countries and introduction of new vaccines. In addition a number of guidelines have been prepared, or are in preparation, that will assist DCVRN members and the regulators of other developing countries with the regulation, control and inspection of vaccine clinical trials and trial sites. Regulatory support centres are being established in South Africa and Indonesia that are functioning at the moment as training centres. Other similar-groups of regulators have been formed in the WHO Africa and Asian Regions that receive support from the DCVRN members.

There are several future activities in development or under consideration, including joint reviews of clinical trial applications, joint inspections of clinical trial sites, development of an IND-like process for new vaccines (already in the pilot stage), and a co-inspection program leading to possible mutual recognition of GCP Certification of vaccine clinical trial results.
AVAREF: a regional network to support regulators in the oversight of clinical trials

Bartholomew D. AKANMORI
WHO Regional Office for Africa - Congo

The promotion of research and development in Africa has the potential to lead to the identification of appropriate medicines to tackle priority diseases, including HIV/AIDS, malaria and tuberculosis. However African countries are faced with the challenge of providing adequate regulatory oversight of clinical trials consistent with international guidelines and standards. This will ensure the safety of their populations, while promoting the benefits of research for those who will eventually use the products.

Recognizing the challenges faced by countries in the African region, WHO initiated activities for strengthening the National Regulatory Authorities (NRAs) and Ethics Committees (ECs) in Africa in order to ensure the safety of vaccines being tested in the countries, which will also lead to vaccines of high efficacy and quality which are also compatible with existing products.

This has been achieved through the establishment of the African vaccine Regulatory Forum (AVAREF), a network of NRAs and Ethics committees which is an effective initiative to build capacity and promote regulatory harmonization of vaccine clinical trials. As an informal structure, AVAREF allows rapid and dynamic response based on the needs identified and with the help of more experienced regulators in Europe and North America.

AVAREF has functioned through its annual meetings and other activities including joint reviews of clinical trial applications and joint inspections of clinical trial sites.
Overview of the Pan American Health Organization (PAHO) strategy and activities to support and strengthen National Regulatory Authorities in the Americas

Maria DE LOS ANGELES CORTES
PAHO - USA

One of the main objectives of the Essentials Medicines and Technologies project at the Pan American Health Organization (PAHO) is to strengthen National Regulatory Authorities (NRA) in Latin America and Caribbean countries, in order to guarantee the quality safety and efficacy of the medicines and vaccines to be used in the Region.

In the vaccine area, the support provided to NRA has been developed through the creation of regional networks such as the Pan American Network for Drug Regulatory Harmonization (PANDRH), the Regional Network of Vaccines Quality Control Laboratories (RNVQCL) and coordinating or facilitating several initiatives in support of vaccines post-marketing surveillance activities (SANEVA group, International Study of Risk of GSB after pandemic H1N1 vaccine introduction, WHO initiatives, etc.)

The PANDRH is a regional initiative created in 1999 with the following purposes:

- To establish a Pan American Forum of Drug Regulatory Agencies (DRA) to discuss and find solutions to common problems. Drug Regulatory Agencies lead and participate in this process.
- To strengthen the establishment of priorities in drug regulatory harmonization processes and to encourage convergence of drug regulatory systems in Region.
- To improve access to quality drugs which are safe and efficacious and to advance the quality of pharmaceutical markets.
- To promote technical cooperation through the sharing of knowledge and experience by more developed DRA with less advanced ones.

The current PANDRH Working Groups are:

- Good Manufacturing Practices
- Bioequivalence and Bioavailability
- Good Clinical Practices
- Drug Classification
- Counterfeit Drugs
- Good Laboratory Practices
- Pharmacopoeia
- Medicinal Plants
- Drug Registration
The PADRH Vaccines Working Group was created in 2005 and its main product is the Harmonized Requirements for Licensing of Vaccines in the Americas and the Guidelines for preparation of applications. The purpose of these documents is to achieve greater harmonization in the information submitted in the application for licensing of vaccines for human use. They apply to all vaccines to be registered, regardless of whether they are manufactured in the country of origin or not. Since the same information should be submitted to all countries in the Americas, the licensing process and ultimately the availability of vaccines should be facilitated. It is expected that having a common document will also benefit the region by making more efficient use of technical and financial resources, as well as facilitating mutual recognition processes where appropriate.

The future activities for the PANDRH Working Groups will focus on creating one single, harmonized proposal for some of the regulatory activities for medicines and vaccines, in the countries of the Region. In order to optimize the experience and knowledge obtained from them. These activities include Good Manufacturing and Laboratory Practices, Good Clinical Practices and Pharmacovigilance.

Suite

- Pharmacovigilance
- Vaccines
- Promotion and Marketing
Prequalification of vaccines for UN supply, facilitation of registration of prequalified vaccines

Nora DELLEPIANE
WHO - Switzerland

Objective:

WHO has developed a procedure for expedited review of imported prequalified vaccines for the purpose of giving a marketing authorization. The presentation will briefly describe the procedure and the circumstances under which the procedure is recommended to be implemented.

Summary:

The Vaccines prequalification programme is a service provided by WHO to the UN purchasing agencies with regards to assuring the quality, safety and efficacy of the vaccines for purchase. The prequalification procedure relies on functional National Regulatory Authorities in producing countries and evaluates only vaccines that have been granted a marketing authorization (or a surrogate to a MA, i.e. scientific opinion by EMA). The added value of the prequalification evaluation is that in addition to the assessment performed by the NRA in country of manufacture, it focuses on the specific aspects that are relevant to the UN target population, such as immunization schedules compatible with those in developing countries, non-interference with vaccines co-administered following these schedules, clinical data relevant to the target population, product characteristics suitable for use in developing countries such as presentation in vials rather than in pre-filled syringes, stability profile suitable for tropical countries with weak cold chain systems, etc.

Such vaccines are therefore evaluated first by the NRA in country of origin and secondly by WHO to ensure that the WHO recommendations and the UN specifications which reflect the needs of the national immunization programmes are met.

The expedited review procedure proposes a facilitated review of documents (Summary lot Protocols), checking of the appearance of samples submitted by the manufacturer and a review of the labels of vials and boxes and package inserts.
The procedure is recommended to be used by countries procuring vaccines through UN agencies or self procuring countries purchasing WHO prequalified vaccines. The advantage of adopting such a procedure is that scarce resources available in the NRA of the importing country can be dedicated to other regulatory functions that are more relevant and for which no replacement is possible, i.e. post-marketing surveillance, particularly surveillance of adverse events following immunization.

Conclusions:

The procedure for expedited review of imported prequalified vaccines for use in national immunization programmes is a tool for countries to make an efficient use of resources, to avoid repetition of efforts in the evaluation of vaccines for registration (particularly vaccines that have been in the market for some time) and to dedicate their resources either to the review of novel vaccines or to other essential regulatory functions.

Ref. Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes. WHO/IVB/07.08
WHO’s Global Network for Post-marketing Surveillance of Pre-qualified Vaccines

Patrick ZUBER
WHO - Switzerland

With an increasing market segmentation in vaccine products, low- and middle-income countries with weak vaccine pharmacovigilance systems tend to use products that do not benefit from adequate monitoring in other parts of the world. The Global Network for Post-marketing Surveillance of Pre-qualified Vaccines is a WHO initiative that aims at developing a standardized approach to monitoring and assessing the safety of WHO pre-qualified vaccines. This Network will improve knowledge about the safety profile of those vaccines in the post-marketing phase and improve the interpretation and use of safety data on a global level. It will also provide a set of model countries that share common methodologies and procedures and could become a resource for capacity building in their respective regions. Initially eleven countries (distributed across the six WHO Regions) have been selected on the basis of evidence of adequately functioning post-marketing surveillance systems. Network activities involve national regulatory agencies, immunization programmes and other local bodies dedicated to vaccine safety to ensure a seamless collaboration. The project provides resources and capacity for enhancing post-marketing surveillance in those countries with the use of international standards and terminologies for pharmacovigilance; support for data management and analysis; and improvement of synergies between drug and vaccine pharmacovigilance activities. At the global level, the WHO Programme for International Drug Monitoring (through its Collaborating Centre, the Uppsala Monitoring Centre or UMC) has been selected as the common reporting site. Data from the Network countries will be sent to the global database of the WHO-UMC programme for vaccine data mining and signal detection. Those activities will enhance the analysis of all reported vaccine adverse events and provide many opportunities to further develop the methods for vaccine safety signal detection.
A Pilot International Study of the Risk of Guillain-Barré Syndrome following H1N1 Vaccination

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FDA - USA

Background:

Many countries worldwide have limited capacity and/or experience implementing epidemiological vaccine safety studies and, unavoidably, must rely almost exclusively on passive surveillance for post-marketing safety. In the past the availability of comprehensive vaccine safety assessment systems in the US and EU has served most of the global need to evaluate newly released vaccines because most new vaccines were manufactured and introduced in the US and Europe prior to release elsewhere. However, new vaccines are now being introduced either exclusively in the developing world or concurrently with their release in Europe and the US. These changes indicate the need for improved vaccine safety assessment in low and middle income countries to ensure the safety of new vaccines.

The global spread of a novel influenza A (H1N1) virus during 2009 led the World Health Organization (WHO) to declare a pandemic. Because of this, vaccine manufacturers worldwide dramatically increased efforts for pandemic H1N1 vaccine production, to make it available to a sizable proportion of the world’s population. These efforts have resulted in a large number of H1N1 vaccine products, including live vaccines, and adjuvanted and non-adjuvanted inactivated vaccines, some of them from manufacturers with limited prior experience in influenza vaccine production.

Objectives:

To demonstrate the feasibility of a collaborative, WHO-sponsored consortium of vaccine safety researchers and their respective organizations from developed and middle income countries that can utilize medical hospitalization databases to assess the risk of a medical outcome following vaccination. Because of its association with the 1976 swine flu vaccine, we chose to investigate the association between GBS and H1N1 influenza vaccination for this proof of concept study.
Methods:
The protocol will be implemented in sentinel hospitals of selected countries. An effort will be made to include hospitals from countries that, despite having technical capacity for increased surveillance, have relied almost exclusively on passive surveillance activities and outbreak control efforts, as well as countries with prior experience with epidemiological studies of vaccine safety.

All patients with GBS hospitalized in the selected institutions during the study period will be evaluated. Confirmed cases will be described by age, gender, Brighton level of case definition, and H1N1 and seasonal influenza vaccine exposures. As a primary analysis, only those cases classified under the Brighton Criteria as level 1 or 2 will be included. Data will be analyzed using the self control case series methodology to investigate whether H1N1 influenza vaccination is associated with an increased risk of GBS during a pre-specified high-risk time window (days 1-42 post vaccination). WHO will be the host institution for the protocol and data repository. The VAESCO project, coordinated by the Brighton Collaboration, comprises nine European countries (Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Sweden, United Kingdom). These countries follow a common protocol also including cases reported via neurological networks and utilize a shared infrastructure. Options to integrate these data as part this study will be explored.

Results:
As of February, 2010, the protocol has been finalized and was approved by WHO’s ethical committee. Including the VAESCO project, institutions from 23 countries, representing five continents, have either initiated the study or expressed interest in participation. Of them, institutions from 14 countries, including Australia, Canada, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Singapore, Spain, Sweden, United Kingdom, and the U.S.) have already initiated the study.

Discussion:
A consequence of the remarkable success of vaccines in decreasing disease incidence, and even in eliminating some diseases, has been an increased public attention on the possible association between vaccines and rare but serious adverse events. Developing global capacity to evaluate vaccine safety signals that arise out of passive surveillance systems or from other sources is highly desirable both to assure the safety of the world’s vaccine supply and also to address public concerns about vaccine safety, which can undermine successful programs. In addition, evaluation of serious but very rare events - such as Guillain-Barré Syndrome, anaphylaxis, or death - would be facilitated by the increased statistical power that could be achieved through international collaborations. This WHO-sponsored collaborative approach should become an important part of the armamentarium for global vaccine safety monitoring.
The view of Sanofi Pasteur on the evolution of regulatory systems at the international level

Andrea ARANCIBIA - Isabelle DESCHAMPS
Sanofi Pasteur - France

Vaccine industry has a core ethic that it shares with its regulators for providing safe and efficient vaccines to medical professionals and patients.

In the current evolving regulatory environment, industry and regulators continually face pressure to make better and more efficient use of resources to accelerate the worldwide access of vaccines without compromising neither the quality of distributed products nor the national obligations of NRAs. In this perspective, five axes have been identified: Regulatory requirements and review processes, manufacturing site inspections, national lot release, initiatives of harmonization and clinical trials.

Moving toward a more unified and simplified system would limit the redundancy and duplication of reviews during regulatory procedures allowing to focus resources on other most relevant areas that can jeopardize the quality, safety or efficacy of vaccines.
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