PROPOSED ADDENDUM TO: WHO TRS 927, Annex 3.

*Recommendations for the production and control of influenza vaccine (inactivated)*

**LABELLING INFORMATION OF INACTIVATED INFLUENZA VACCINES FOR USE IN PREGNANT WOMEN**

**NOTE:**
This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed WHO document on *Labelling Information of Inactivated Influenza Vaccines for Use in Pregnant Women* to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text MUST be received by **February 2016** in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Hye-Na Kang at email: kangh@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).

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1. Introduction

Morbidity and mortality due to seasonal influenza virus infection is considered as substantial worldwide (1, 2). Pregnant women are especially vulnerable. They have an increased risk of severe disease and death from influenza and the infection may also lead to foetal complications such as stillbirth, neonatal death, preterm delivery and decreased birth weight (3). For these reasons, in 2012, the WHO position paper on vaccines against influenza (3), endorsed by the WHO Strategic Advisory Group of Experts in Immunization (SAGE), recommended the immunization of pregnant women with trivalent inactivated influenza vaccine (IIV) at any stage of pregnancy (3). It also recommended that pregnant women should have the highest priority for countries considering the initiation or expansion of immunization programmes for seasonal influenza vaccination (3). The recommendation is based on evidence of a substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe throughout pregnancy and effective in preventing influenza in the women as well as in their young infants, in whom the disease burden is also high (3, 4). However, for various reasons, the implementation of influenza immunization remains suboptimal (5). One reason is the perceived risk of administering influenza vaccine, or indeed any vaccine, to this population group and, in particular, the precautionary language used in some product labels and its likelihood of misinterpretation.

This addendum considers the regulatory aspects of product labelling information and provides clarification and interpretation of the labelling information provided in the product insert of IIVs so as to facilitate the much needed immunization of pregnant women.

2. Background

Activities to enhance the uptake of vaccines during pregnancy are important elements of WHO’s ongoing initiative to improve maternal and child health. As part of this work, WHO held a consultation in July 2014 on influenza vaccines for pregnant and lactating women which focused on the clinical data requirements for product labelling information (6). This was organized by the WHO Technology, Norms and Standards Team and the WHO Initiative for Vaccine Research Team and brought together researchers, manufacturers and regulators with experience in vaccines. A further consultation was organized by the WHO Technology, Norms and Standards team in 2015 to review existing guiding principles related to product package information for IIVs as well as to explore the possibility of providing WHO guidance document to help clarify the benefits of vaccination during pregnancy that could remove any negative perceptions and improve uptake of inactivate influenza vaccines during pregnancy (7). Regulatory policy and practice with regard to permitted text in the product insert sections related to pregnancy and lactation from Brazil, Canada, European Union, Ghana, India, Indonesia, Thailand and the United States of America were described. The results of a 2014 survey of the WHO Developing
Country Vaccines Regulators Network regarding the regulatory policies and perceptions of the wording of the product insert related to vaccines use during pregnancy were also presented. The diversity of approach and understanding in different countries and regions was evident. In addition, it became clear that in countries that import IIVs, the format, data and language included in the product insert usually reflected the text approved by the national regulatory authority (NRA) in the respective country of manufacture and licensing. However, some developing countries require additional language that makes the perceived cautionary message for use even stronger. The regulatory position is based on the fact that licensing is product specific and reliant on data generated during the clinical evaluation of the vaccine and submitted by the manufacturer. Pregnant women are usually excluded from clinical studies during vaccine development, so licensure dossiers generally do not include information on safety and efficacy of the particular vaccine in pregnant women.

The regulatory language used in the “Specific Populations” section of product labelling reviewed did not contraindicate the use of IIV in pregnant women, nor was it intended to be a barrier to use. Nevertheless, this language may be perceived as opposing advisory statements from National Immunization Advisory Groups (NITAGs) and the WHO SAGE. After careful analysis of data worldwide, the WHO Global Advisory Committee on Vaccine Safety (GACVS) concluded that there was no evidence of adverse pregnancy outcomes associated with vaccination of pregnant women with several inactivated viral or bacterial vaccines, including IIVs (4). This outcome, combined with the known possible serious outcomes of influenza infection in pregnant women, led to the strong advice from the WHO SAGE that the benefits of immunization with IIV outweigh any risk and to the recommendation that immunization of pregnant women should be given the highest priority (4, 8).

Regulatory authorities are conscious of the perceived conflict between regulatory and programmatic needs and revision of current practice and language is underway in some countries (9). Others have considered how to integrate post-market surveillance data into the regulatory process (5). Some NRAs include a statement to the effect that their national advisory committee on immunization considers influenza vaccination safe during pregnancy and indicating that the vaccine should be used when needed (10-12).

This document arises from the recommendations of the WHO SAGE regarding the advice to immunize pregnant women with IIV and the resulting discussions of the two WHO consultations mentioned above (6,7), as well as discussions at the 2015 meeting of the WHO Expert Committee on Biological Standardization (ECBS Report 2015 to be published later). The intention is to provide clarification and interpretation of the labelling information provided in the product insert of IIVs, as well as to raise awareness of the convergence of the different regulatory positions, in spite of differing approaches, regarding the use of these vaccines in pregnant women.
3. Scope

This document applies to inactivated influenza vaccines. It is intended for manufacturers, NRAs, end-user programme managers and NITAGS.

Although the focus is on IIVs, some of the concepts and guidance given could be expanded to cover other influenza vaccines when sufficient data are available, as well as other inactivated vaccines, such as Td (13) and pertussis vaccines.

This document will align with further guidance on the clinical design and evaluation of vaccines in pregnant women in the *WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations* that is currently being updated to include expanded text on clinical trials in pregnant women (14,15).

Liability issues are beyond the scope of this document.

4. Terminology

The definitions given below apply to the terms as used in this document. They may have different meanings in other contexts.

**Maternal immunization:** Frequently used to refer to vaccination prior to, during, or after pregnancy. For the purposes of this document, “maternal immunization” refers to vaccination during pregnancy.

**Label(ling):** all forms of product information, i.e. label(ling), product/package insert, package leaflet, and prescribing information.

5. Labelling Information

IIVs, like all prescription drugs and biological products, must be accompanied by labelling that summarizes scientific information concerning the safe and effective use of the product.

Labelling includes the package insert which is also referred to as prescribing information or summary of product characteristics (SmPC) (16). This component of labelling is the primary mechanism through which regulatory agencies and vaccine manufacturers communicate essential, science-based information that is used by health care professionals in making prescribing decisions and in counseling patients about a product’s risks and benefits. The content and format requirements for labelling are prescribed by regulations specific to the country where the vaccine is licensed and may differ between countries (9,16). Nevertheless, common principles include
that prescribing information must not be misleading and should not contain implied claims or uses for which there is inadequate evidence of safety or effectiveness (17).

5.1 Indications and Usage

The “Indications and Usage” section of labelling communicates a product’s approved indication(s) and should clearly convey the use(s) for which the product has been shown safe and effective. Specific regulatory requirements and standards for demonstrating safety and effectiveness of vaccines may vary between NRAs. However, in general, the standards for demonstrating the safety of a vaccine for its intended indication take into consideration the condition of the recipients and the characteristics of the product. It is expected that data demonstrating the effectiveness of a vaccine for the intended indication and use are derived from adequate and well-controlled clinical studies. While data from related vaccines may be supportive, typically safety and effectiveness are evaluated for the specific vaccine intended for licensure. For currently licensed IIVs, data from adequate and well-controlled studies to evaluate the safety and effectiveness of these vaccines in the pregnant woman or newborn infant may not be available for labelling. Data from studies published in the literature about use of IIV in pregnancy may not have been submitted to NRAs or may not meet the regulatory requirements for evidence of safety and effectiveness. For example, product (brand) specific safety and effectiveness data may not be available. Consequently, the prescribing information for IIVs often does not include an indication and usage statement that specifically addresses use in pregnancy. However, IIVs are not contraindicated for use in pregnancy, and this use is acceptable following a risk-benefit assessment, that may be conducted by the NITAG. In this case, IIVs may be used to immunize pregnant women.

5.2 Warnings and Precautions

The “Warnings and Precautions” section of labelling is intended to describe and identify adverse events that are serious or clinically significant because they have implications for prescribing decisions or for management of patients. To include an adverse event in this section, there should be reasonable evidence of a causal association between the drug and the adverse event but a causal relationship does not have to be established. Serious adverse events may be defined as those that result in the following outcomes: death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious (18). Other adverse events that do not meet the definition of a serious adverse event, but are clinically
significant because of implications for prescribing decisions and patient management should also be included under this section. The description of an adverse event in the “Warning and Precaution section” may cross-reference a more detailed discussion of the risk elsewhere in labelling, e.g. “Use in Specific Populations”.

A drug or biological product should be contraindicated only in those situations where the risk from use clearly outweighs any possible benefit. Only known hazards, not theoretical possibilities, should be the basis for a contraindication. For example, evidence in humans or animals that the vaccine poses a serious risk of developmental toxicity during pregnancy would usually warrant a contraindication for use during pregnancy.

5.3 Use in Specific Populations

The “Use in Specific Populations” section of labelling summarizes important differences in response or recommendations for use of the product in specific populations. Information relevant to use of a product during pregnancy is generally found under this section and is sometimes referred to as the “Pregnancy subsection” of product labelling. However, depending on the labelling requirements of the NRA where the vaccine was licensed, information regarding use of IIV in pregnancy may also be found in other sections of product labelling, e.g. the “Warnings and Precautions” section (7). The pregnancy subsection of labelling includes data, when available, from reproductive toxicity studies conducted in animal models to assess the potential developmental and reproductive risk of the product. Data that may be available concerning the safety of the product in pregnant women, e.g. data from a pregnancy registry or data derived from clinical trials where pregnant women were inadvertently exposed to the product are also described in this section. As with other sections of the product labeling, country specific requirements prescribe the information and, frequently, the specific wording to be included in the pregnancy subsection about what is known about the risks of use of the product in pregnancy. WHO pre-qualified IIVs generally have prescribing information reflecting the requirements of the regulatory agency in the country of vaccine licensure. Statements included in the pregnancy subsection of labeling often have been precautionary, e.g. “should be used only following advice of a health care professional”, “if pregnant, please inform your doctor or pharmacist”, “use only if clearly needed”. Some countries, in an effort to improve the clarity of information included in the pregnancy subsection of the labeling, have recently revised their labelling regulations (9). The revised regulations require that labelling include relevant available clinical information from use of the product in pregnant and lactating women, as well as relevant available animal and pharmacologic data to help inform prescribing decisions and counselling of women about the use of the product during pregnancy and lactation. In general, data from use of vaccines during pregnancy that is included in the pregnancy subsection is derived from post-marketing studies and/or from maternal immunization studies published in the literature.
1 Of note, labelling policies for IIVs differ with regard to the information that can be included in
the pregnancy subsection of labeling. For example, in the US, according to recent rule making,
human data that may be included in the pregnancy subsection for any drug or biological product
describe what is known about the risks of use of the product in pregnancy (9,19). These data may
be derived from clinical trials, pregnancy exposure registries, other large scale epidemiologic
studies, or case series reporting a rare event. However, inclusion of data that imply efficacy for a
claim that is not an approved indication cannot be described in this section. In contrast, the
European Medicines Agency (EMA) has implemented a policy based on an evaluation of the
available published evidence relating to both the safety and effectiveness of IIVs and expects all
IIV license holders in the EU to amend the pregnancy subsection of the labelling to include
advice that inactivated influenza vaccine can be used during all stages of pregnancy (6). The
differences in the manufacturing technologies and residual materials in the final product could be
an obstacle in other countries to making recommendations that include several products, as there
is the potential for these differences to influence the safety or efficacy of the different vaccines
when used in pregnant women (7).

18 Data and information contained in the pregnancy subsection of labeling must be approved by the
NRA in the country of vaccine licensure; however, use of IIVs in pregnant women is also guided
by recommendations from health policy makers (e.g. WHO, ACIP, and other NITAGs).

6. Conclusions and interpretation of labelling information

The general conclusion is that the benefit of vaccination with IIVs among pregnant women
usually outweighs the risk for potential adverse effects in the mother or developing foetus when
the risk for disease exposure is high, when infection poses a special risk to mother and foetus,
and when the vaccine is unlikely to cause harm. In some countries, these recommendations may
be included in the pregnancy subsection of labelling. Also, the lack of a specific “indication and
usage” statement about use of an IIV in pregnant women does not preclude its use during
pregnancy. In particular, licensed IIVs are not contraindicated for use during pregnancy. Thus,
programmatic recommendations for use of IIVs during pregnancy are not inconsistent with the
labelling.
Authors and acknowledgements

The first draft of this guidance document was prepared by Dr E. Griffiths, Consultant, United Kingdom; Dr M. Gruber, US FDA, USA; Dr H-N. Kang, World Health Organization, Switzerland; Dr M. Pfleiderer, Paul-Ehrlich-Institut (PEI); and Dr J. Southern, Consultant, South Africa, taking into consideration comments received from the WHO working group meeting on the development of guidelines on labelling information of influenza vaccines intended to be used for pregnant women held in Geneva, Switzerland, 24-25 September 2015, and attended by:

Dr D. Baswal, Ministry of Health and Family Welfare, India; Dr G. Coleman, Health Canada, Canada; Dr E. Griffiths. Consultant, UK; Dr M. Gruber, Food & Drug Administration (FDA), USA; Mrs N. Hidayati, The National Agency of Drug and Food Control (NADFC), Indonesia; Mrs T. Jivapaisarnpong, Ministry of Public Health, Thailand; Dr H-N. Kang, World Health Organization, Switzerland; Mr A. Kukrety, CDSCO, India; Dr P. Lambach, World Health Organization, Switzerland; Dr O. C. Lapujade, World Health Organization, Switzerland; Dr A. Meek, World Health Organization, Switzerland; Dr P. Neels, Consultant, Belgium; Dr E. Nkansah, Food and Drugs Authority, Ghana; Dr J. Ortiz, World Health Organization, Switzerland; Dr C. Rodriguez Hernandez, World Health Organization, Switzerland; Dr J. Southern, Consultant, South Africa; Dr M. F. Thees, National Health Surveillance Agency(ANVISA), Brazil; Dr B. Voordouw, Medicines Evaluation Board (MEB), Netherlands.

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