Off-label use of vaccines

Neels, Pieter; Southern, James; Abramson, Jon; Duclos, Philippe; Hombach, Joachim; Marti, Melanie; Fitzgerald-Husek, Alanna; Fournier-Caruana, Jacqueline; Hanquet, Germaine

Published in:
Vaccine

DOI:
10.1016/j.vaccine.2017.02.056

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Vaccine 35 (2017) 2329–2337

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Off-label use of vaccines

Pieter Neels [a,b,c,*], James Southern [d], Jon Abramson [e], Philippe Duclos [f], Joachim Hombach [f], Melanie Marti [f], Alanna Fitzgerald-Husek [g], Jacqueline Fournier-Caruana [f], Germaine Hanquet [c,h]

[a] Independent Regulatory Consultant, Vaccine Advice BVBA, 281 Sint Antoniusbaan, 2980 Zoersel, Belgium
[b] University of Namur, 61 rue de Bruxelles, 5000 Namur, Belgium
[c] University of Antwerp, Department of Vaccinology, 13 Prinsstraat, 2000 Antwerpen, Belgium
[d] Medicines Control Council South Africa, PO Box 622, Simons Town 7995, South Africa
[e] Department of Pediatrics at Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA
[f] World Health Organization, 20 Ave Appia, CH-1211 Geneva 27, Switzerland
[g] Dalla Lana School of Public Health, University of Toronto, 155 College Street, Toronto, Ontario M5T 3M7, Canada
[h] Independent Consultant, 64 Avenue de Jette, 1081 Brussels, Belgium

ARTICLE INFO

Article history:
Received 26 April 2016
Received in revised form 21 February 2017
Accepted 24 February 2017
Available online 22 March 2017

Keywords:
Vaccination
Safety
Off-label use
Regulatory authority

ABSTRACT

This article reviews the off-label recommendations and use of vaccines, and focuses on the differences between the labelled instructions on how to use the vaccine as approved by the regulatory authorities (or "label"[1]), and the recommendations for use issued by public health advisory bodies at national and international levels. Differences between public health recommendations and the product label regarding the vaccine use can lead to confusion at the level of vaccinators and vaccinees and possibly result in lower compliance with national vaccination schedules. In particular, in many countries, the label may contain regulatory restrictions and warnings against vaccination of specific population groups (e.g. pregnant women) due to a lack of evidence of safety from controlled trials at the time of initial licensure of the vaccine, while public health authorities may recommend the same vaccine for that group, based on additional post-marketing data and benefit risk analyses.

We provide an overview of the different responsibilities between regulatory authorities and public health advisory bodies, and the rationale for off-label use[2] of vaccines, the challenges involved based on the impact of off-label use in real-life. We propose to reduce off-label use of vaccines by requiring the manufacturer to regularly adapt the label as much as possible to the public health needs as supported by new evidence. This would require manufacturers to collect and report post-marketing data, communicate them to all stakeholders and regulators to extrapolate existing evidence (when acceptable) to other groups or to other brands of a vaccine (class effect[3]). Regulatory authorities have a key role to play by requesting additional post-marketing data, e.g. in specific target groups. When public health recommendations for vaccine use that are outside labelled indications are considered necessary, good communication between regulatory bodies, public health authorities, companies and health care providers or vaccinators is crucial. *Recommendations as well as labels and label changes should be evidence-based.* The rationale for the discrepancy and the recommended off-label use of a vaccine should be communicated to providers.

* Corresponding author at: Sint Antoniusbaan 281, 2980 Zoersel, Belgium.
E-mail addresses: pieter.neels@vaccine-advice.be (P. Neels), jamess@icon.co.za (J. Southern), jabrams@wakehealth.edu (J. Abramson), duclosp@who.int (P. Duclos), hombachj@who.int (J. Hombach), martim@who.int (M. Marti), alanna.fitzgerald-husek@medportal.ca (A. Fitzgerald-Husek), fourniercaruanaj@who.int (J. Fournier-Caruana), ghanquet@skynet.be (G. Hanquet).

[1] Label: The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article. This includes the Summary of the approved Product Characteristics (SmPC) and Package Insert.

[2] Off-label use: Any use of an authorised product not covered by the terms of its marketing authorisation and therefore not in accordance with the SmPC, labelling.

[3] Class effect: An effect for a group of drugs with similar chemical structure and/or drugs with similar mechanism of action and/or drugs with similar pharmacological effects.

http://dx.doi.org/10.1016/j.vaccine.2017.02.056
0264-410X/

Contents

1. Introduction

The introduction of vaccines into the market, as for any medicinal product, is a multi-step process and the result of a complex interaction between several players. The first step is the granting of the market authorization[4] of the vaccine by the National Regulatory Authority (NRA), i.e. authorizing the use of the vaccine for a given indication after assessment of the evidence supporting quality, safety and efficacy in the population where it will be used. The next step involves a public health advisory body which will issue public health recommendations for the use of the vaccine.[5]

However, the public health recommendations may differ from the indications contained in the label [1]. Discrepancies will result in settings where the vaccine has been granted a marketing authorization for a certain indication in a certain population with a specific schedule, while it is recommended for use by the public health bodies for a different or extended indication and/or in a different target group within a population and/or with a different schedule. This would lead to a so called "off-label" public health use. This occurs for instance when a vaccine label contains restrictions and warnings against vaccination of specific population groups such as pregnant women, based on a lack of evidence of safety in this group, while public health authorities may recommend that the same vaccine should be used in this group, based on benefit risk analyses and post-marketing data. Another example of differences in schedule is the recommendation of the Canadian public health authorities in 2006 to use the heptavalent pneumococcal conjugate vaccine (PCV7) in infants in a 3 dose schedule (2 + 1) although the vaccine was licensed for 4 doses (3 + 1) in Canada [2]. Yet another example is that of the recommended use of fractioned doses of inactivated poliomyelitis vaccine recommended by Strategic Advisory Group of Experts on immunization (SAGE) in the context of the current challenges in the supply of vaccine [3]. These discrepancies may create confusion for vaccinators as well as for vaccinees and could contribute to vaccine hesitancy and reduced vaccination coverage. There is thus a need to understand and, where possible, develop strategies to reduce discrepancies between the labelled indication of a vaccine and public health recommendations for its use that fall outside the label.

This article focuses on the off-label use of vaccines in public health recommendations. Based on assessment of regulatory documents, literature review and consultation with key stakeholders, we review the processes and responsibilities involved in marketing authorization and public health recommendations for a vaccine use, describe the rationale and circumstances for public health recommendations beyond the vaccine label, present the challenges involved and propose a number of approaches to address these complex situations.

2. Market authorization and vaccine label

2.1. The registration process

Before a market authorization is granted by a NRA, a vaccine has to go through a registration process[6] that includes an assessment of the vaccine quality, safety and efficacy for the requested indication in the population where it will be used. The long process of registration begins with the assessment of the quality data (on the production process) as well as non-clinical data (from in vitro and animal models) to support the first-in-human studies [4,5]. Thereafter, the data generated during the clinical trials in the phases 1, 2 and 3 are assessed and a risk-management plan is developed that describes the planned post-marketing studies that should take place after vaccine introduction [6]. The decision to grant a market authorization for the vaccine is driven by the concept of "Benefit Risk Balance". This process of assessing the Benefit Risk Balance involves the evaluation of all available data on the desirable (benefits) and undesirable effects (risks) of the vaccine, taking into account as well the scientific evidence (data from clinical trials) and the uncertainties (e.g. real world use of the vaccine, missing data, rare events, etc.). The beneficial effects are then weighted against the potential undesirable effects, taking into account the uncertainties, possible outcomes and their respective importance [7].

In proposing a vaccine label, manufacturing companies[7] should comply with regulatory standard requirements (policies) and include all required information in the vaccine label. In the European Union, this is called the Summary of Product Characteristics (SmPC)

[4] Granting of the market organization: Positive outcome from the registration process: the regulatory authority has decided that the benefit/risk balance is positive for a given indication (not necessarily the requested indication). In many countries a synonym is: giving a license, registration or approval.

[5] In several industrialized countries there is also a price setting and decision on reimbursement step.

[6] Registration process: All activity performed by the regulatory authority to come to a benefit risk balance to grant or not a marketing authorisation. The process is characterized by assessment of all the available evidence on the quality, non-clinical and clinical safety and efficacy aspects of the product.

[7] In order to simplify the text, only one word is used to indicate the owner of the medicinal product, the legal entity responsible for the product, see Glossary for more details.

Table 1
Label definitions in the Summary of Product Characteristics (SmPC) according to EU guidance [9].

4.1 Therapeutic indications	The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.
4.2 Posology and method of administration	In case of restricted medical prescription, this section should be started by specifying the conditions. In case of specific safety need, any recommended restriction to a particular setting should also be stated (e.g. "*restricted to hospital use only*" or "*appropriate resuscitation equipment should be availa*ble").
4.3 Contraindications	Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include a particular clinical diagnosis, concomitant diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, a particular genotype and prior adverse reactions to the medicine or class of medicines). The situations should be unambiguously, comprehensively and clearly outlined.
4.6 Fertility, pregnancy and lactation	*Pregnancy* In general, clinical and non-clinical data should be followed by recommendations. With respect to non-clinical data, • Only conclusions of the reproductive toxicity studies should be included in this section. Further details should be provided in Section 5.3.With respect to clinical data, • The section should include comprehensive information on relevant adverse events reported in the embryo, the foetus, neonates and pregnant women, when appropriate. The frequency of such events (for example the frequency of birth defects) should be specified when available. • The section should specify the extent of the human experience if no adverse events have been reported in pregnancy.

Table 2
Label for use in Pregnant women as documented in the EMA summary of product characteristics (SmPC) [9].

"...There are no or limited amount of data from the use of [Vaccine] in pregnant women,
A: Studies in animals have shown reproductive toxicity (see Section 5.3).
[or]
B: Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3).
[Vaccine] is not recommended during pregnancy and in women of childbearing potential not using contraception

[8,9], that contains structured information for both the prescriber and the vaccinee. The information for use of the vaccine is supported by the evidence generated by clinical trials [8,9]. In some instances, regulators may not authorize the vaccine use for an indication that is requested by the company,[8] if they consider that the evidence is not convincing.

After an initial label is approved, additional post-marketing data may support or require a change in the label. The company may perform additional clinical studies (observational or clinical trials) to support an extension of the label to specific population groups, other age groups or support different schedules or routes of administration.[9] These additional data may also be requested by the NRAs. Additional data considered by the NRA can include data generated by the company or by academia or public health institutes.

2.2. Specific population groups

Current practice for many regulators is that the initial label indications for a vaccine will be limited to the populations tested in the clinical trials where evidence supports safety and efficacy of vaccine use or where convincing bridging data exist. Label advice for other high-risk and special populations may contain cautionary statements when there is insufficient evidence to support the use in these groups. This lack of evidence means that it is unknown if the vaccine is safe or effective in these groups.

A downside of this approach is that clinical trials usually involve healthy and immune-competent populations, to optimize the probability to demonstrate efficacy and avoid harm to vulnerable populations. They tend to exclude participants with underlying diseases, such as cardiovascular disorders, renal failure, diabetes, neuro-degenerative or psychiatric disorders and immune deficiencies. Some groups may also be excluded for ethical, liability or safety concerns.

There is a clear paradox. Patients with underlying disease are generally at higher risk of serious infections from vaccine-preventable diseases and could thus benefit most from vaccination. However, their exclusion from clinical trials results in a lack of robust evidence either for the efficacy or the safety of the vaccine in these groups. Where high-risk groups have been excluded from clinical trials, it is often not justified to extrapolate safety and efficacy to these groups without further evidence.

An important example of a group often excluded from the initially approved label is that of pregnant women. Pregnant women (and their foetus) are routinely excluded from clinical trials and a general warning in the label is included in the section on Pregnancy due to lack of data (Tables 1 and 2) [10]. Requests for label changes related to use in pregnant women would likely not be supported by robust clinical trial evidence, but rather by surveillance reports of sporadic and/or inadvertent use of the vaccine in pregnant women. These data are rarely published in peer reviewed journals and their evaluation is hampered by limited details on the vaccine used, medium or longer term outcomes, and lack of access to the medical records of mother and infant. Regulatory authorities are reluctant to accept these lower levels of evidence for the purpose of label change. The United States (US) Food and Drug Administration (FDA) issued new standards for pregnancy and lactation product label in June 2015 that are intended to simplify the use of vaccines and other medicinal products for this group [11,12]. Under the new Pregnancy and Lactation Labelling Rule, labels will be required to include three detailed subsections *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential.* Each section will include a risk summary, a discussion of the supporting data, and relevant information to help providers make prescribing and counselling decisions [13,14]. If no data are available to guide decision making, this must be stated [15].

[8] Company: Marketing authorisation holder (license holder): the legal entity that was granted the permission to market/sell the medicinal product. Manufacturer: the legal entity that is producing the medicinal product. Not necessarily the same legal entity that has the marketing authorisation.

[9] Every change of the label has to be submitted to the NRA for approval, this is called a variation procedure.

2.3. Class effect

Another problem is that, even when evidence is sufficient to approve the use of a particular vaccine from one company, NRAs will be reluctant to accept the extrapolation and application of this evidence to a similar vaccine from another company, due to the uncertainty that the two vaccines will have the same quality, clinical safety and efficacy. However, exceptions have occurred when sufficiently justified. For instance in the EU, a "class effect" has sometimes been accepted by regulators to change the label for all brands of a certain vaccine. A class effect is "an effect of a group of drugs with similar chemical structure and/or drugs with similar mechanism of action and/or drugs with similar pharmacological effects" [15,16]. The US FDA also developed the concept of "class-wide label changes" which assumes that all products within a class are closely related in chemical structure, pharmacology, therapeutic activity, and adverse reactions [17,18].

There are a number of examples of class effects accepted by regulators, usually for safety reasons. In vaccinology, intussusception is considered by regulatory authorities as a class effect of live rotavirus vaccines [19]. For the trivalent inactivated influenza vaccines (TIV), the EU regulators have now accepted a generic wording for pregnancy based on class label [20,21], advocating that TIV use during pregnancy in all trimesters is acceptable. EU regulators also accept to some extent the concept of interchangeability in case of co-administered vaccines: PCV7 (Prevenar®) has shown efficacy in co-administration with one brand of Diphtheria-Tetanus-Pertussis (DTP) -containing vaccine, and all vaccines of the DTP class have been approved for co-administration. Thus the class effect may be accepted by regulators on a case-by-case basis.

2.4. Variations between countries

Vaccine labels may also differ between countries as a consequence of the variation among independent regulatory authority assessments, policies and other criteria used in the vaccine assessment. First, the same evidence could lead to a label indicating use in specific groups in one country, while another country's regulatory body may have a different interpretation of the evidence and science and decide that the evidence is not sufficient to approve that same vaccine for the labelled use in the same groups in their country. Second, the assessment of the benefit risk balance by the NRA will be based on national methods, standards and laws. Divergent regulatory decisions are illustrated by the following examples. The live-attenuated seasonal influenza vaccine Flumist®,[10] is indicated in adults aged up to 49 years in the US while EU regulators have granted Fluenz® the marketing authorisation for children only (up to 18 years) based on the same evidence [22,23]. In 2013, the EMA approved the change from a three-dose Human Papillomavirus (HPV) vaccine schedule to a two-dose schedule for children between 9 and 14 years [24,25], whereas HPV vaccines in the US were still approved in a three-dose schedule in this age group [26,27].

3. Public health recommendations for vaccine use

In an increasing number of countries, national policies are formulated by a National Immunization Technical Advisory Group (NITAG), composed of independent experts in the field of immunization and serving as technical resource providing guidance to national policy-makers and programme managers to enable them to make evidence-based immunization-related policy and programme decisions. This sometimes causes off-label recommendations as the package insert text is not available to the NITAG until after the license is granted.

In 2015, 64% of World Health Organization (WHO) Member States had their own NITAGs, which provide recommendations to decision makers, vaccinators and the general public on the implementation and use of vaccines at the (sub)national level [1,28]. Independent scientific assessments by NITAGs will inform the public health recommendations for a particular vaccine. However, NITAG assessments may reach different conclusions from those of regulatory authorities, and NITAG's recommendations may lie outside the approved labelled use [1,8]. Discrepancies may then arise when a vaccine has been granted marketing authorisation by the regulatory authorities for a particular indication in a certain population with a specific schedule, whereas the NITAG may recommend its use with a different indication, schedule, and/or population group.

Global public health recommendations are developed on an international level by WHO. SAGE is a WHO committee formulating recommendations on vaccine use at the global level [29]. A WHO SAGE recommendation is intended to help provide guidance to national recommendations formulated by NITAGs. For example, SAGE recommended to include pregnant women among the priority target groups for influenza vaccines [30,31], although the label of these vaccines at the time did not recommend use during pregnancy in most countries. This SAGE recommendation contributed to the inclusion of pregnant women in the influenza vaccination target groups in a substantial number of countries, including 27 EU countries by 2015 [32].

There are four main reasons why recommendations for vaccine use issued by NITAGs and SAGE may differ from the labelled indications initially issued by regulators. First, NITAGs and regulators do not use exactly the same information to inform their decisions. NRAs mostly consider the information that is submitted by the company in the applications, as well as published and unpublished data. NITAGs may not have access to all the scientific information available during the registration process, as part of it is not publicly available and they also consider additional information from other sources such as trials published after vaccine authorisation and post-marketing data on vaccine effectiveness, as well as impact and safety generated after large-scale use of the vaccine. This additional information will be considered by the NRA for updates of the label. For instance, the public health recommendation to use PCV7 (Prevenar®) in a 2 + 1 schedule (instead of the licensed 3 + 1 at that time) in Canada, Belgium and the United Kingdom was based on evidence from immunogenicity trials and a large US effectiveness study published after PCV7 authorisation [2,33]. Second, NITAGs' decisions regarding vaccine use are not based exclusively on the scientific evidence of efficacy and safety; they also take into consideration a wide range of parameters including the age-specific pre-vaccine disease burden, public health needs, other health interventions, costs and cost-effectiveness, programmatic issues such as existing schedules, acceptability, impact on equity and policies that are specific to the country or region [1,34,35]. Likewise, SAGE recommendations consider data relevant for different epidemiological settings, as some data (including local epidemiology) from one region may not be appropriate for extrapolation to another region. Thus, public health recommendations may differ across countries and WHO regions. Third, both NITAGs and SAGE have a different perspective than regulators. Their focus is on optimizing the impact of vaccines and health benefits in the population keeping in mind the potential role of other health intervention and opportunity costs. Fourth, NITAGs will usually not make a product-specific recommendation unless only a single product is granted a marketing authorisation in a country (e.g. NITAGs usually do not specify which of the available hepatitis A vaccines should be used). One or more of these reasons may lead to public health recommen-

[10] In the EU this vaccine is named Fluenz®.

Table 3
Definitions of off-label use.

EMA [57]	Off-label use relates to situations where a medicine is intentionally used for a medical purpose not in accordance with the authorised product information. Off-label use includes use in non-authorised paediatric age categories. Unless specifically requested, it does not include use outside the EU in an indication authorised in that territory which is not authorised in the EU.
FDA [58–60]	Off-label use is defined (called unlabelled indication) under the perspective of the health care provider only, i.e. when a marketed drug is prescribed to treat a patient for an unlabelled indication
American academy of pediatrics committee on drugs [42]	Off-label use of an approved drug refers to a use that is not included in the approved label
MEDRA [61]	Off-label use is defined as a practice of prescribing pharmaceuticals outside the scope of the drug's approved label, most often concerning the drug's indication.
Health Canada [62]	Health Canada approves drugs for specific indications included in the drug's official product monograph which is part of the Notice of Compliance (NOC). Many off-label drug uses are effective, well documented in the peer-reviewed literature, and widely used. Off-label or unlabelled drug use occurs when a drug is used in a treatment regime or patient population that is not included in the NOC, and a drug is used for an indication other than those specifically included in the NOC.
L'Ecluse et al. [63]	The term off-label use refers to the prescribing or administration of an authorised medicinal product outside any of the terms of the marketing authorisation, as reflected in the Summary of Product Characteristics (SmPC). This might include use for a different indication, at a different dosage (or dosage frequency) or in a different patient group (for example, children or pregnant women).
Prof. Y. Hekster MEB (Medicines Evaluation Board, the Dutch NRA) [64]	Off-label use is the practice of prescribing drugs outside the scope of the drug's indication and dosing, and especially for other patient groups such as children. Off-label use is no use of a registered medicine: no registration, no label and is not experimental use of a medicinal product, either in a clinical trial or outside of a clinical setting (approved by an Ethics Committee).

Table 4
Examples of off-label use of vaccines.

Section	Vaccine	Text from SmPC	Intentional off-label use
Posology	Prevenar conjugated pneumococcal vaccine	At licensure, Prevenar (PnC7 conjugated 7-valent pneumococcal vaccine) was approved in a 3 + 1 schedule: infants should receive a primary vaccination of 3 injections with a booster in the second year of life.	In Canada the National Advisory Committee on Immunization (NACI) [2] decided to recommend an off-label schedule: 2 + 1 instead of the approved 3 + 1. In 2004 the EU regulators accepted the 2 + 1 schedule, which is now included in the label [65,66].[a]
Pregnancy and lactation	Repevax dTap/ polio	*Fertility* No fertility data are available. *Pregnancy* The effect of REPEVAX on embryo-foetal development has not been assessed. No teratogenic effect of vaccines containing diphtheria or tetanus toxoids, or inactivated poliovirus has been observed following use in pregnant women. Limited post-marketing information is available on the safety of administering REPEVAX to pregnant women. The use of this combined vaccine is not recommended during pregnancy [67].	The recommendation of this vaccine in this group, which is official in the UK– is off-label considering the approved SmPC.
Posology	Gardasil tetravalent human papilloma virus vaccine	US FDA: GARDASIL should be administered intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, 6 months [27]. EMA: Individuals 9 to and including 13 years of age Gardasil can be administered according to a 2-dose schedule (0.5 ml at 0, 6 months) (see Section 5.1). If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should 3 always be administered [25].	The WHO SAGE recommended the 2-dose schedule for adolescents in 2014 [68], which would be off-label use of Gardasil in the US and in some other regions of the world (as of March 2015). EMA has approved recently the 2 dose schedule for adolescents for both HPV vaccines.
Indication	Dukoral vaccine against vibrio cholera	DUKORAL is indicated for active immunization against disease caused by Vibrio cholera serogroup O1 in adults and children from 2 years of age who will be visiting endemic/ epidemic areas. The use of DUKORAL should be determined on the basis of official recommendations taking into consideration the variability of epidemiology and the risk of contracting disease in different geographical areas and travelling conditions. DUKORAL should not replace standard protective measures. In the event of diarrhoea measures of rehydration should be instituted [69].	The company claims not only efficacy against cholera but also against *E. Coli*. However this indication was not accepted by the EU authorities [70]. A recommendation to vaccinate with this vaccine in order to prevent *E. Coli* would thus be off-label
Indication	Synflorix conjugated pneumococcal vaccine	Active immunization against invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants and children from 6 weeks up to 5 years of age. See Sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes [71].	Recommendation for use after the age of 5 year is an off-label use of Synflorix.
Indication	Fluenz live attenuated flu vaccine	Prophylaxis of influenza in individuals 24 months to less than 18 years of age [23].	Recommendation before or after this age category is off-label use in the EU.

[a] In reference [67] on page 13 a description is given on the type II variation that led to a change of the SmPC to add the 2 + 1 schedule in the posology.

dations that are off-label when the vaccine is recommended for an indication, population group or schedule that differs from the indications granted in the marketing authorization [1].

4. Off-label public health use of vaccines

Off-label use of medicines or vaccines has no standard definition, and a number of published definitions are provided in Table 3. Most of them define off-label use as a prescription for a different indication, posology, age or, population group from that included on the label. This review addresses the public health recommendation for off-label use of a vaccine, in which the vaccine is explicitly recommended outside the approved label, as illustrated by examples in Table 4.[11]

There are differences in how off-label use is perceived throughout the world [36]. In the EU, off-label use by health care providers is a reason for concern and has received increasing attention as illustrated by a 2013 resolution of the European Commission (EC) calling for specific action regarding the off-label use of medicines [37]. In particular, an EC study has been conducted to further investigate off-label use in the EU. The European Federation of Pharmaceutical Industry and Associations (EFPIA) has stated that the off-label use should not be promoted by NITAGs or other official bodies [38]. However, off-label use of certain medicines is commonly accepted in some countries, such as the United Kingdom and France [39,40]. In countries such as in North America, off-label use is more accepted as prescribers are responsible for their prescriptions, including off-label use of a particular drug [41]. For vaccines, public health recommendations set the standard of care and even if off-label, these recommendations should be and most often are followed by those delivering vaccines.

5. Challenges encountered in off-label use

Without proper explanation and communication from public health authorities to health care providers, vaccinators and vaccinees may not understand the reasons for discrepancies between the label and the recommendations. This could diminish confidence in public health recommendations and contribute to vaccine hesitancy, decreased adherence to national immunization schedules and/or public health recommended vaccine use if it is outside the labelled use [42]. Decreased vaccine coverage rate in a given region may ensue. For instance, the US Advisory Committee on Immunization Practices (ACIP) recommended in 2011 routine vaccination of pregnant women against pertussis to confer short-term, early protection against pertussis for their infants through maternal immunization [43]. The US label for combined tetanus, diphtheria, pertussis (dTap)[12] vaccines does not include that use; for instance the US label for the dTap vaccine Boostrix® states: "Safety and effectiveness of BOOSTRIX have not been established in pregnant women" [18]. Low uptake was observed as in 2012, only 16–20% of women with live births at the Vaccine Safety Datalink sites received dTap during pregnancy [44].

Safety is another issue. Vaccines are designed and tested to ensure safety in the vaccinated population. However the use of some vaccines outside the label may be unsafe in certain instances. For instance, age labelling can be related to proven safety issues, e.g. the use of yellow fever vaccines in infants below six months of age is an absolute contraindication in the EU due to a risk of encephalitis, as evidenced by studies conducted during the early 1950s (four cases per 1000 reported among vaccinated children aged <6 months) [45,46]. The EU label for yellow fever vaccine also contains a warning for vaccinating adults above 60 years for which the decision to vaccinate should be made on a case-by-case basis after weighting the risk of contracting the disease against the potential of vaccine-associated neurotropic and viscerotropic disease, in subjects >60 years [47–49]. It is thus essential that public health advisory bodies possess all available safety information in order to make appropriate recommendations. This requires that companies and other involved bodies (regulators, advisory groups, public health authorities and the research community) collaborate and exchange all available safety data on vaccines used worldwide. This also requires that the regular submission of periodic safety update report (PSUR) by the companies as well as safety data gathered from the field by all stakeholders should be made publicly accessible and that updated data on specific products regularly be published.

Another issue surrounds legal consequences associated with adverse events potentially related to vaccines used off-label. If a product use is based on its label, regulators or the company may be held responsible for the adverse events that occur. Conversely, if a public health authority recommends the use outside the label, the health authority could be held responsible for the adverse events that occur.

A challenge is that potential adverse events are reported based of their temporal association with the vaccine administration, regardless of causality [50]. An assessment of an adverse event report is necessary to determine if some causal relationship exists or may exist between the vaccination and the adverse event and if these points to a vaccine related (due to the inherent characteristics of the vaccine or production problems) or programmatic issue, or whether the relationship was merely coincidental. This assessment requires a strong collaboration between all stakeholders. If the assessment is that there is a causal relationship, then the manufacturer and public health authorities should collaborate and give due diligence to try to understand the potential biological mechanisms resulting in the adverse event.

For example, pregnant women may be vulnerable to a number of adverse events related to the pregnancy and it is difficult to distinguish whether the event was due to the vaccine or to an unrelated event that was temporally linked.[13]

The biggest challenge lies in reducing discrepancies between authorised vaccine use and public health recommended use that falls outside the current label but is based on sound evidence generated after the initial label. This discrepancy will not align until the label is updated to reflect the new evidence. Reducing these discrepancies depends on the willingness of the company to apply for a label change and the regulators to approve the requested change.

Key barriers to changing a vaccine label include:

- The reluctance of the companies to apply for a label change to extend the vaccine use to additional groups. This reluctance may be driven by liability concerns (especially regarding pregnant women and their foetuses when vaccine use is not clearly indicated) and/or the absence of a sufficient market, e.g. when the proposed extension of use on the label concerns a very small population group at risk and there is little economic incentive.
- The reluctance of the regulators to accept the label change after assessment if the evidence is found insufficient to support the label change. This may occur when data is derived from uncontrolled, non-randomized clinical trials, or from observational studies (e.g. case control or cohort studies or surveillance).

[11] In addition to this public health off-label use, an individual clinician may also decide to use a vaccine outside the labelling advice. This may occur when, after considering the benefits and the risks for a specific patient, the clinician considers that the patient would likely benefit from the vaccination. This type of off-label use is not considered in this review.

[12] dTap: diphtheria/Tetanus/acellular pertussis, adult dose (lower than infant dose).

[13] An adverse event is not necessarily causal related. Any event temporarily related to a medical act is an adverse event. A medicinal product label has a lot of temporal, not necessary causal related adverse events.

- The lack of application for a label change by the company. In most countries only the company may apply to amend the label of a licensed product. Even when an independent body has published evidence, the regulator cannot change the label without the company's application. However in some countries (e.g. in the EU), regulatory bodies can impose on companies to change the label (e.g. class label for the use of TIV in pregnant women).
- Regulatory authorities have the authority to require manufacturers to amend their label based on new information relating to safety and efficacy. However a mechanism is required to ensure that regulatory authorities are alerted and take action in light of new information.

6. The way forward

The most effective way to reduce differences between the vaccine label and public health recommended use would be for companies and regulators to collaborate on adapting the label as much as possible to meet the public health and target population needs. Label changes should be based on suitable evidence.

Vaccine clinical development is far from being finalised when it first reaches the market. Post-licensure studies are needed and should be agreed at the time of vaccine introduction. This concept could be officially introduced in the regulatory approval process in countries, and require that all involved parties (industry, regulators, public health bodies) work together towards a well-defined post-licensure programme, including how to share the respective tasks, responsibilities and costs. This programme could cover epidemiological surveillance, studies of different specific population and risk groups, alternative schedules, co-administration with other vaccines, etc. The purpose of the post-marketing risk management plan (RMP) [14] is to generate additional data that are not available at the time of granting the marketing authorisation [6,51]. The RMP should cover a long time period and should be revised if new evidence arises.

Regulators have a key role to play in requesting vaccine companies to collect or generate the missing evidence that would allow, through regulatory procedures, to adapt the label to the public health needs. Regulators are not always aware of the full impact of the vaccine at the time of the adoption of the benefit/risk analysis. Additional data may be generated on specific population groups (e.g. pregnant women, persons with underlying diseases) but may also involve other dosage or schedule recommended by NITAGs. Post-marketing data are also gathered by academic and public health institutions and should be evaluated and incorporated as well, after assessment of their quality. Companies may also be requested to collect and report post-marketing data on inadvertent use of the vaccine, such as safety data on vaccine use during pregnancy.

As stated by Chocarro et al. [1] there is need for increased and more formal interactions between NRAs, NITAGs and immunization programmes and for a clear framework establishing a formal interaction and early interactions between these bodies before market authorization. The NITAG should be encouraged to approach the NRA when a potential for off-label use is identified and then the NRA should set up the review process leading to a request for the manufacturer to provide the necessary data.

NRA experts serving as ex-officio members on NITAGs and NITAGs' members or immunization managers serving on NRA review panels are solutions which can be adopted by countries. If there is a need to make recommendations that are not covered by the license evidence, then there should be interactions between the NITAG, the NRA and the license holder to encourage the license holder to submit appropriate evidence, or to ensure that the justification for the off-label recommendation is communicated to the recipients of the vaccine.

Another approach would be that the regulatory authority sets up an independent review board to assess the label requested for a new vaccine by a company, with the possibility to recommend studying the vaccine in additional groups that were not requested for the initial label. This is similar to the US Best Pharmaceuticals for Children Act (BPCA), enacted in 2002, that requires that any new drug that requests FDA approval without having a label for use in children be presented to an oversight board composed of pediatric experts to determine if there is a need for the drug in children [52,53]. If this is the case the US FDA can require the company to conduct relevant phase IV studies after the drug is approved.

Regulatory processes are generally conservative and averse to exposing patients or the public to unknown risks, but it can happen that for some vaccinators, the unknown risks can appear to outweigh the known benefits, as has happened in some instances with the use of influenza vaccines in pregnant women despite the WHO recommendation that pregnant women were the highest priority group for vaccination [54–56].

Another aspect to address is the difference in information available to regulators versus to public health groups. As the detailed data submitted by the company for registration are not publicly available, the rationale of the regulator's decision to warn against use of a vaccine in a certain group should be communicated when justified by a negative benefit risk evaluation. This involves providing a summary of the detailed data and scientific discussion and making them available to all stakeholders in a transparent way (e.g. EMA European Public Assessment Report).

In addition, the use of "class effect", as explained above, may be accepted by regulators (on a case-by-case basis) to extend the label to other groups, as illustrated by the generic wording for TIV in pregnancy based on class label in the EU (see above) [20,21].

Since off-label recommendations will persist, it is important that NRAs and public health authorities clearly and jointly communicate on the differences between the off-label recommendations and the labels and why these are justified. This is important for the credibility of each group and for the acceptance of the recommendations.

7. Conclusion

Discrepancies exist between the public health recommendations and the labelled use of some vaccines. Boundaries of off-label use are not so firmly defined and vary between countries. Also, differences in the legislation across countries and liability aspects have an impact in these matters. An approach to decrease discrepancies would be that regulators require vaccine companies to provide evidence to adapt the label as much as possible to the public health needs, during the whole life-cycle of a product. This would require collecting and reporting post-marketing data by the company and the NRA, communicating them to all stakeholders and extrapolating existing evidence (when the data are adequate) to other groups or to other brands of a vaccine (class effect). Where companies request a label change based on new data, regulators should conduct a benefit risk balance assessment based on all available evidence, which should be made available to all stakeholders. Good communication between regulatory and public health authorities should be encouraged to harmonise vaccine label with the local recommendations. Exchanges of information and close collaboration between immunization programmes, NITAGs, and NRAs are essential.

[14] Risk Management Plan: The risk Management Plan is an EU obligation for the Marketing Authorization Holders to further study both efficacy and safety of the medicinal product once it has been granted a marketing authorization.

Conflict of interest statement

Pieter Neels is an independent regulatory expert. He works for governmental and non-governmental organizations as for pharmaceutical companies. He received a grant for the work on this article from WHO, but not from any other organization. AFH, GH, JA, JH, JS, MM and PD declared no conflict of interest.

Author contribution

PN and GH have performed the review and wrote the first draft of this work, with important contributions from JS. AFH, JA, MM and JH have critically revised the manuscript and provided comments. All authors have approved the final version.

Role of the funding source

The World Health Organization (WHO) has provided financial support for this review, and contributed to the final text by reviewing and further elaborating the concepts and conclusions of this article.

Acknowledgements

We thank Ann Ottosen for providing useful information for this work.

References

[1] Chocarro L, Duclos P, Senouci K, Southern J. Consultation on interactions between national regulatory authorities and national immunization technical advisory groups. Expert Rev Vaccines 2011;10:1265–70.
[2] National Advisory Committee on Immunization (NACI). Update on the recommendations for the routine use of pneumococcal conjugate vaccine for infants. Canada: NACI; 2006.
[3] Weekly epidemiological record. Meeting of the strategic advisory group of experts on immunization, October 2016 – conclusions and recommendations. No. 48, 2016, 91, 561–584.
[4] European Commission. Medicinal products for human use. Clinical trials; 2014.
[5] Food and Drug Administration US. Clinical trials and human subject protection; 2014.
[6] European Medicines Agency. Risk-management plans. London: EMA. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp. [accessed February 2017].
[7] European Medicines Agency. Guidance document on the content of the <Co-> Rapporteur Day 80 critical assessment report. London: EMA; 2015. p. 27–33. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004856.pdf. [accessed February 2017].
[8] Food and Drug Administration US. Regulatory information. Chapter II—definitions 1; 2012.
[9] European Commission. A guideline on summary of product characteristics (SmPC). Brussels: European Commission; 2009.
[10] European Medicines Agency. Appendix 3 to the ‘‘guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling; 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003307.pdf. [accessed February 2017].
[11] Food and Drug Administration US. Pregnancy and lactation labeling final rule. USA; 2014. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm. [accessed February 2017].
[12] Worcester Sharon. FDA issues new pregnancy/lactation drug label standards; 2014.
[13] Food and Drug Administration US. Guidance for industry labeling for human prescription drug and biological products – implementing the PLR content and format requirements FDA; 2013. Available at: http://www.fda.gov/downloads/drugs/guidances/ucm075082.pdf. [accessed February 2017].
[14] Food and Drug Administration US. Guidance for industry safety labeling changes —implementation of section 505(o)(4) of the FD&C Act; 2013. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf. [accessed February 2017].
[15] McAlister FA, Laupacis A, Wells GA, Sackett DL. Users Guides to the Medical Literature: XIX. Applying clinical trial results B. Guidelines for determining whether a drug is exerting (more than) a class effect. JAMA 1999;282:1371–7.
[16] Bandolier. When can we say that drugs have a ‘‘class effect’’?.
[17] Furberg CD. Class effects and evidence-based medicine. Clin Cardiol 2000;23. IV15-9.
[18] Food and Drug Administration US. Labeling supplement and PMR required. Maryland; 2014.
[19] Vesikari T. Rotavirus vaccination: a concise review. Clin Microbiol Infect: the Official Publ the Eur Soc Clin Microbiol Infect Dis 2012;18(Suppl 5):57–63.
[20] European Medicines Agency. Summary of product characteristics, Intanza. London: European Medicines Agency; 2014. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000957/human_med_000842.jsp&mid=WC0b01ac058001d124. [accessed 2017].
[21] Electronic Medicines Compendium U. Summary of product characteristics, Fluarix. EMC; 2014.
[22] Food and Drug Administration US. Highlights of prescribing information, Flumist; 2012. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM294307.pdf. [accessed February 2017].
[23] European Medicines Agency. Summary of product characteristics, Fluenz. London: European Medicines Agency; 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001101/WC500103709.pdf. [accessed February 2017].
[24] European Medicines Agency. Summary of product characteristics, Cervarix. London: European Medicines Agency; 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf. [accessed February 2017].
[25] European Medicines Agency. Summary of product characteristics, Gardasil. London: European Medicines Agency; 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf. [accessed February 2017].
[26] Food and Drug Administration US. Highlights of prescribing information, Cervarix; 2009. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf. [accessed February 2017].
[27] Food and Drug Administration US. Highlights of prescribing information, Gardasil; 2006. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf. [accessed February 2017].
[28] Global Vaccine Action Plan. Secretariat annual report; 2016. Available at: http://www.who.int/immunization/global_vaccine_action_plan/gvap_secretariat_report_2016.pdf?ua=1. [accessed February 2017].
[29] World Health Organization. Strategic advisory group of experts (SAGE) on immunization. Available at: http://www.who.int/immunization/policy/sage/en/. [accessed February 2017].
[30] World Health Organization. Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiological Record. 2012; 47, 2012, 87: 461–76.
[31] World Health Organization. Meeting of the strategic advisory group of experts on immunization, April 2012 – conclusions and recommendations. Weekly epidemiological record. 2012; 47, 2012, 87, 461–476: 207–8.
[32] European Centre for Disease Prevention and Control. Technical report, seasonal influenza vaccination and antiviral use in Europe, Overview of vaccination recommendations and coverage rates in the EU Member States for the 2013–14 and 2014–15 influenza seasons, Available at: http://ecdc.europa.eu/en/publications/Publications/Seasonal-influenza-vaccination-antiviral-use-europe.pdf. [accessed February 2017].
[33] Beutels P, Van Damme P. Effectiveness of seven-valent pneumococcal conjugate vaccine. Lancet 2007;369:460. author reply.
[34] Duclos P, Okwo-Bele JM, Salisbury D. Establishing global policy recommendations: the role of the strategic advisory group of experts on immunization. Expert Rev Vaccines 2011;10:163–73.
[35] Nohynek H, Wichmann O, F DA, Gatekeepers VN. National Advisory Groups and their role in immunization policy-making processes in European countries. Clin Microbiol Infect: the Official Publ Eur Soc Clin Microbiol Infect Dis 2013;19:1096–105.
[36] WebMD. Off-Label Drug Use: What you need to know. Available at: http://www.webmd.com/a-to-z-guides/features/off-label-drug-use-what-you-need-to-know. [accessed February 2017].
[37] Commission E. Pharmaceutical Committee. Study on off-label use; 2014. Available at: http://ec.europa.eu/health//sites/health/files/files/committee/72meeting/pharm655.pdf. [accessed February 2017].
[38] European Federation of Pharmaceutical Industry and Associations. Promotion of off-label use of medicines by European healthcare bodies in indications where authorised medicines are available; 2011. Available at: www.efpia.eu/documents/62/85/Promotion-of-off-label-use-of-medicines-by-European-healthcare-bodies-in-indications-where-authorised-medicines-are-available-November-2011. [accessed February 2017].
[39] Council GM. Good practice in prescribing and managing medicines and devices; 2011. Available at: http://www.gmc-uk.org/Prescribing_guidance.pdf_59055247.pdf. [accessed February 2017].
[40] The European Federation of Pharmaceutical Industries and Associations (EFPIA). EFPIA: French legislation undermines EU regulatory framework by endorsing off-label use of medicines for economic reasons; 2014. Available at: http://www.efpia.eu/mediaroom/189/43/EFPIA-French-legislation-undermines-EU-regulatory-framework-by-endorsing-off-label-use-of-medicines-for-economic-reasons. [accessed February 2017].
[41] Drugs Co. Uses of drugs not described in the package insert (off-label uses). Pediatrics 2002;110:181–3.

[42] Expert Committee on Biological Standardization. Appendix 4. Labelling information of inactivated influenza vaccines for use in pregnant women. Available at: http://who.int/biologicals/expert_committee/Label_after_ECBS_HK_28_Oct_2016.clean.pdf?ua=1. [accessed February 2017].
[43] (CDC). CfDCaP. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months – advisory committee on immunization practices (ACIP), 2011. MMWR Morbidity and Mortality Weekly Report 2011; 60: 1424–6.
[44] Kharbanda EO, Vazquez-Benitez G, Lipkind H, Naleway AL, Klein NP, Cheetham TC, et al. Receipt of pertussis vaccine during pregnancy across 7 vaccine safety datalink sites. Preventive Med 2014;67:316–9.
[45] Staples JE, Gershman M, Fischer M. Centers for Disease C, Prevention. Yellow fever vaccine: recommendations of the advisory committee on immunization practices (ACIP). MMWR recommendations and reports: morbidity and mortality weekly report recommendations and reports/centers for disease control 2010;59:1–27.
[46] Monath T. Yellow fever vaccine. 5th ed. Philadelphia: Saunders Elsevier; 2008.
[47] Electronic Medicines Compendium U. Summary of product characteristics, Stamaril. EMC; 2013.
[48] Rafferty E, Duclos P, Yactayo S, Schuster M. Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: a systematic review. Vaccine 2013;31:5798–805.
[49] Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. Expert Rev Vaccines 2012;11:427–48.
[50] Collet JP, MacDonald N, Cashman N, Pless R. Monitoring signals for vaccine safety: the assessment of individual adverse event reports by an expert advisory committee. Advisory committee on causality assessment. Bull World Health Organization 2000;78:178–85.
[51] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Product- or population-specific considerations I: vaccines for prophylaxis against infectious diseases. London: EMA; 2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp. [accessed February 2017].
[52] Field M, Boat T. Safe and effective medicines for children: pediatric studies conducted under the best pharmaceuticals for children act and the pediatric research equity act. Washington (DC); 2012.
[53] Ren Z, Zajicek A. Review of the best pharmaceuticals for children act and the pediatric research equity act: what can the obstetric community learn from the pediatric experience? Semin Perinatol 2015.
[54] European Commission. Communication from the commission on the precautionary principle. Brussels: European Commission; 2000. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV%3Al32042. [accessed February 2017].
[55] World Health Organization E. The precautionary principle: protecting public health, the environment and the future of our children. Copenhagen: WHO Europe; 2004. Available at: http://www.euro.who.int/__data/assets/pdf_file/0003/91173/E83079.pdf?ua=1. [accessed February 2017].
[56] World Health Organization. Pandemic influenza in pregnant women; 2009. Available at: http://www.who.int/csr/disease/swineflu/notes/h1n1_pregnancy_20090731/en/. [accessed February 2017].
[57] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VI – management and reporting of adverse reactions to medicinal products (Rev 1). London: EMA; 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf. [accessed February 2017].
[58] Food and Drug Administration US. Guidance for clinical investigators, sponsors, and IRBs investigational new drug applications (INDs) — determining whether human research studies can be conducted without an IND. In: FDA, editor. Maryland: FDA; 2013. Available at: http://www.fda.gov/downloads/drugs/guidances/ucm229175.pdf. [accessed February 2017].
[59] Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clinic Proc 2012;87:982–90.
[60] Stafford RS. Regulating off-label drug use–rethinking the role of the FDA. New Engl J Med 2008;358:1427–9.
[61] Revelle P. Use of MedDRA: focus on the new scope of adverse event reporting. MEDDRA; 2012. Available at: https://www.meddra.org/sites/default/files/page/documents_insert/revelle_icsr_info_day_nov_2012_final.pdf. [accessed February 2017].
[62] Canada Go. Prescription Drugs (POC 10); 2012.
[63] L'Ecluse P, Longeval C, T'Syen K. Off-label use of medicinal products and product liability. Practical Law 2013. Available at: http://us.practicallaw.com/8-525-5657. [accessed February 2017].
[64] Hekster YA. Off-label Use from the Regulatory Perspective: A necessary evil or a blessing in disguise?: Medicines Evaluation Board; 2013.
[65] European Medicines Agency. Summary of product characteristics, Prevenar. London: European Medicines Agency; 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001104/WC500057247.pdf. [accessed February 2017].
[66] European Medicines Agency. Prevenar: EPAR - procedural steps taken and scientific information after authorisation; 2014. p. 13.
[67] Electronic Medicines Compendium U. Summary of product characteristics, Repevax. EMC; 2012.
[68] World Health Organization. Human papillomavirus vaccines: WHO position paper, October 2014. Weekly epidemiological record. 2014; No. 43, 2014, 89, 465–492:465–92.
[69] European Medicines Agency. Summary of product characteristics, Dukoral. London: European Medicines Agency; 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000476/WC500037570.pdf. [accessed February 2017].
[70] European Medicines Agency. Scientific discussion, Dukoral. London: European Medicines Agency; 2005. p. 19–20.
[71] European Medicines Agency. Summary of product characteristics, Synflorix. London: European Medicines Agency; 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000973/WC500054346.pdf. [accessed February 2017].