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Review

Off-label use of vaccines

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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.

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[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.

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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.

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