Pharmacovigilance for vaccines and immunotherapies: What does the medical writer need to know?

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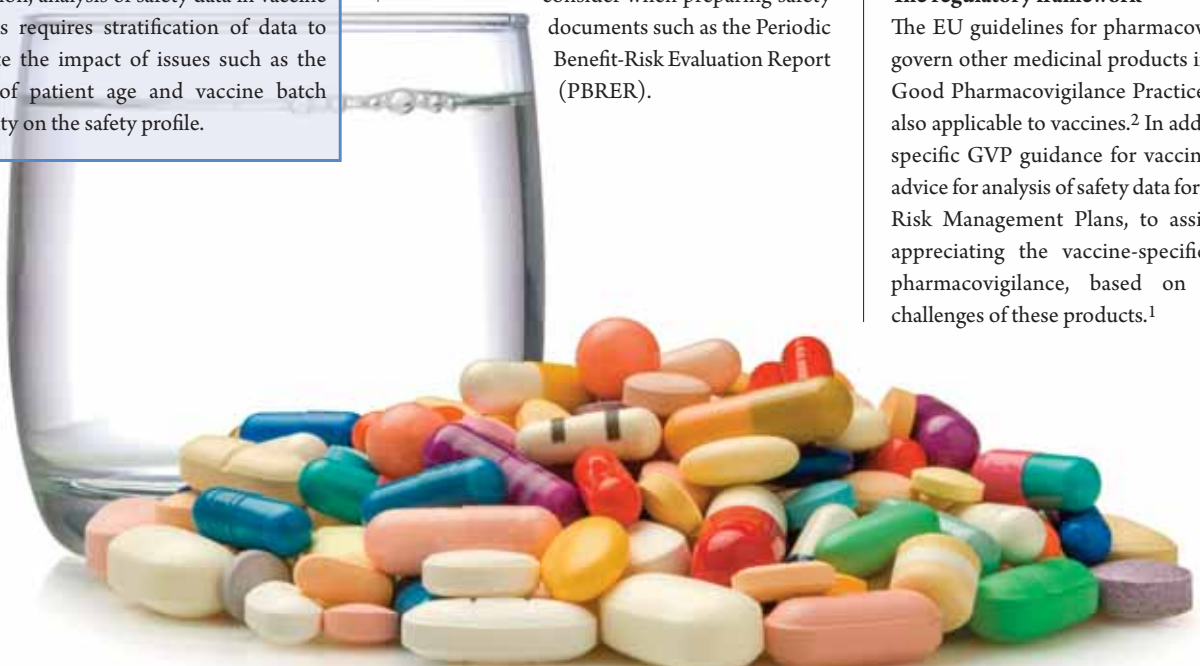
Abstract
Although the content of EU Periodic Benefit-Risk Evaluation Reports (PBRERs) for vaccines is governed by the same regulatory framework as applies to other medicinal products, the complex nature of vaccines presents vaccine-specific challenges that need to be considered when preparing safety documents. Notably, the complex multi-component nature of vaccines necessitates inclusion of additional data elements in vaccine PBRERs, to allow assessment of the resultant impact on the safety profile. In addition, analysis of safety data in vaccine PBRERs requires stratification of data to elucidate the impact of issues such as the effects of patient age and vaccine batch variability on the safety profile.

Introduction
Vaccination remains one of the most effective public health measures, with well documented benefits for the individual patient and community. Vaccination triumphs include the eradication of infectious diseases such as smallpox in addition to more recent and exciting developments such as the human papillomavirus vaccination programmes for adolescent girls and the rapidly advancing area of therapeutic vaccines as used for the immunotherapy of cancer. Like all medicinal products, the use of vaccines is not without safety concerns and requires stringent processes to ensure continuous surveillance of quality, efficacy, and safety. The pharmacovigilance of vaccines was defined by a Council for International Organizations of Medical Sciences (CIOMS)/WHO working group as the "science and activities related to the detection, assessment, understanding and communication of adverse events following immunisation and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation".[1] Although pharmacovigilance processes for vaccines are similar to those applied to other medicinal products, there are a number of vaccine-specific aspects that the pharmacovigilance medical writer should consider when preparing safety documents such as the Periodic Benefit-Risk Evaluation Report (PBRER).



PBRERs for prophylactic/preventative vaccines
Vaccines are complex biological products that may include multiple antigens, live organisms, adjuvants, and preservatives. These components all have potential implications for safety and require specific manufacturing processes underpinned by constantly evolving technology. Consequently, vaccines require specific pharmacovigilance systems and present many challenges that have implications for the analysis of the safety data in PBRERs, including the following:

- The need to ensure efficient handling and assessment of a high volume of suspected adverse reactions, which can be reported to the marketing authorisation holder (MAH) in a short period of time during mass vaccination programmes.
- The need to ensure real-time signal assessment during mass vaccination programmes to allow for timely identification of potential new risks. This is of specific importance for prophylactic vaccines against infectious diseases, as they are administered to an otherwise healthy population and therefore the acceptable level of risk is lower than for other medicinal products.[1]

The regulatory framework
The EU guidelines for pharmacovigilance that govern other medicinal products in the form of Good Pharmacovigilance Practices (GVP) are also applicable to vaccines.[2] In addition, there is specific GVP guidance for vaccines, including advice for analysis of safety data for PBRERs and Risk Management Plans, to assist MAHs in appreciating the vaccine-specific aspects of pharmacovigilance, based on the unique challenges of these products.[1]

The additional GVP guidance on vaccines intended for prophylaxis against infectious diseases advises that reports of vaccination failures be reported as lack of therapeutic efficacy within 15 days of the MAH becoming aware of them, as they represent potential signals of reduced immunogenicity in the patient population, declining immunity, or loss of coverage for the target antigen(s). The concept of signals for vaccines is consistent with the definition as applied to other medicinal products (i.e., information pointing to a new potentially causal relationship between a medicinal product and an adverse effect, or a new characteristic of a documented relationship). However, unlike for other medicinal products, data suggestive of reduced efficacy, vaccine failures, and changes to product quality could also constitute a safety signal for vaccines. For these reasons, vaccine pharmacovigilance requires extremely detailed post-marketing surveillance data, to ensure that information pertaining to the specific vaccine batch administered to each patient is recorded in the case reports entered into the MAH's safety database.[1]

Compared to review of safety data for other medicinal products, there are also some other notable differences in the assessment of vaccine safety data, with five possible designated categories used for the review of adverse events following immunisation:[3]

- vaccine product-related
- vaccine quality defect-related
- immunisation error-related
- immunisation anxiety-related
- coincidental event

In the review of safety data for vaccine PBRERs, these five categories support the analysis of root causes for the reported adverse events, thereby enabling the MAH to further refine the applicable risk minimisation measures.

Additional data for presentation in vaccine PBRERs

In line with other authorised medicinal products, the content of EU PBRERs for vaccines is governed by GVP Module VII (Revision 1) and ICH E2C (R2).[4,5] However, there are additional considerations for vaccine PBRERs. In the first instance, there are additional data elements for inclusion in vaccine PBRERs, as outlined in Figure 1.

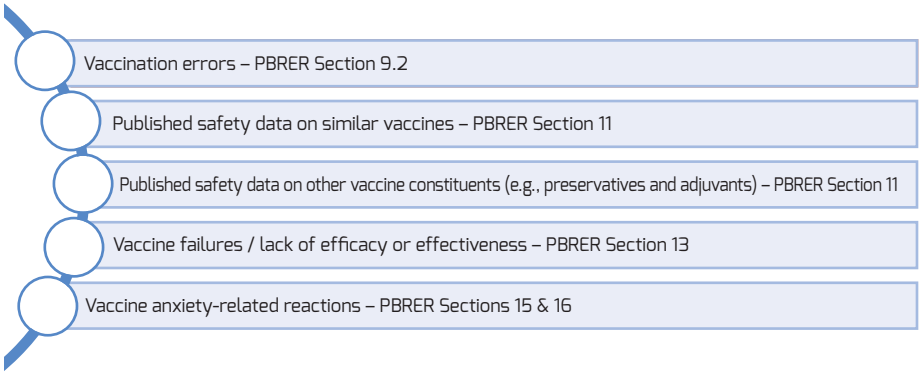


Figure 1. Additional data elements for presentation in the vaccine Periodic Benefit-Risk Evaluation Reports (PBRER)

Vaccination errors

In the same way that medication errors are reviewed in Section 9.2 of the EU PBRER for other medicinal products, vaccine PBRERs require analysis of any data pertinent to vaccination errors, which may include case reports describing inappropriate methods of vaccine administration (e.g., use of the incorrect route of administration, administration of insufficient doses, and failure to use the authorised diluent) or failure to comply with the authorised vaccination schedule. Review of such vaccination errors needs to include information on the cause of the error (e.g., confusion regarding the product labelling or multiple vaccination programmes leading to too many administrations), when available, and an assessment of the associated clinical consequences (which may include the onset of specific adverse events or vaccination failure).

In addition to vaccination errors occurring due to inappropriate administration of the vaccine, Section 9.2 of vaccine PBRERs should also include assessment of any reports describing improper handling and/or storage of the product, as such issues could lead to adverse effects consequent to contamination of the vaccine product with bacterial or other potentially infectious agents.

Published data

Section 11 of the EU PBRER for other medicinal products requires analysis of any new and significant safety information from published literature. The same requirement is applicable to vaccines and also extends to the need for inclusion of published data relevant to other products of the same class. However, vaccine PBRERs go a step further in requiring review of published information pertinent to other vaccine constituents, such as preservatives, stabilisers, and adjuvants. Therefore, search and review criteria used for published literature for inclusion in vaccine PBRERs need to be designed to account for this difference in requirements for vaccine PBRERs.

Vaccine failures/lack of efficacy or effectiveness

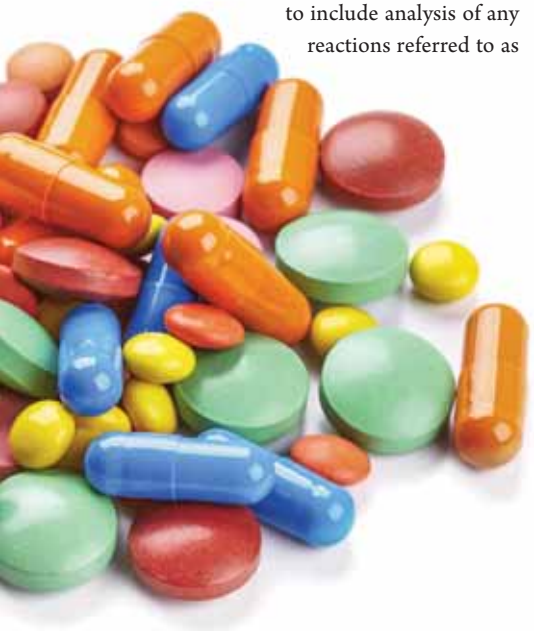
For other medicinal products developed for the treatment or prevention of serious or life-threatening illnesses, Section 13 of the EU PBRER requires analysis of controlled clinical data that are indicative of lack of efficacy or diminished efficacy when compared to established therapies for the target disease.[4] Similarly, vaccine PBRERs require analysis of any case reports describing vaccine failures, which are determined based on clinical endpoints or immunological parameters used to monitor disease progression.[3] In the analysis of these data for vaccine PBRERs, there is a need to differentiate primary vaccine failure (e.g., lack of sero-

conversion or seroprotection) from secondary vaccine failure (e.g., declining immunity after an otherwise successful vaccination).

In addition, analysis of data for vaccine PBRERs should also determine the reason for the vaccination failure, which could be attributed to actual "vaccine failure" or "failure to vaccinate" (e.g., administration errors leading to an inadequate dose or lack of recommended booster vaccinations). The failure-to-vaccinate scenario involves inappropriate administration of the vaccine and therefore the ensuing analysis should be linked by appropriate cross-references to the analysis of vaccination errors as presented in PBRER Section 9.2. Analysis of vaccine failure data in the PBRER should further aim to determine whether the failure was "vaccinee-related" or "vaccine-related". Vaccinee-related failures may be linked to the patient's health status and may include issues such as pre-existing infections, immunodeficiency, immunosuppression, and age-related decline in immune responsiveness. In contrast, vaccine-related failures indicate lack of vaccine effectiveness against the target antigen, which may be associated with manufacturing issues or insufficient coverage (or loss of coverage) against the organism(s) responsible for the target disease.

Vaccine anxiety-related reactions

For other medicinal products, Section 15 of the EU PBRER should include an analysis of data pertaining to topics of special interest and any analyses specifically requested by regulatory authorities,[6] and Section 16 should include further analysis of signals and important risks.[4,5] In the vaccine setting, this requirement extends to include analysis of any reactions referred to as "vaccine or immunisation anxiety-related reactions", such as vasovagal syncope, hyperventilation-mediated reactions, and stress-related psychiatric disorders.[3] In addition, consideration should be given to the analysis of adverse events associated with co-administration of the vaccine with other vaccines, and the consequent implications for safety should be reviewed.



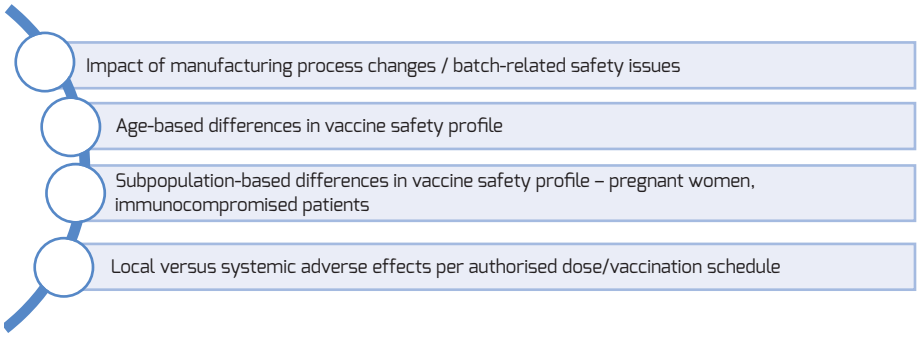


Figure 2. Additional considerations for data analysis in the vaccine Periodic Benefit-Risk Evaluation Reports

Additional considerations for data analysis in vaccine PBRERs

After consideration of the additional data for inclusion in EU PBRERs for vaccines, there are also numerous other factors that affect the manner in which safety data are analysed, as outlined in Figure 2.

Impact of manufacturing changes/ batch-related safety issues

Assessment of safety data for vaccine PBRERs relies on the understanding that, in contrast to other medicinal products, vaccines tend to be multi-component products prepared using complex biological systems that are constantly evolving due to technological advances, but which are also subject to more variability dependent on differences in manufacturing sites. These factors can have an inherent impact on the safety profile of the vaccine product, due to batch variability. Therefore, batch analyses may need to be included within the safety reviews of vaccine PBRERs.

Age-based differences in vaccine safety profile

Since immunological responses to vaccines evolve with age, the analysis of safety and efficacy data for vaccine PBRERs should be stratified by patient age groups, to support the identification of risks that may be more prevalent in a specific age group. Stratification of vaccine safety data analysis by age group can also permit enhanced assessment of causality, particularly for adverse events concerning children, as it can provide a rationale for the exclusion of clusters of adverse events that may be coincidental (i.e., unrelated to vaccine exposure), if they are known to occur at a specific time during childhood. To support analysis and presentation of vaccine safety data stratified by age in vaccine PBRERs, it is worth also presenting an analysis of patient exposure data with stratification by age; however, achieving such data stratification requires high quality post-marketing surveillance data.

Subpopulation-based differences in vaccine safety profile

As with age, analysis of safety data in vaccine PBRERs should also be stratified by patient subpopulations, which can include pregnant women and immunosuppressed or immunocompromised patients.

Local versus systemic adverse effects

Another consideration for data analysis in vaccine PBRERs is the review of data to characterise the product's safety profile with respect to the potential for local versus systemic adverse reactions. This is of particular significance in that it supports MAH refinement of the selected risk minimisation measures.

A word on the benefit-risk assessment

The integrated benefit-risk assessment undertaken for EU PBRERs for other medicinal products remains a contentious issue for many MAHs, with ongoing debates on the methods used to assess benefit-risk and the respective merits of qualitative or quantitative approaches.

Naturally, these issues remain relevant for vaccine PBRERs, but, as one would expect given the nature of these products, there are additional vaccine-specific factors that bring more complexity to integrated benefit-risk assessments for vaccine PBRERs:

- Prophylactic vaccines for infectious diseases are usually administered to an otherwise healthy population, including very young children and vulnerable people, and therefore the acceptable level of risk is very low compared to medicines intended for serious illnesses such as cancer. It is worth mentioning that, rightly or wrongly, this low acceptance of risk is often driven by public perceptions. That notwithstanding, benefit-risk assessments for vaccine PBRERs need to consider the clinical consequences of contracting the vaccine-preventable diseases.
- Based on the low acceptable level of risk, rare and non-serious events that may not have a significant impact on benefit-risk assessment for other medicinal products can have a profound impact in the vaccine setting and are therefore reviewed with greater scrutiny in vaccine PBRERs.
- In stark contrast to many other medicinal products, one could consider that there is no such thing as an "established safety profile" in the vaccine setting, as the safety profile is liable to change over time due to vaccine product variability based on the manufacturing process, in addition to potential changes in strains of the organism(s) behind the target disease, which may also be affected by seasonal or geographical differences. This has significant implications for the integrated benefit-risk assessment undertaken in EU PBRERs, as the benefit-risk balance is more dynamic and changeable than that for many other medicinal products.

Conclusions

Although governed by the same regulatory expectations as other medicinal products, preparation of the EU PBRER for vaccines requires the inclusion of additional elements, to account for the more complex nature of these products and the resultant potential impact on the safety profile. Furthermore, the analysis of safety data in vaccine PBRERs is enhanced by stratification of data to elucidate the potential impact of age, product batches, and patient subpopulations on the safety profile.

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Conflicts of Interest

The author is the owner/founder of Acadustri (Medical Writing) Ltd.

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