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Vaccines Europe Position Paper on a proposal for a revision of the Annex to the European Commission guideline on "*Excipients in the labelling and package leaflet of medicinal products for human use*" (SANTE-2017-11668)

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1. Background and objective

The requirements with regards to the information about excipients that should be included in the labelling and package leaflet of medicinal products are described in the European Commission (EC) guideline "*Excipients in the labelling and package leaflet of medicinal products for human use*" (SANTE-2017-11668) that was revised in March 2018. The list of excipients which should be stated on the label and the information for those which must appear on the package leaflet (PL) are presented in an annex to the guideline. In October 2017, the European Medicines Agency (EMA) published an update of the annex to the EC guideline with a corrigendum on 19 November 2018 (EMA/CHMP/302620/2017 corr 1) and a final revision on 22 November 2019 (EMA/CHMP/302620/2017 Rev. 1).

Article 59(1) of Directive 2001/83/EC requires that the package leaflet shall be drawn up in accordance with the Summary of Product Characteristics (SmPC) (DIRECTIVE 2001/83/EC). Therefore, consistent information should be stated in both documents for all excipients listed in the Annex to the guideline. Article 59(1)(f)(iv) requires the full qualitative composition (in active substances and excipients) and the quantitative composition in active substances to be included in the package leaflet. Article 59(1)(c) states that the package leaflet must include a list of information which is necessary before taking the medicinal product. Article 59(2)(c) provides that the aforementioned information shall list those excipients whose knowledge is important for the safe and effective use of the medicinal product and which are included in this guideline published pursuant to Article 65(e).

Excipients are defined in Directive 2001/83/EC as any constituent of a medicinal product other than the active substance and the packaging material. According to Annex I of Directive 2001/83/EC, such constituents may include: colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.; constituents intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, film-coated tablets, etc.). Of note, excipients are in general considered to be 'inert'. Whilst it is desirable that excipients should have little or no pharmacological action of their own, some do indeed have a recognised action or effect in certain circumstances. The EC guideline on "*Excipients in the labelling and package leaflet of medicinal products for human use*" states that "*It is accepted that excipients may only show an effect above a certain amount. This potential effect has been taken into account in the overall benefit/risk evaluation of the approved medicinal product."* It is also important to highlight that the guideline indicates that in the context of the guideline, residues of substances arising from the manufacturing process, impurities, residual solvents, degradation products, etc. are not included in the definition of excipients.

Vaccines Europe (VE) understands and supports the intended purpose of the EC excipients guideline and associated annex in making healthcare practitioners and patients aware of the risks due to exposure to certain excipients in medicinal products, especially when the use is chronic. It is the position of VE, however, that there are key differences between drugs and vaccines, that result in very different levels of exposure and risk that needs to be taken into

consideration when applying precautionary language from the guideline annex in the SmPC/PL.

Medicines are designed to achieve a therapeutic dose level in the individual and can potentially be administered over prolonged periods (years), leading to substantial lifetime exposure to the medicinal components, including excipients. Prophylactic vaccines are formulated to induce an immune response in the recipient. As such, pharmacokinetic and pharmacodynamic factors relating to drug absorption, metabolism and excretion do not apply to vaccines (EMEA/CHMP/VWP/164653/2005). Vaccines also differ from other medicinal products in that they are given infrequently over a lifetime; typically, 1-4 doses, although some may be administered more frequently, for example annually (influenza) or decennially (tetanus-diphtheria boosters). Compared to medicines, the exposure of excipients in vaccines is punctual and the cumulative life-time exposure is very small.

It should be noted that these specificities of vaccines have been acknowledged for fructose and sorbitol in EMA guideline on "*Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use*" (EMA/CHMP/460886/2014). This document states that due to the low levels of sorbitol as an excipient and given the fact that vaccines containing sorbitol have been administered for a long time without any known incidence of severe events due to hereditary fructose intolerance, the warning for vaccines should differ from the warning for products administered intravenously. As a consequence, a threshold above zero is applied for vaccines and other oral and parenteral (other than intravenous products) to avoid misleading warning in the package leaflet of vaccines.

As the intent of safety-related information in SmPC/PL is to provide *meaningful* information to help healthcare providers and patients understand the benefit/risk of product use, it is imperative that the safety-related information in the product information is proportional to the risk. The inclusion of extraneous precautionary text, based solely on a threshold from the guideline, may unintentionally result in addition of unnecessary precautionary text to the SmPC/PL. This additional text introduces complexity to the labelling which may reduce the prominence of other text describing important safety issues, or potentially divert their attention from the more important information to read. Moreover, it raises unfounded safety concerns that could contribute to vaccine hesitancy.

The aim of this position paper is to outline that the updated annex, as currently written, does not provide optimal guidance about excipients that should be included in the labelling of vaccines. To illustrate VE's position, some examples of vaccine excipients and related assessment are presented in section 2 (non-exhaustive list).

VE therefore proposes to revise the guideline and annex on excipients to exempt vaccines from the mandatory inclusion of warnings based solely on the limits currently listed in the annex. Instead, it is proposed that for selected excipients, the inclusion of safety text in the product labelling should be based on a safety evaluation that takes into account the negligible cumulative exposure following vaccination, the extensive post-marketing experience with certain excipients that have been used in vaccines for decades and the benefit of vaccination.

2. Vaccines Europe assessment

Vaccine manufacturers have reviewed the excipients listed in the Annex that are present in vaccines (i.e., excipients associated with potential risks through oral, parenteral and/or all routes of administration) and have evaluated their potential safety risk based on the level above the threshold determined in the EC guideline. The examples below illustrate the specific issues associated with the implementation of the thresholds and related statements as currently described in the Annex to the EC guideline on "*Excipients in the labelling and package leaflet of medicinal product for human use*" for prophylactic vaccines.

Illustrative examples are presented below (non-exhaustive list).

2.1. Para-aminobenzoic Acid (PABA)

Exposure level

The Company A has a portfolio of several vaccines registered in Europe to prevent infectious diseases. These vaccines are administered subcutaneously or intramuscularly to infants and children according to a 2 or a 3-dose vaccination regimen, with potentially one booster dose administered later in life in accordance with official recommendations.

The total quantity of PABA present in the final dose of these vaccines ranges from <0.07 ng/dose to 0.26 ng/dose.

What is the safety concern highlighted in the Annex?

PABA is included in the Annex (i.e., category parahydroxybenzoates and their esters) with a threshold of zero triggering a warning due to a potential safety concern for sensitized subjects.

Safety risk assessment

PABA may induce type IV delayed hypersensitivity reactions in sensitive individuals (Eggleston et al., 1996; Mackie et al., 1999).

No safety limit has been established by International Health regulatory bodies. For impurities and leachables, the Product Quality Research Institute (PQRI), an industry consortium, has recommended an acceptable safety limit of 5 µg/day for leachable classified as skin sensitizer. As such, provided the potential leachable would remain at quantities below the threshold limit of 5 µg/dose, it would not be expected to present a risk for patient safety (Error**! Reference source not found.**Paskiet et al., 2013).

Amounts of PABA in the vaccines from the Company A are substantially lower (>10^4-fold) than the PQRI acceptable level of sensitizing impurities.

It is considered unlikely that levels of PABA present in the vaccines of Company A would represent a safety concern. Therefore, including the amount of PABA and a warning concerning its use to the SmPC and package leaflet is considered unwarranted.

2.2. Phenylalanine

Exposure level

The Company B has a portfolio of several vaccines registered in Europe to prevent infectious diseases. These vaccines are administered orally, subcutaneously or intramuscularly to infants, children, adolescents and adults according to a 1,2 or a 3-dose vaccination regimen.

The total quantity of phenylalanine present in the final dose of these vaccines ranges from 0.0298 µg/dose to 828 µg/dose.

What is the safety concern highlighted in the Annex?

Phenylalanine is included in the Annex with a threshold of zero triggering a warning due to a potential safety concern for individuals with phenylketonuria (PKU). PKU is an autosomal recessive disorder of amino acid metabolism characterized by the accumulation of phenylalanine in blood and brain due to a deficiency in phenylalanine hydroxylase. Toxic levels of phenylalanine may result in permanent intellectual disability (van Wegberg et al., 2017).

Safety risk assessment

The treatment of patients with PKU includes a diet restricted in phenylalanine to lower blood levels to within a recommended range that supports optimal growth, development, and mental functioning. The recommended minimum intake of phenylalanine for 0-6 months old infants is 20-70 mg/kg (100-350 mg/day if 5 kg body weight); and 10-35 mg/kg for 7-12 months old (MacLeod et al., 2010).

The amount of phenylalanine contained in the vaccines from Company B (maximum of 828 µg/dose) represents a negligible contribution to the overall daily intake of phenylalanine in individuals with PKU. It is considered unlikely that levels of phenylalanine present in vaccines would represent a safety concern to vaccinated subjects with PKU. PKU is not a contraindication for vaccination, and vaccination of individuals with PKU should not be withheld due to concerns about phenylalanine content (van Wegberg et al., 2017). Therefore, including a warning concerning the presence of phenylalanine to the SmPC and package leaflet is considered unwarranted.

2.3. Sodium and potassium

Exposure level

Several companies have seasonal influenza vaccines registered in Europe to prevent (seasonal) influenza. These vaccines are administered subcutaneously or intramuscularly to infants, children, adolescents and adults. They are administered on annual basis according to a single dose vaccination regimen (with a one-time booster for infants if they have not been vaccinated before).

The SmPC/PL of these products has the following statement on the presence of sodium and potassium in the product:

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially "potassium- free".

What is the safety concern highlighted in the Annex?

For products, administered orally or parentally, which have the above-mentioned statements and information in the labeling, the Annex has the following comments on sodium and potassium:

Sodium:

1 mmol of sodium (Na) = 23 mg Na = 58.4 mg salt (NaCl). Information relates to a threshold based on the total amount of sodium in the medicinal product.

It is especially relevant to products used in children or in patients on a low sodium diet, to provide information to prescribers and reassurance to parents or patients concerning the low level of sodium in the product.

Potassium:

Information relates to a threshold based on the total amount of K^+ in the medicinal product.

It is especially relevant to products used in children or in patients on a low sodium diet, to provide information to prescribers and reassurance to parents or patients concerning the low level of K^+ in the product.

Safety risk assessment

Seasonal influenza vaccines usually contain per dose far less sodium and potassium salts than the above mentioned 1 mmol per dose (typically even < 5 mg of sodium and potassium salts per dose). Given that these vaccines are only administered once a year (initially followed by a second vaccination), the informative value of these statements is limited, and the need for inclusion of these statements in the product labeling may be re-considered.

2.4. Ethanol

Exposure level

The Company D has a portfolio of several vaccines registered in Europe to prevent infectious diseases. These vaccines are administered subcutaneously or intramuscularly to infants, children, adolescents and adults. They are administered either according to a 1,2 or a 3-dose vaccination regimen (with a booster for some of them) or decennially.

The maximum quantity of ethanol present in the final dose of these vaccines is 2.5 µL corresponding to 2 mg.

What is the safety concern highlighted in the Annex?

Ethanol is included in the Annex with a threshold of zero triggering a warning due to a potential safety concern for adverse effect on children (feeling sleepy, changes in behavior, ability to concentrate), on healthy adults (ability to drive or use machines), on patients with epilepsy, liver diseases, addicted to alcohol, and pregnant or lactating women.

According to "Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use" EMA/CHMP/43486/2018 dated 20 September 2018, it is required to convert the quantity of ethanol in ml beer and wine. Below is an example of how it would translate for a vaccine:

"This medicine contains 2 mg of alcohol (ethanol) in each 0.5 ml dose. The amount in 1 dose of this medicine is equivalent to less than 0.1 ml beer or 0.1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects."

Safety risk assessment

As mentioned as above-mentioned guideline, ethanol is present in a number of food stuffs, such as fruit, bread and yogurt. It has been estimated that the diet of a 6 year old would result in exposure to ethanol from food of 10.3 mg/kg/day (Gorgus et al., 2016). Therefore, the amount of ethanol (2.5 µL or 2 mg) contained in vaccines represents a negligible contribution to the overall intake of ethanol and is unlikely to have any adverse effects on vaccine recipients.

Therefore, including the amount of ethanol and a warning concerning its use to the SmPC and package leaflet is considered unwarranted. Moreover, the conversion to quantity of alcoholic beverage for injectable vaccine could be misleading.

3. Discussion and recommendation

The product label is a primary source for healthcare providers and for the general public to inform them on how to use the medicinal product safely and effectively. According to the European guideline on Summary of Product Characteristics, information on a specific risk should be given in section 4.4 of the SmPC only when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk.

Prophylactic vaccines are intended for use by the whole population and they also differ from medicines in their targeted action, and in how they are used over a lifetime. Compared to some medicines, the lifetime exposure to vaccine excipients is almost immeasurably small. The need to include warnings linked to the presence of some excipients in vaccines should be evaluated on a case-by-case basis based on a thorough review of the potential safety risks for vulnerable persons based on the level of excipient in each vaccine, balanced with the responsibility to encourage vaccination of all individuals. The present evaluation highlights major differences between medicines given over long periods, and vaccines for which the immediate (at the time of vaccination) and lifetime exposure to excipients is extremely small. These fundamental differences between vaccines and other medicinal products justify a distinction in labelling requirements, notably with respect to the inclusion of excipients and accompanying warning statements which are not relevant in the context of vaccine

administration. The vaccine particularities were taken into consideration in the guideline for sorbitol, a similar approach is also relevant for other excipients.

Vaccines Europe proposes to revise the guideline and annex on excipients to exempt vaccines from the mandatory inclusion of warnings based solely on the limits currently listed in the Annex. Instead, it is proposed, for selected excipients, to perform a safety evaluation that takes into account the negligible cumulative exposure following vaccination, extensive post-marketing experience with certain excipients have been used in vaccines for decades and the benefit of vaccination.

4. Literature References

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