

EVM reflection paper on the Safety Assessment of Residuals and Contaminants in Vaccines

1. Scope

Vaccines; vaccine adjuvants

2. Purpose

To start discussions with the Regulatory Agencies' regarding the Safety Assessment of residuals and contaminants in vaccines.

The paper provides background information (section 3) and an overview of the existing regulatory framework (section 4), which can be used as a basis to formulate a general approach for the safety assessment of residuals and contaminants in vaccines (section 5).

3. Background and rationale

Most vaccines are prophylactic and administered to healthy subjects; hence there is a stringent emphasis on safety.

Polymers are used in various stages of vaccine production, including: syringes, stoppers, flexible tubing, flexboy bags, and final or intermediate containers for liquid storage. The use of polymers can result sometimes in the presence of unexpected extractable/leachables in the product. Furthermore, vaccine manufacturing processes occasionally result in the presence of residuals or contaminants in vaccines, for example: coupling agents used to link multivalent antigens, inactivating agents, antifoaming agents, preservatives, inducing agents used to induce expression of recombinant antigen, or antibiotics.

For these reasons, there is a potential need for common safety assessment processes when residuals or contaminants are detected.

Of note; currently, there are no specific regulatory guidance (FDA, EMA, PMDA, WHO) for the safety assessment of vaccine residuals or contaminants. Although some guidelines exist, they are in support of more conventional pharmaceutical products rather than biologicals (see below section 4 regulatory framework).

An extensive review of the existing guidelines was conducted, which then supported the development of this paper by the EVM. This reflection can be the basis for starting the discussion with authorities, to gather their views and have a common understanding on how to proceed forward if needed.

4. Current Regulatory Framework

The objective of this section is to provide a comprehensive overview of the existing Regulatory Framework.

4.1 Threshold of Toxicological Concern

The “Threshold of Toxicological Concern” (TTC) is described in EMEA *Guideline on the Limits of Genotoxic Impurities (CHMP QWP/251344/2006)*¹. The principle of the TTC is derived from FDA’s Threshold of Regulation (TOR) approach for food contact materials, which states that a dietary concentration below 0.5 ppb is so negligible that it presents no public health concern. Assuming an average intake per day of 1500 g diet and 1500 g fluids this is equal to 1.5 µg/person/day. Food contact materials with exposures below this level are exempted from regulation.

The TTC concept implies that lifetime exposure to an untested compound at levels below the TTC will most likely pose a cancer risk of less than 1 additional case per million people, and enables a “virtual” risk-assessment to be conducted without animal carcinogenicity data. For most genotoxic carcinogens, lifetime exposure to 0.15 µg/day/person induces less than 1/10⁶ cancers, resulting in a generic TTC level of 0.15 µg/day/person. Because pharmaceuticals are considered to have a benefit, CHMP increased the TTC limit by a factor of 10 to 1.5 µg/day/person, corresponding to an acceptable cancer risk of <1 in 100000 over a lifetime.

A TTC of 1.5 µg/day/day is applicable for lifetime exposure, and this level may be too stringent for short than ‘lifetime exposure situations’. Consequently, EMA and FDA have also proposed “Staged TTC” values for shorter than lifetime exposures, as shown below², which may be considered during clinical development.

Duration Of Treatment	Single Dose	≤ 1 month	≤ 3 months	≤ 6 months	≤ 12 months	> 12 Months
µg/day	120	60	20	10	5	1.5

*These values have been considered applicable for an adult population, and no specific requirement has been mentioned for paediatrics by the regulatory authorities.

4.2 ICH Q3C and Permitted Daily Exposure

ICH Q3A (*Note for Guidance on Impurities Testing: Impurities in New Drug Substances, CPMP/ICH/2737/99*)³, and ICH Q3B (*Note for Guidance on Impurities in New Drug Products, (CPMP/ICH/2738/99)*)⁴ address the issue of impurities in drug substances and drug products, respectively. These guidance documents define an impurity as any component of the new drug substance or product that is not the chemical entity defined as the drug substance or an excipient in the drug product. However, the scope of ICH Q3A and Q3B excludes biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin. Consequently vaccines are out of scope of ICH Q3A and Q3B.

The scope of ICH Q3C (EMA/CPMP/ICH/283/95 *ICH Topic Q3C (R4) Impurities: Guideline for Residual Solvents*)⁵ includes residual solvents in drug substances, excipients, and drug products and applies to all dosage forms and routes of administration. In contrast to ICH Q3A and Q3B, Q3C contains no specific exemption for biological/biotechnological products. Currently, two new guidelines are being written: ICH3D and ICH 7, which will also address the subject of impurities, and may also be consulted, noting as with the above guidelines, these will also exclude biological/biotechnological products.

ICH Q3C sets acceptable concentration limits or permissible daily exposures for various classes of solvents. The term “Permitted Daily Exposure” (PDE) in ICH Q3C is defined as the pharmaceutically acceptable intake of residual solvents. PDE is used in Q3C to avoid confusion with Tolerable Daily Intake” (TDI) used by WHO/IPCS for environmental and occupational exposures and “Acceptable Daily Intake” (ADI) used by WHO for food residue exposures.

Appendix 3 of Q3C provides a method for establishing exposure limits for residuals, based on: Assessing Human Health Risk of Chemicals (IPCS, EHC 170, 1994); Procedures for Setting Exposure Limits in Pharmaceuticals (Pharmacopeial Forum, Nov-Dec 1989); and is similar to US EPA IRIS and US FDA (Red Book) methods. Appendix 3 states that “*The assumption of 100% systemic exposure is used in all calculations regardless of route of administration*”. PDE values are derived preferably from the NOAEL, however if none is obtained the LOAEL may be used.

The method for the calculation a PDE is shown below:

$$\text{PDE} = \frac{\text{NOAEL} \times \text{weight adjustment}}{F1 \times F2 \times F3 \times F4 \times F5}$$

F1 = factor for extrapolation from test species to humans

F2 = default factor of 10 to account for variability between individuals

F3 = factor to account for lack of chronic toxicity studies, if applicable

F4 = factor to account for any evidence of genotoxicity, carcinogenicity, or reproductive/developmental toxicity

F5 = factor of 10 to account for a lack of a NOAEL, if applicable

Weight adjustment = 45 kg small adult or 5 kg for infant

4.3 Metals

The EMA Note for Guidance on Specification Limits for Residues of Metal Catalysts (EMA/CPMP/SWP/4446/00)⁶ is primarily focused on metal catalysts used in the synthesis of pharmaceutical substances, but states that it “*can be updated to include other sources of metal residues and additional elements*”. It contains no specific exemption for biological or biotechnological products, and applies to all dosage forms. Different PDE limits are applied to oral and parenteral routes of administration because many transition element metals have low oral bioavailability due to poor GI absorption. If a substance is administered by a route other than oral or parenteral, either the oral or the parenteral PDE should be used, depending on the expected absorption by that particular route. The oral or parenteral PDEs specified in this Guidance are based on chronic use, so higher limits may be acceptable in cases of short term (< 30 days) use.

5. Safety Assessment Process

5.1 General considerations

Once the identity of the residual or contaminant has been established, the first step in the safety assessment process is to determine or estimate the ‘worst case’ mass of the residual or contaminant per vaccine dose. When the mass per dose is estimated rather than measured, the assumptions made in deriving the estimate should be documented. It may be prudent to make a ‘worst case’ assumption that 100% of a residual or contaminant will enter the final vaccine formulation, even when it is detected in a manufacturing step prior to final formulation and might be removed in subsequent processing steps.

5.2 TTC

As mentioned above, a single TTC value of 1.5 µg/day might be considered too stringent. Indeed, EMA and FDA have also proposed “staged TTC” values for shorter than lifetime exposures. For this reason, the EVM would support a staged TTC approach. Furthermore, the “staged TTC” approach could take into consideration criteria in addition to the duration and frequency of administration (short vs. long-term), such as:

- Pediatric or adult target population: consideration should be given to the target population for the vaccine in which the residual or contaminant is present, as this may influence the selection of an appropriate TTC value.
- Therapeutic vaccines versus prophylactic vaccines: the patient population (healthy vs. ill subjects) should be considered when selecting a TTC value, since this may influence the risk-benefit assessment.
- Presence of structural alerts in the residual or contaminant: the presence of structural alerts in the residual or contaminants should be considered when selecting a TTC value. Some structural groups have been identified as high potency and would be associated with a high probability of a significant carcinogenic risk (Cheeseman et al., 1999) For example: aflatoxin-like, N-nitroso-, and azoxy compounds and are excluded from the TTC process. Risk assessment of members of such groups requires compound specific toxicity data (see guideline EMEA/CHMP/QWP/251344/2006)⁷.
- Frequency of vaccine administration: For vaccines that are administered on a yearly basis- for example flu vaccine or vaccines that may be administered more frequently – for example therapeutic vaccines, the frequency might influence the TTC value to be considered

5.3 Existing Safety Limits

For some residuals or contaminants, existing human safety limits have been established by various national or international agencies. EVM considers safety limits established by the following organizations potentially useful for the safety assessment of vaccine residuals or contaminants:

- US or EU pharmacopea

- FDA inactive ingredients list
- PDEs for class 2 solvents (ICH Q3C)
- PDEs for metals ((EMEA/CPMP/SWP/4446/00)
- EPA RfD
- ATSDR MRL
- WHO/IPCS Environmental Health Criteria documents
- WHO CICAD
- FDA GRAS list
- FAO/WHO JECFA
- OECD SIDS

In general, if safety limits exist, the EVM considers that the calculation of the PDE might not be necessary. Indeed, vaccine manufacturers could refer to established safety limit to assess whether the identified residual/contaminant present any risk in terms of safety

There are some cases where the existence of safety limits might still require the calculation of a PDE. For instance, where the safety limit has been set for a food additive, based on limited oral data- perhaps a safety factor could be added, depending on the context and detail

A list of existing limits which are satisfactory for the safety assessment of vaccine residuals or contaminants and do not require the calculation of a PDE could be developed.

5.4 PDE

When safety limits described in section 5.3 (above) are not available or sufficient and residuals or contaminants present are above the applicable TTC, EVM recommends that the method described in Appendix 3 of ICH Q3C be used to calculate a Permitted Daily Exposure (PDE) level, as shown in section 4.2 (above).

It should be noted that PDE values are acceptable daily exposure levels, while most prophylactic vaccines are administered in only one or two doses, and not on a daily dosing schedule. The PDE calculation also includes modifying factors to account for interspecies extrapolations, inter-individual variability, etc. Thus, not only are the calculated PDE values conservative because the uncertainty factors used for their derivation are 'worst case', the value for a short term administered vaccine, would be more conservative than for a product administered chronically

The quantity and quality of toxicological data available for residuals and contaminants can be highly variable. EVM recommends that the following data should be available for a substance in order to calculate a PDE value:

- Repeated dose data in which either a NOAEL or NOEL can be determined
- At least one genotoxicity study.

When genotoxicity data are available, but repeated dose data are unavailable, acute toxicity data (preferably via intended route(s) of administration) could be used to estimate a LOAEL/NOAEL for the acute systemic toxicity of the residual or contaminant. However, there

may be limitations depending on the study design, which will need to be assessed on a study by study basis.

The use of GLP data is preferable, although this may not always be available. Consequently, the use of professional judgment is essential in selecting appropriate studies from which to obtain a NOAEL/LOAEL for use in the calculation of the PDE for a residual or contaminant⁸.

When evaluating toxicology data obtained from a literature review, the following should be considered:

- quality and reliability of the data (critical review of the type of existing data compliance with regulatory current requirements and missing information),
- route of administration
- frequency and duration of administration
- species
- findings in terms of dose response and no effect dose levels, severity and reversibility
- The classification of a chemical substance and the context of the situation and risk benefit in terms of safety (see section 4). For in vitro data, reproducibility should also be considered. Sometimes, physico-chemical properties and metabolism information (chemical stability, reactivity, potential metabolites, etc) can be useful.

In light of the considerations described above, EVM would like to share for discussion the following general approach for the safety assessment of residuals and contaminants in vaccines:

STRATEGY AND DECISION TREE

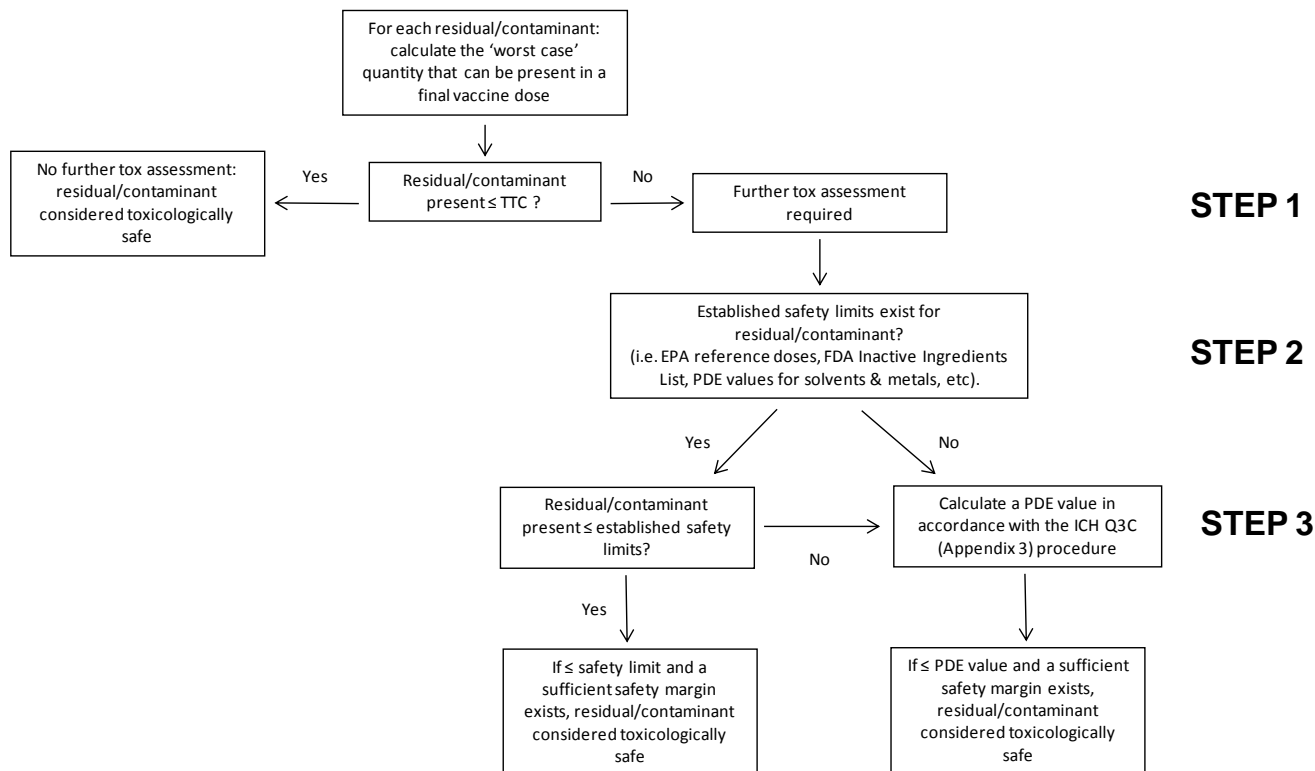


Chart description

Step one – based on the use of the TTC, manufacturers should be able to establish whether the identified residual/contaminant presents a potential risk in terms of safety, which require further assessments

Step two – if further assessment is needed, manufacturer should refer to established safety limit to assess whether the identified residual/contaminant present any risk in terms of safety

Step three – in the absence of existing safety limits / unsatisfactory safety limits (see above), manufacturers should use the PDE to determine whether the residual/contaminant can be considered as toxicologically safe

References

¹ EMEA/CHMP/QWP/251344/2006 *Guideline on the Limits of Genotoxic Impurities*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002903.pdf

² EMA/CHMP/SWP/431994/2007 *Questions and answers on the 'Guideline on the limits of genotoxic impurities'*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002907.pdf

³ EMEA/CPMP/ICH/2737/99 ICH Topic Q3A (R2) *Impurities Testing: Impurities in New Drug Substances*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002675.pdf

⁴ EMEA/CPMP/ICH/2738/99 ICH Topic Q3B (R2) *Impurities in New Drug Products*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002676.pdf

⁵ EMEA/CPMP/ICH/283/95 ICH Topic Q3C (R4) *Impurities: Guideline for Residual Solvents*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002674.pdf

⁶ EMEA/CPMP/SWP/4446/00 *Note for Guidance on Specification Limits for Residues of Metal Catalysts*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50003588.pdf

⁷ EMEA/CPMP/SWP/5199/02 *Guideline on the limits of genotoxic impurities*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002903.pdf

⁸ Klimisch H-J, Andreae M, Tillmann U A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol.* 1997;25:1-5.