Analytische Standards Andre Stratmann
Service Labor GmbH

Extractables/leachables assessment of COVID vaccines
Part 1: Rubber oligomers

Usually, the primary packaging of COVID vaccines consist of a glass vial and a rubber stopper. Pfizer/BioNtech, AstraZeneca, Moderna and Johnson&Johnson uses halobutyl rubber [1] [2] [3]. Common extractables from halobutyl rubber stoppers are rubber oligomers like C13H24, C21H40, C13H23Br (or Cl) and C21H39Br (or Cl). The halogenated oligomers are of special interest, due to their their toxicological properties (structure alerts for genotoxicity and sensitizing potential) and their possible reactivity towards the active pharmaceutical ingredient (API) and/or excipients. Reference standards are essential to develop and validate leachable methods for reliable quantification and investigation of possible interactions with API's and/or excipients.

For the Moderna COVID vaccine, the EMA stated: “For the container closure components, vendor-generated extractables data were used for an initial quantitative toxicological assessment. The assigned safety concern threshold for some stopper oligomers is exceeded in the estimated amount per dose. However, a product-specific leachable study indicated no reportable organic compounds over the analytical evaluation threshold.”[4]

However, the absence of rubber oligomers in a drug product doesn’t mean necessarily, that no leaching occurred. Once released, they might react with e.g. amino groups and lead to modified API's. The reactivity of halogenated rubber oligomers towards proteins is already known [5].

ASAS Labs has initiated a project to investigate the interaction of the brominated rubber oligomer C13H23Br with nucleosides like adenosin, uridine and guanosine as model substrates for RNA.

Two major reaction products for each nucleoside were observed. The adducts were identified using high resulution accuracte mass spectometry. Deteils can be found here. Its has to be mentioned, that the reaction conditions (elevated temperature, presence of organic solvent, alkaline pH) were quite different from the formulation and storage conditions of vaccines. The intention of this experiment was to force formation of adducts to gather information on their chromatographic and spectral behaviour. In upcoming experiments, possible adduct formation under "mild" conditions (e.g. neutral pH, room temperature) will be investigated.

Part 2 of the article will deal with the reactivity of BHT-quinone methide, an oxidation product of the rubber leachable BHT, towards nucleosides.

[1]: https://www.anaphylaxis.org.uk/covid-19-advice/pfizer-covid-19-vaccine-and-allergies/
[2]:https://www.sps.nhs.uk/articles/advising-individuals-with-allergies-on-their-suitability-for-moderna-covid-19-vaccine/
[3]: https://covid-vaccine.canada.ca/info/pdf/janssen-covid-19-vaccine-pm-en.pdf
[4]: https://www.actasanitaria.com/wp-content/uploads/2021/03/covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf
[5]: Heap et al, Pharm. Ind. 80, Nr.1, 2018