General.

1. The CNPPA report title specifies extractables for inhalation packaging systems. There are instances throughout the report that refer to extractables/leachables. Because the intent of the report is for extractables, we recommend removing reference to leachables studies from some of the discussions and definitions where they seem to be used together. Extractables and leachables should be understood and expressed as separate studies and which are not considered interchangeable. For example in Section 2, Part 2.9 Analytical Evaluation Threshold, for the purposes of this guideline, consider removing mention of leachables.

Introduction.

2. The draft guideline mixes terms found in European and US guidance. For example, the term "interaction study" found in EMA guideline is not a term used in FDA guidance.

Please change the term "interaction study" to "leachable study" or use the term "interaction study" consistently throughout the draft guideline and clearly define it.

3. We agree with the Chinese original text of the draft guideline. However, the official English translation does not express the same meaning as the "not only . . . but also" sentence in the original Chinese text. On the contrary, due to the absence of a critical word "only" and grammatical error, the official English translation currently reads as: "*Extraction studies of packaging material of inhaled aerosols can not be used to screen analytical methods for leachables study…"* Please make sure that the English translation is corrected. The sentence should read, "*Extraction studies of packaging material of inhaled aerosols can ~~not~~ be used to screen analytical methods for leachable study, to create potential extraction profile in extreme cases, lay the essential foundation for leachable study and subsequent risk assessment, ~~but~~ and also to characterize construction material of key components of packaging systems, to support routine quality monitoring of extractable, and potential studies on changes in the packaging system*."

4. Section 2. Terms and Definitions.

Part 2.9. The guideline states, *Definition of the Analytical Evaluation Threshold (AET): According to the maximal individual daily exposure or safety concern threshold/limit, dosage and packaging characteristics of the drug product, limits for certain extractable and/or leachable in a single packaging container are derived. When the level of a certain extractable/leachable reaches or exceeds this amount, it is necessary to start the analysis of this extractable/leachable, and report to the relevant departments for safety assessment.*

This definition is confusing. It may be clearer to instead explain that the AET is a threshold that is derived from the Safety Concern Threshold (SCT), which can then be used to assess levels of extractables in extractables studies. The SCT, as stated in section 4.2.3. of the draft guideline, is based on patient exposure and thus is expressed in µg/day can be converted to an AET (which is expressed in, e.g., µg/gram of container, component or sample)

5. Section 6.5.

Not all elastomers / rubbers contain PAHs, Nitrosoamines or MBT. The need to develop specific testing methods to extract and detect "special carcinogens" should be based on information

from the suppliers. If the elastomers are specifically formulated to avoid these substances, it should be possible to avoid this testing.

6. Appendix.

Please consider removing the appendix as it is an incomplete list and focused only on elastomeric additives to some kinds of elastomers. If the Association decides to keep the Appendix, please consider adding further clarification about the scope and purpose of this list.