Summary of the PQRI Leachables and Extractables Recommendations

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The PQRI Leachables and Extractables Working Group made several conclusions and proposals addressing safety thresholds, safety qualification, and best practices for extractables and leachables testing.

The key conclusions and recommendations are:

Safety Thresholds

- Scientifically justifiable safety evaluation and qualification thresholds for leachables in OINDP can be established. The Working Group proposes for an individual leachable in an OINDP[1]
  - a Safety Concern Threshold (SCT) of 0.15 micrograms per day, and
  - a Qualification Threshold (QT) of 5 micrograms per day
- The SCT is the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects.
- The QT is the threshold below which a given leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity relationship (SAR) concerns.
- The SCT and QT are represented as absolute exposures, expressed in total daily intake. They must be converted into relative amounts, expressed in terms such as amount of an individual leachable in a particular drug product, e.g., micrograms per canister in an MDI, to be useful to analytical chemists conducting leachables and extractables studies.

This conversion is performed by using information about the drug product configuration, such as the number of actuations per canister, number of doses per day, number of actuations per dose, number of actuations per day, etc.

The converted SCT, which should be used by the analytical chemists, is called the **Analytical Evaluation Threshold (AET)**.

1 The views in this poster do not necessarily reflect those of the Food and Drug Administration.

Analytical Evaluation Threshold

- The AET is defined as the threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.
- The AET is developed during extractables studies and is applied to both extractables and leachables.
- The AET will vary depending on (i) the particular drug product configuration and (ii) the method(s) used to detect and quantify the extractables and leachables.
- The analytical techniques used for extractables and leachables studies will affect the AET value because of the analytical uncertainty inherent in the response factors of individual leachables (or extractables) analyzed by any given analytical technique/method. A database of extractables response factors should be developed by the sponsor to estimate this uncertainty, which will then be used to help determine the AET.
- AETs for MDIs, nasal and inhalation sprays, DPIs, and inhalation solution/suspension leachables profiles should be based on the Safety Concern Threshold (SCT) of 0.15 µg/day for an individual organic leachable.
- It is recommended that MDI actuator/mouthpieces, and critical components of DPIs, nasal spray and inhalation spray drug product container closure systems that are not in continuous contact with the drug product formulation, have an extractables Estimated AET of 20 µg/g for an individual organic extractable. For all these components, adequate extraction conditions should be used. Comprehensive Controlled Extraction Studies should always be performed on non-contact DPI critical components, even if they do not have continuous long term contact with the drug product formulation.
- Leachables studies (either stability studies or "one-time" characterization studies) would only be required for DPIs if potential leachables of safety concern were identified at the AET level during comprehensive Controlled Extraction Studies
- It is recommended that if it can be scientifically demonstrated that aqueous and/or drug product formulation extracts of inhalation solution direct formulation contact container closure system material yield no extractables at Final AET levels, or no extractables above Final AET levels with safety concern; AND there is no evidence for migration of organic chemical entites through the unit dose container into the drug product formulation; THEN drug product leachables studies are not required
- Analytical uncertainty can be evaluated in order to establish a Final AET for any technique/method used for detecting and identifying unknown extractables/leachables
- It is recommended that analytical uncertainty in the Estimated AET be defined as one %Relative Standard Deviation in an appropriately constituted and acquired Response Factor database OR a factor of 50% of the Estimated AET, whichever is greater

Integration of Safety Evaluation

- Safety evaluation or "risk assessment" should be integrated into the pharmaceutical development process so that extractables (and potential leachables) may be assessed for safety at early and appropriate stages of development. This evaluation should be performed at three key points in the pharmaceutical development process:
  - During the selection of components and materials
  - On extractables during Controlled Extraction Studies
  - On leachables during Leachables Studies for drug product registration.

Componentry

- The pharmaceutical development team should obtain all available information on the composition and manufacturing/fabrication processes for each component type to the extent possible, and determine which components are "critical."
- Component formulation should inform component selection.
- Risk assessment should be performed during the selection of components and materials.
- The potential for leachables posing a safety concern should be considered during the selection of components
- Extractables testing, including Controlled Extraction Studies and the development and validation of Routine Extractables Testing methods, should be performed for all critical OINDP components.

Controlled Extraction Studies

- Controlled Extraction Studies should
  - Employ vigorous extraction with multiple solvents of varying polarity.
  - Incorporate multiple extraction techniques, based on an assessment of the material and potential extractables.
  - Include careful sample preparation based on knowledge of analytical techniques to be used.
  - Employ multiple analytical techniques.
  - Include a defined and systematic process for identification of individual extractables.
- Controlled Extraction Study "definitive" extraction techniques/methods should be optimized.
- During the Controlled Extraction Study process, sponsors should revisit supplier information describing component formulation.
- Controlled Extraction Studies should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety evaluation threshold.
- Polyaromatic Hydrocarbons (PAH's; or Polynuclear Aromatics, PNA's), N-nitrosamines, and 2-mercaptobenzothiozole (MBT) are considered to be "special case" compounds, requiring evaluation by specific analytical techniques and technology defined thresholds.
- Qualitative and quantitative extractables profiles should be discussed with and reviewed by pharmaceutical development team toxicologists so that any potential safety concerns regarding individual extractables, i.e., potential leachables, are identified and evaluated early in the pharmaceutical development process.

Leachables Studies and Routine Extractables Testing

- Analytical methods for the qualitative and quantitative evaluation of leachables should be based on the analytical technique(s)/method(s) used in the Controlled Extraction Studies.
- Leachables Studies should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety evaluation threshold.
- A comprehensive correlation between extractables and leachables profiles should be established.
- Specifications and acceptance criteria should be established for leachables profiles in OINDP.

Routine Extractables Testing

- Analytical methods for Routine Extractables Testing should be based on the analytical technique(s)/method(s) used in the Controlled Extraction Studies.
- Routine Extractables Testing should be performed on critical components using appropriate specifications and acceptance criteria.
- Analytical methods for Leachables Studies and Routine Extractables Testing should be fully validated according to accepted parameters and criteria.
- Polyaromatic Hydrocarbons (PAH's; or Polynuclear Aromatics, PNA's), N-nitrosamines, and 2-mercaptobenzothiazole (MBT) are considered to be "special case" compounds, requiring evaluation by specific analytical techniques and technology-defined thresholds for Leachables Studies and Routine Extractables Testing.
- Qualitative and quantitative leachables profiles should be discussed with and reviewed by pharmaceutical development team toxicologists so that any potential safety concerns regarding individual leachables are identified as early as possible in the pharmaceutical development process.