THERE IS MORE TO ENDS SAFETY EVALUATION THAN HPHCS – A HOLISTIC APPROACH

Ed Carmines, Manoj Misra, Lise Fraissinet, Bryan Burd and Kevin Burd
Chemular Inc, Hudson, MI

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ABSTRACT
The FDA PMTA guidance suggests that ENDS be analyzed for HPHCs as part of the application. The ENDS device is complex and needs to be analyzed from the perspective of the materials that are used to generate the aerosol and also come in contact with the E-Liquid. The components of the E-Liquid need to be evaluated to determine if they are appropriate for their intended use and, when aerosolized, if they are likely to lead to the production of hazardous constituents (HPHCs) as well as generate potential new unknown toxic chemicals. We have developed a wholistic approach tying extractables and leachables, HPHC analysis of liquid and vapor, toxicity testing (Ames, cytotox, in vitro and in vivo micronucleus, and sensitization (in silico, in vitro, and human) and ingredient safety evaluation. Inhalation thresholds of concern are used to identify potential chemicals of concern. The results are normalized to normal daily usage and compared to conventional cigarettes to demonstrate that the products are appropriate for the protection of public health. Market comparator data is used to show that the products are not different from currently marketed products. Total ion chromatograms are used to demonstrate that no new chemicals of toxicological concern are created in the vaporization process of newly manufactured materials as well as at the end of storage stability and end of life of the pod. The approach will be described in the presentation.

INTRODUCTION
Each applicant that submits a PMTA is required to conduct constituent testing and submit the results as part of their application. As described in detail throughout the rule, the information is necessary to ensure FDA has sufficient information to consider the potential risks and benefits of a new tobacco product to the health of the population as a whole in determining whether the marketing of that product would be appropriate for the protection of public health. There are four major elements of the PMTA: the product design, the product labeling, the manufacturing process and studies designed to show that the product is appropriate for the protection of public health. The population as a whole includes users, former users, and never users.
The evaluation of the effects of the new product in users involves evaluation of the materials and ingredients used to manufacture the product, determination of the stability of the product, the determination of the potential leachables and extractables coming from the container closure system and evaluation of the HPHCs and any potentially unknown new materials in the vapor generated either by intrinsic chemical reactions between ingredients or degradation (due to heat – vaporization process - or oxidation – storage conditions).
The FDA does not set limits for what constitutes acceptable ranges for known constituents or total acceptable limit of unknown constituents. FDA's APPH determination includes a consideration of constituent levels and their resulting health risks relative to comparable products (market comparators) as well as conventional cigarette smoking.

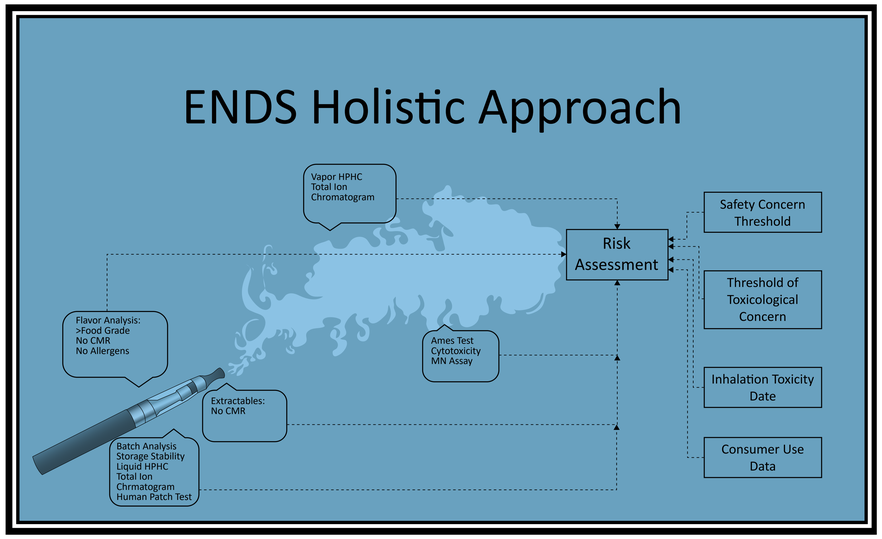
APPROACH
The approach to evaluating the chemicals found in or generated by vaporization is the same:
- Determine level of chemical in product
- Estimate exposure based on use
- Determine if exposure is above the Safety Concern Threshold
- Determine if exposure exceeds Threshold of Toxicological Concern
- Perform risk assessment

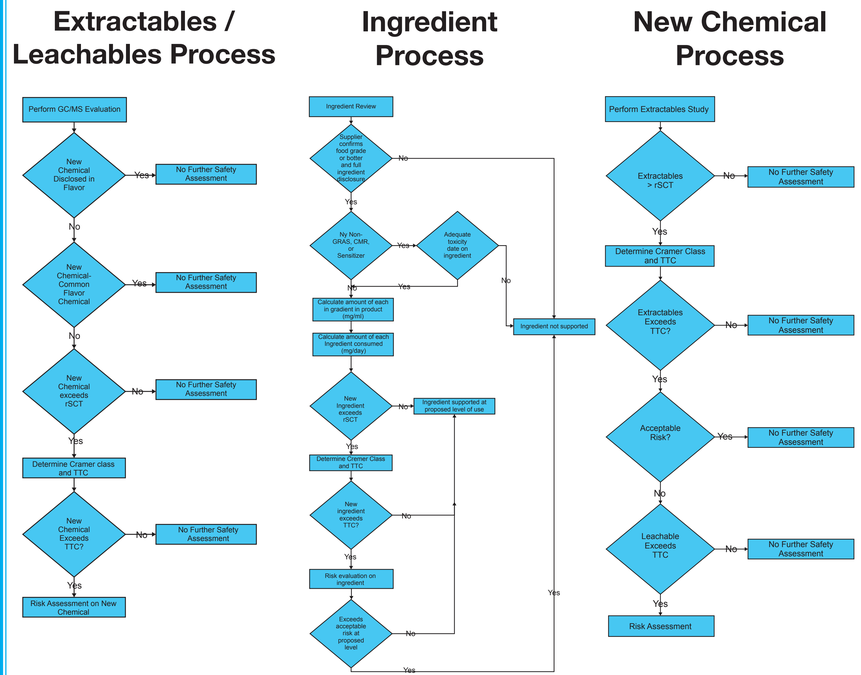
There are a number of determinations that should be made to make sure that the product is APPH.
- All ingredients and materials should be free of toxicologic properties at their intended inhalation use levels
- The product should be stable for the stated shelf life
- The container closure system must protect the product and also not contribute significant toxicants to the product
- The product, when used, should not increase the risks to users when compared to market comparators or conventional cigarettes.
- Risk is a function of hazard and exposure

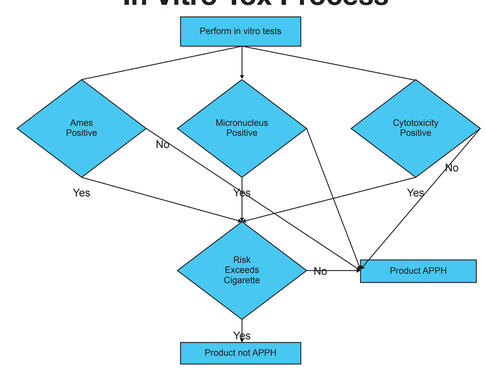
Inherent in this analysis is understanding the actual use of the product. Ideally this is documented by an actual use study. Hazard is determined by
- Evaluating the ingredients and materials in the product
- Measuring known toxic materials in the vapor (HPHCs)
- Confirming the absence of production of any new toxic chemicals in the vapor.
- The hazard determination above is based on evaluation of the toxicities of individual chemicals. The combined or synergistic effects of the chemicals in the product can be evaluated by various in vitro toxicity tests:
- Mutagenicity in the Ames test
- Chromosomal Damage in the Micronucleus test
- Respiratory irritation and damage in the Cytotoxicity test
- Sensitization can be evaluated in the Human Repeat Insult Patch Test (HRIPT)

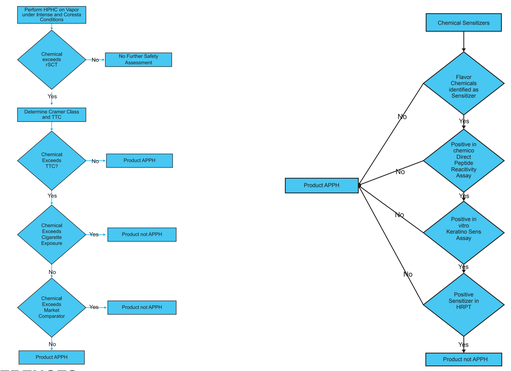
The Approach uses two different recognized regulatory thresholds:

- Safety Concern Threshold (SCT) – The threshold below which a chemical would have a dose so low as to present negligible safety concerns from mutagenic and non-mutagenic toxic effects. The FDA threshold of regulation for substances used in food-contact packaging of 1.5 µg/day was utilized as the SCT (Office of the Federal Register 2000).
- Threshold of Toxicological Concern (TTC)- If an chemical exceeded the SCT, the TTC was determined based on its Cramer Classification. The Cramer decision tree (Cramer, Ford, and Hall 1978) classifies chemicals into one of three classes (I - low, II - intermediate and III - high, i.e. Cramer classes) reflecting the probability of low, moderate, and high toxicity in an explicit way. It is based on the structure of the chemical as indicated by the SMILES designation. TTC is an exposure- concept used in chemical safety assessment. It assumes that a chemical is considered to be safe if the exposure is below a certain threshold. Chemicals with different Cramer Classes have different thresholds. The TTC is based on the Threshold of Regulation, FDA's priority-based assessments of food additives (Hattan and Rulis 1986), which was expanded to include consideration of toxicity data (Munro et al. 1996) (Kroes et al. 2004) Schüürmann (Schüürmann et al. 2016) developed structural alerts that separated high from low repeated dose inhalation toxicities. Tluczkiewicz et al. 2016 further developed the TTC for the high and low toxicities equivalent to 2 µg/day and 4.26 mg/day for Cramer Class III and I compounds, respectively. Since it does not seem possible to separate out Cramer Class II chemicals from an inhalation perspective, any Cramer Class II chemicals are presumed to be Class III for this safety evaluation process.









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