NICOTINE TOBACCO PRODUCT HAZARD ASSESMENT

Lise Fraissinet, Manoj Misra, Ed Carmines, Bryan Burd, Kevin Burd.
Chemular Inc, Hudson, MI USA and Black Buffalo Inc. Chicago, IL, USA

TSRC Poster #63

ABSTRACT

Nicotine Tobacco Products (NTP) should be determined to be appropriate for the protection of public health (APPH). The PMTA guidance to industry (2019) states the requirements for "…manufacturing processes and controls for product design, including a hazard analysis that details the correlation of the product design attributes with public health risk, and any mitigations for identified hazards". Products reaching the market should undergo a sufficient level of hazard assessment in line with their intended use. We present a step-by-step approach that considers the user – product interface and ensures that an acceptable level of risk has been verified prior to product launch.

The assessment is a continuous process that takes place throughout the lifecycle of the product. It requires a 360-degree approach, input from relevant experts and top management engagement. While NTP are not medical devices their risks should still be evaluated and mitigated. Using a detailed understanding of the products and their use, we have developed an approach to identify and mitigate the product risks based on ISO 14971 standard.

The approach consists of four steps: Identify, Evaluate, Mitigate, then Monitor. A Risk Management Plan is established as a starting point and assessment with Subject Matter Experts, Quality Assurance, Senior Management and Independent Reviewer is implemented. The Design, Process, and User Interface are analysed for potential failures and all Hazardous situations are then evaluated. Mitigation of unacceptable risks is done by adjusting the design, the process, adding protective measures or as a last resort by informing the user by labelling or warnings.

Once all mitigations have been implemented, control measures are verified. A Risk Report is prepared to document that the product is APPH.

IINTRODUCTION

The goal of a Risk Management cycle is to identify Hazards and Foreseeable Misuse of Product and ensure that sufficient mitigation is implemented to lower the risk to an acceptable level.

Why is this particularly difficult to implement for NTP? Simply because there is no guidance as for Medical Devices and there is no therapeutical benefit to weigh the risks against. So how do you identify the Hazards and mitigate them? What does "Foreseeable misuse" mean? When do you start and how do you defend your number scale for risk evaluation?

The difficulty in establishing the Risk Management Process and releasing the products to the market is that in the case of NTP, the benefit-risk balance cannot be based on a claimed therapeutical benefit. We therefore propose an approach that focuses on the APPH-risk balance in comparison to Combustible Products. This poster describes the process from start to finish and uses examples of the key "pain points" and main risks encountered.

Figure 1. Risk Management Process Figure

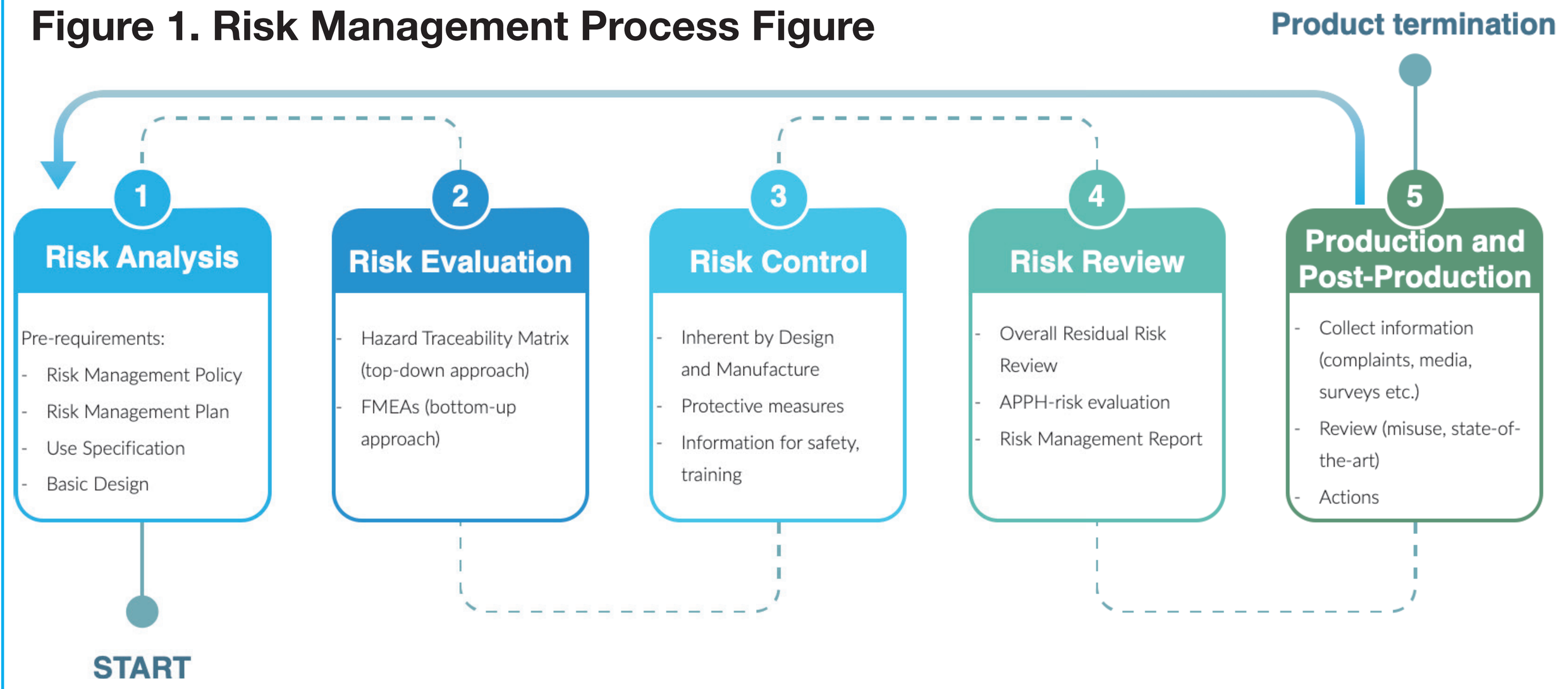
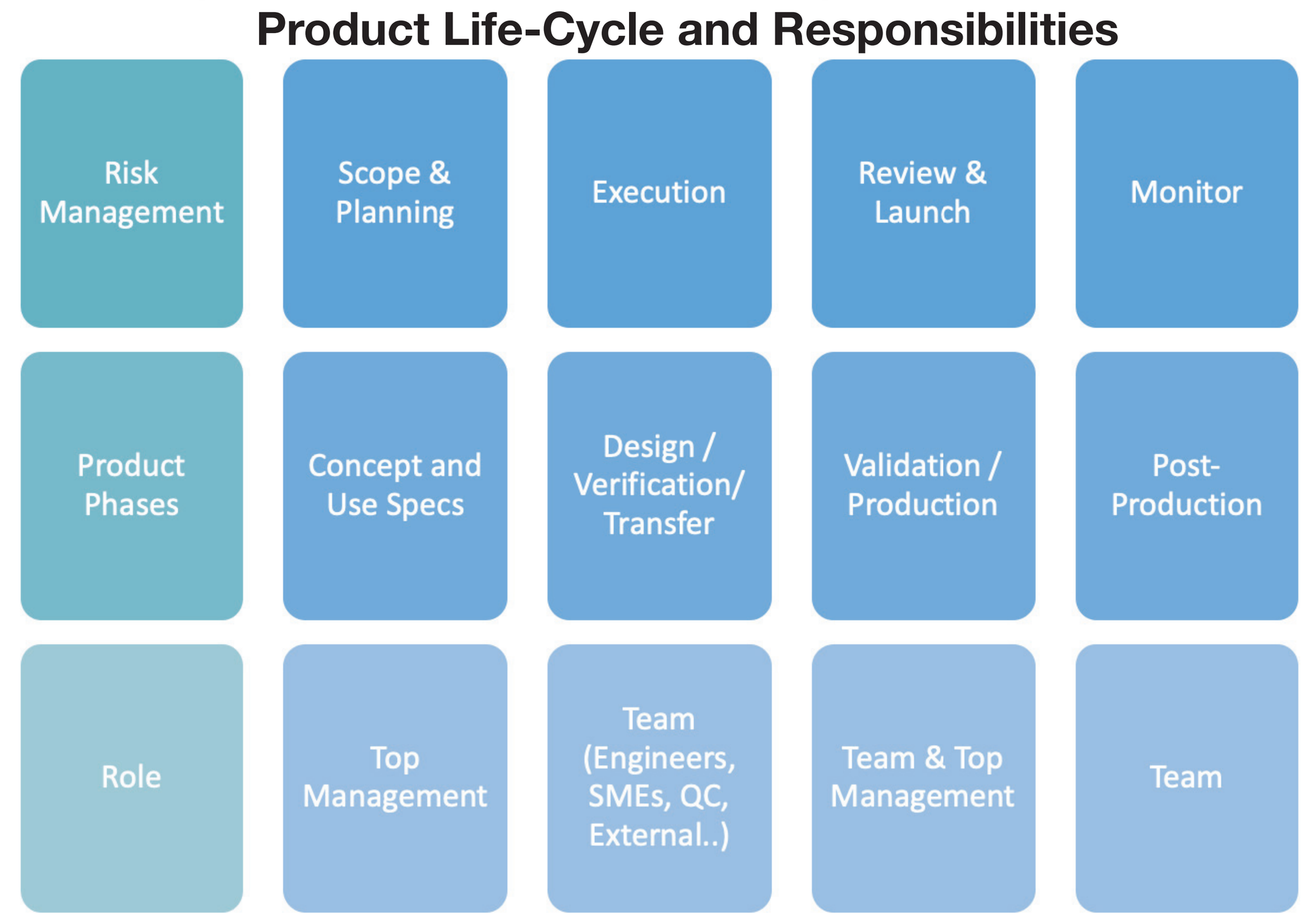


Figure 2. Phases of Risk Management in line with Product Life-Cycle and Responsibilities



PROCESS: WHO IS RESPONSIBLE FOR WHAT AND WHEN

Even though NTP are not medical devices, it is the responsibility of the manufacturer to ensure that they are appropriate for their intended use. Risk Management is the systematic and continuous work done to reduce the risk. ISO 14971:2019, 21 CFR 820 and the forthcoming Medical Device Requirements provide a baseline guidance on best practices to establish a process from initial design, through production, post-production and until the last piece of product on the market is sold or discarded.

The Overall Risk Management Process described in Figure 1, should be started as early as possible in the product development planning phase as illustrated in Figure 2. This will ensure that risks can be mitigated throughout development via design and process and for protective measures to be implemented. It also assists in discovering risks later on that could result in costly changes.
The team taking part in Risk Management should at least be composed of someone trained on Risk Management and someone with clinical expertise.

1 IDENTIFY: Hazard Traceability Matrix – Risk Analysis

We recommend starting the Risk Analysis as soon as the product concept and use specifications are defined.
Two types of documents can support this process:
Design and Process FMEAs: these focus on the materials levels with a bottom-up approach and will focus on the reliability of the product. They do not look at Hazards and Harms but focus on the reliability of the product. As the product reliability is key to its good performance, the outcome of the FMEAs should be considered when working on the Hazard Traceability Matrix (HTM).
Hazard Traceability Matrix – Risk Assessment Section: this document focuses on a top-down identification of hazards that could arise from the use of the product. One important aspect is that normal use as well as misuse/unintended use should be considered.
The Risk Assessment consists of two parts: Risk Analysis and Risk Evaluation.
- **Risk Analysis:** identification of Hazards related to the intended use and reasonably foreseeable misuse of the product and Hazardous situations that could lead to Harm and resulting Risk Estimation.
- **Hazard:** Injury to people, property or the environment. Common hazards can be found in Table 1 but available questionnaires or brainstorming can also help identify additional ones.
- **Risk Evaluation:** the level of risk (Acceptable or Non-Acceptable) based on the probability of occurrence of harm multiplied by its severity.

Table 1. Example of Hazards List

HAZARDS LIST
1. Energy Hazards
1.1 Electrical Energy Hazards
1.2. Thermal Energy Hazards
1.3. Mechanical Energy Hazards
1.4. Acoustical Energy Hazards
1.5. Vibrational Energy Hazards
2 Bio-compatibility, Particulate, Biological and Chemical Hazards
2.1. Chemical & Particulate Hazards
2.2. Biocontamination / Biocompatibilty Hazards
3. Operational Hazards
3.1. Device Function Hazards
3.2. System Interface Function Hazards
3.3 Use Hazards
3.4 Usability / Ergonomic / Human Factor Hazards
3.5. Environmental Hazards
4. Shipping, Installation, Service and Maintenance Hazards
4.1. Shipping Hazards
4.2 Installation Hazards
4.3. Service and Maintenance Hazards
5. Information Hazards
5.1. Labeling Hazards (Includes IFU, Quick Guides, Physical Labels)
5.2 Alarm Systems / Warning Hazards
6.0 Cybersecurity Hazards

The Risk Analysis needs to be done on the assumption that nothing has been done to reduce the risk. This will show what was done to mitigate the risk later on and estimate how far it was reduced. Reasonably foreseeable misuses are ways in which people could, intentionally or non-intentionally, and without too much difficulty use the product not as intended.

Combining both Top-down and bottom-up approaches will ensure that the product will be both reliable (because you will have assessed potential failures from a design and assembly point of view) and safe for its intended use (because you will have looked at risks potentially resulting from its use and misuse).

Table 2 below illustrates how 3 key NTP hazards could get processed in the HTM.

Table 2. Hazard Traceability Matrix – Examples of Risk Analysis and Risk Evaluation.

RISK ANALYSIS								RISK EVAL
ID	HAZARD	Reasonably Foreseeable Sequence or Combination of	Hazardous Situation	Harm	Notes			
1	NICOTINE	Intended user (adult & smoker or vapor) uses the product	User vapes and gets exposed to unknown amount of nicotine	Addiction	Normal use	5	2	N ACC
2		Unintended user (adult & smoker or vapor) uses the product	Unintended user vapes and gets exposed to nicotine	Addiction	Misuse	4	3	N ACC
3		Unintended user (<21 y.o.) uses the product	Unintended user vapes and gets exposed to nicotine	Addiction	Misuse	4	4	N ACC
4		A child gets access to the product and swallows the content	Child ingests nicotine	Poisoning	Misuse	3	5	N ACC
5	BATTERY	Device is transported at high pressure and variable temperatures	Device is stressed to point of explosion	Physical injury	Normal use	3	5	N ACC
6		Device is transported and store in extreme heat	Device is stressed to point of explosion	Physical injury	Misuse	2	5	N ACC
9	HARMFUL CONSTITUEN TS	System overheats and generates products of degradation	User inhales and gets exposed to HPHC	Irritation/ Sensitization/ Poisoning	Normal use	5	3	N ACC
10		User refills the product with own liquid	User inhales and gets exposed to HPHC	Irritation/ Sensitization/ Poisoning	Misuse	3	4	N ACC

Note: the Probability of Occurrence (Po), Severity (S) and Acceptability Levels and criteria are to be established by the Company's Policy. In this example, we used our own established criteria.

2 EVALUATE: Hazard Traceability Matrix – Risk Evaluation

In order to estimate and evaluate the risks, it is necessary to obtain tangible information, either through published literature, complaints, scientific data, expert's advice and if none of the above is available (in case of innovative product), the best guess. Table 3 shows how Probability of Occurrence (Po) and Severity (S) can be estimated on a scale of 1-5, for example.

Table 3. Severity and Probability of Occurrence Valuesation

SEVERITY RATING	DEFINITION	VALUE
Catastrophic	Results in death	5
Critical	Results in permanent impairment or life-threatening injury	4
Serious	Results in injury or impairment requiring professional medical intervention	3
Minor	Results in temporary injury or impairment not requiring professional medical intervention	2
Negligible	Inconvenience or temporary discomfort	1
POCCURENCE (per use)		
DEFINITION	PROBABILITY	VALUE
Frequent	>=1/ 10	5
Probable	<1/. 10	4
Occasional	<1/ 100	3
Remote	<1/ 1000	2
Improbable	<1/ 10,000	1

Once Po and S have been estimated, Po x S will result in the risk acceptability evaluation.
The proposed evaluation in Table 4 shows a well-balanced repartition that will ensure that borderline risks will be looked into in terms of mitigation. It is possible to define a different acceptability table in the operating policy but, as a general rule, to assess whether the evaluation is suitable, try answer the following question: "would I accept this evaluation for a product I would use or that I would give to a family member or friend?"

Table 4. Example of Evaluation Matrix

	Severity				
Probability	1	2	3	4	5
1	ACC	ACC	ACC	ACC*	ACC*
2	ACC	ACC	ACC*	ACC*	N ACC
3	ACC	ACC*	ACC*	N ACC	N ACC
4	ACC*	ACC*	N ACC	N ACC	N ACC
5	ACC*	N ACC	N ACC	N ACC	N ACC

3 4 MITIGATE: Hazard Traceability Matrix - Risk Control and Residual Risk Review

Risk Control consists of reducing the risk to an acceptable level using the means below in order of priority:
1. Design and process changes to remove the hazard completely. When not possible:
2. Protective measures can be put in place to reduce risk or protect from the hazard. When neither option 1 or 2 is possible:
3. Information for Safety and Training can be put in place to lower the risk.

Once approved and applied, the Risk Control Measures must be verified (to show efficiency) and implemented. All Risk Control Measures should be transferred to the Product Design Requirements/Design Input. Table 5 shows examples of Risk Control Measures options for the examples studied above.

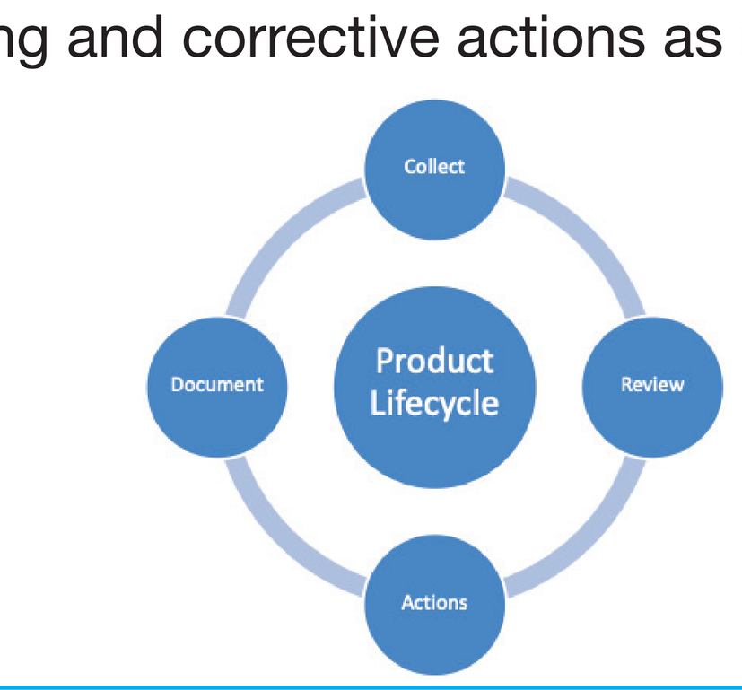
Risk analysis								Risk eval.										
ID	Hazard	Reasonably foreseeable sequence or combination of events	Hazardous situation	Harm	Notes	Po	Severity	Acceptable?	Risk control option inherently by Design and Process	Risk control option by protective measure	Risk control options with information for Safety and Training	Risk control measure	Risk control verification	ImpL?	R-Po	R-Severity	Residual Risk	Residual Risk
1	Nicotine	intended user (adult, non smoker or vaper) uses the product	user vapes and gets exposed to unknown amount of nicotine	addiction	normal use	5	2	N ACC	nicotine cannot be removed as it is the key ingredient	no protective measures can be implemented for adults against the key ingredient	inform user of quantity of nicotine and its addictivity on the label and warnings	Labels and Warnings Specs OQC for presence of label nicotine concentration	Label Comprehension Study Pk Study	Yes	3	2	6	ACC*
2		unintended user (adult, non smoker or vaper) uses the product	unintended user vapes and gets exposed to nicotine	addiction	misuse	4	3	N ACC	nicotine cannot be removed as it is the key ingredient	no protective measures can be implemented for adults against the key ingredient	inform user of risks associated with nicotine	Labels and Warnings Specs OQC for presence of label nicotine concentration	Label Comprehension Study Pk Study	Yes	2	3	6	ACC*
3		unintended user (<21 y.o.) uses the product	unintended user vapes and gets exposed to nicotine	addiction	misuse	4	4	N ACC	nicotine cannot be removed as it is the key ingredient	protective measure to be implemented to verify age of user	inform user of risks associated with nicotine and inform of age restrictions	implement age restriction technology on device/app Labels and Warnings Specs OQC for presence of label	Usability Study Label Comprehension Study	Yes	1	4	4	ACC*
4		a child gets access to the product and swallows the content	child ingests nicotine	poisoning	misuse	3	5	N ACC	nicotine cannot be removed as it is the key ingredient	protective measure to be put in place to prevent access to liquid container	inform user of risks associated with nicotine and to keep out of reach to children	implement child resistant packaging Labels and Warnings Specs OQC for presence of label	Child Resistant Certification Label Comprehension Study	Yes	1	5	5	ACC*
5	Battery	device is transported at high pressure and variable temperatures	device is stressed to point of explosion	physical injury	normal use	3	5	N ACC	change design of battery cell and device to sustain stress to certain level	no protective measure can be implemented	inform user of age restriction for storage and usage temperature	adjust cell and design to comply with UL1642 and UL8139 Labels and Warnings Specs OQC for presence of label	UL8139 Certification Label Comprehension Study	Yes	1	4	4	ACC*
6		device is transported and stored in high extreme heat	device is stressed to point of explosion	physical injury	misuse	2	5	N ACC	change design of battery cell and device to sustain stress to certain level	no protective measure can be implemented	inform user of age restriction for storage and usage temperature	adjust cell and design to comply with UL1642 and UL8139 Labels and Warnings Specs OQC for presence of label	UL8139 Certification Label Comprehension Study	Yes	1	4	4	ACC*
9	Harmful Constituents	system overheats and generates products of degradation	user inhales and gets exposed to HPHC	irritation/ sensitization/ poisoning	normal use	5	3	N ACC	implement temperature control	implement visible liquid level to avoid dry vaping	inform user of alarm meaning	HPHC and Temperature tests under intense smoking regime Signals coding coil and aerosol T assessment	HPHC results tox assessment Usability Study	Yes	2	2	4	ACC*
10		user refills the product with own liquid	user inhales and gets exposed to HPHC	irritation/ sensitization/ poisoning	misuse	3	4	N ACC	action is outside of manufacturer control	implement puff count and cartridge recognition	inform that the product should not be tampered with	HPHC and Temperature tests under intense smoking regime	HPHC results tox assessment Label Comprehension	Yes	2	2	4	ACC*

As quickly seen above, the risks have been reduced (no longer red), however, many of them are yellow and the overall residual risk (sum of all acceptable risks) will require an APPH-risk evaluation.
To do so, multiple aspects can be taken into account for NTP:
- Comparison with combustible products by assessing the abuse liability of the product versus combustible cigarettes
- Comparison of HPHC levels of product with combustible products and competitor products based on daily usage assessed in a use study or topography study
- The review should demonstrate an acceptable Overall Residual Risk.

5 MONITOR: Risk Management Life Cycle.

Once the Risk Review is complete, a Risk Management Report should be reviewed signed-off by top management to release the product for launch. All documents are compiled into a Risk File. From that point, the cycle continues onto production and post-production activities to ensure monitoring and corrective actions as needed.

Information should be collected from:
- Post Market Surveillance
- Service
- Product Inspection
- Feedback and Complaints
- New scientific data
- Recalls on similar products



CONCLUSION

When used early and efficiently, the Risk Management Process can demonstrate an acceptable Overall Residual Risk and defend the Appropriateness of the Product for the Protection of Public Health.

REFERENCES

ISO 14971:2019 21 CFR 820
Medical Device Directive 93/42/EEC
Medical Device Requirement 2017/745

CHEMULAR