CHANGE CONTROL CHALLENGES IN THE CONTEXT OF PMTA

Lise Fraissinet, Lillian Ortega, Chris Woodruff, Randy Freund, Bryan Burd, Kevin Burd - Chemular Inc, Hudson MI, USA

Poster #25

ABSTRACT

Product changes are an integral part of quality improvement and innovation, whether it is for design improvement, supply chain constraints, product standard compliance or business requirements. Navigating the regulatory landscape when product changes are needed is a challenge when changes may potentially result in the product being considered a new tobacco product in the context of PMTA. Section 910(a)(1)(B) of the FD&C Act states that new tobacco products include those that are new because they have been rendered new through any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the U.S. after February 15, 2007.

The FDA has classified “minor” and “major” amendments in terms of their impact on the PMTA review process, but guidance is vague in terms of classification of changes themselves and how to report those changes. The FDA provides examples in the Premarket Tobacco Applications (PMTA) Final Rule, PMTA ENDS guidance and the proposed Tobacco Product Manufacturing Practice rule (TPMP). The aim of this poster is to propose a systematic classification of the changes, establish how to address change requests, change assessment and change order via Good Change Control Practices and how it should be reported to the FDA.

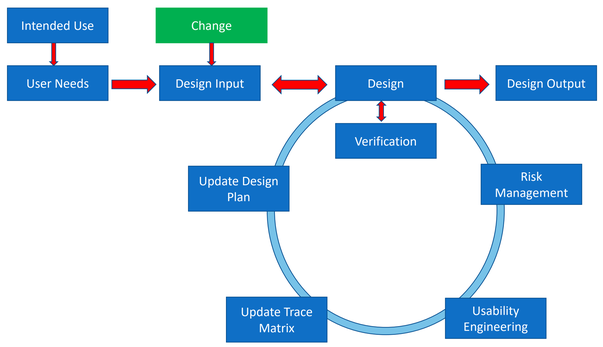
The approach presented below is based on multiple FDA guidance documents and regulations on product changes and when to report to the FDA that have been implemented across regulated industries:

- FDA Medical Device Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device
- FDA ANDA/NDA Guidance: Changes to an Approved NDA or ANDA
- FDA PMTA Final Rule: Premarket Tobacco Products Applications and Recordkeeping Requirements.
- FDA Proposed TPMP requirements

DESIGN CONTROL AND RISK MANAGEMENT

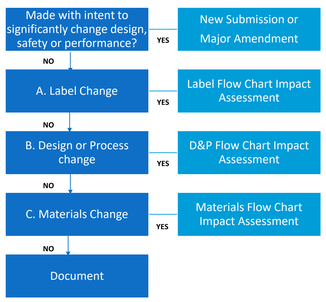
Implementing Change Control practices implies that Design Control and Risk Assessment are fully part of the product development and manufacturing processes. Proposed TPMP §1120.42 addresses risks associated with design and development activities by requiring finished and bulk tobacco product manufacturers to establish and maintain procedures to control the design and development of each finished and bulk tobacco product and its package, including the control of risks associated with the product, production process, packing, and storage. Procedures to control the design and development of finished and bulk tobacco products would need to address risk management as well as design verification and validation. The proposed TPMP requirements incorporate principles similar to those found in, for example, ISO 9001; the Quality System Regulation for medical devices; current Good Manufacturing Practices, risk analysis ISO 14971, risk-based preventive controls for human food 21 CFR Part 117 and HACCP regulations.

Figure 1. Change Control as part of Design Control and Risk Management Systems



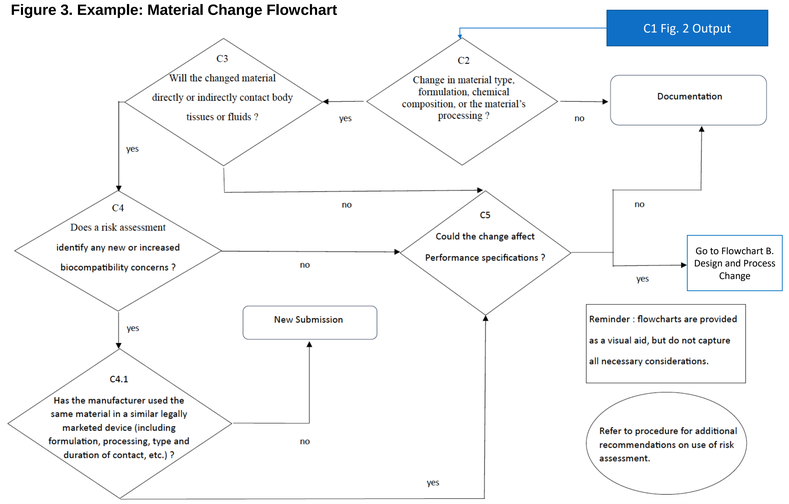
CHANGE CLASSIFICATION AND IMPACT

Figure 2: Change Classification



The FDA have classified minor and major amendments in terms of their impact on the PMTA review process, but the guidance is vague in terms of classification of changes themselves and whether they should result in an amendment. The FDA provides examples in the PMTA final rule, but the aim of a Change Control Procedure is to establish a systematic classification of the change and how it should be managed and reported. Drugs and Medical Devices have a clearly established guidance on how to control and report changes and this is a similar approach that we are proposing to follow.

Figure 3. Example: Material Change Flowchart

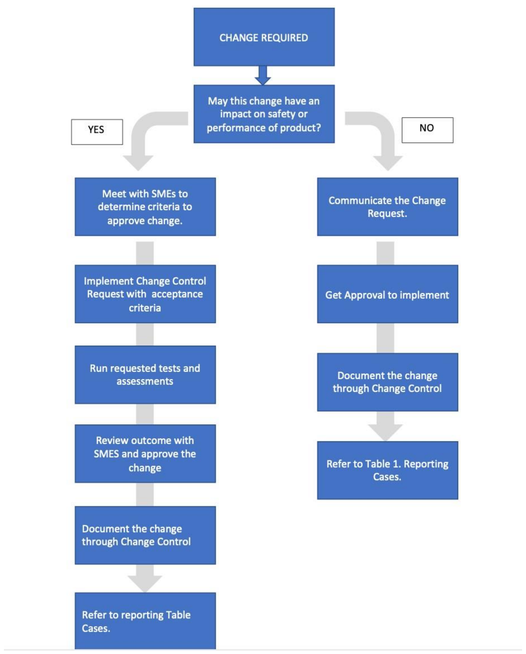


CHANGE CONTROL

The Change Control Process comprises 3 steps:

1. **Change Request**: identify and initiate the request for change by documenting it and involving the necessary resources
2. **Change Impact Assessment**: classify the change, assess its impact using a decision flowchart and implement necessary studies including risk management and define acceptance criteria. See Figure 3 as example.
3. **Change Order**: once all acceptance criteria have been met, approve and implement the change. The Change Control becomes part of the Design History File

Figure 4. Change Control Process



REPORTING CASES ON PMTA AND TPMF

If the change leads to a New Submission, it could be either a New PMTA or a supplemental PMTA depending on the status of the initial submission review.
If only Change Documentation is required:

- Post Marketing Granted Order: The change made to the manufacturing, facilities, or controls during the reporting period would be documented and include:
  a. A comparison of each change to what was described in the PMTAs;
  b. The rationale for making each change and, if any, a listing of any associated changes;
  c. The basis for concluding that each change does not result in a new tobacco product that is outside the scope of the Marketing Granted Order.

- During PMTA Review: The change would be documented as an amendment that could be classified as minor or major by the FDA, the impact of which will depend on the review status (Accepted, Filed, Substantive review) as per the rule.

Table 1. Amendment Filing

Does the change impact the info on file?	PMTA	Own TPMF	Other referenced TPMF	Internal only
YES	File Amendment	Update TPMF	Update TPMF	Keep as internal report, available at audit
NO	Keep as internal report, available at audit	Keep as internal report, available at audit	Keep as internal report, available at audit	N.A.

CASE STUDY: FLAVOR INGREDIENT CHANGE

Change Request: due to discoloration of product over time, vanillin had to be removed from flavor formulation.
Material Change Flowchart:

Chart-Step	Perform Step?
C3	Yes
C4	No
C5	No

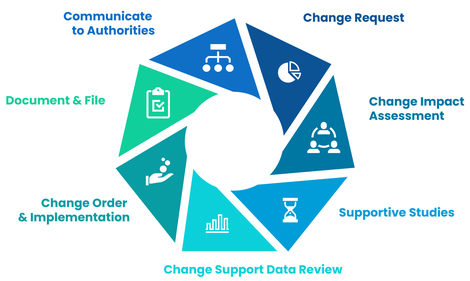
Change Control and Acceptance Criteria:
- Propylene Glycol went from 9.50% to 9.52%
- Vanillin went from 0.02% to 0%

Studies to be re-performed:
- Organoleptic assessment
- Ingredients assessment
- Risk assessment
- Stability study

No new ingredients added, only some removed and minor quantitative changes to existing ingredients.
Documentation: Compiled for Annual audit and updated in TPMF, PMTA amendment filed. If the product is authorized it would be reported as per the postmarket periodic reporting requirements.

CONCLUSIONS

Despite the lack of clarity regarding classification of changes in the PMTA guidance and rule, the forthcoming TPMP provides directions similar to Drug and Devices procedures, recommending a clearly documented change control process as part of Design Control and supported by Risk Management. It is incumbent on manufacturers to implement change control procedures that will fully justify and support the change with a clear assessment of impact on safety and performance which will allow the FDA to incorporate the change as part of the review process, in an efficient manner.



REFERENCES

FDA Proposed TPMP Rule (21 CFR part 1120)
FDA Medical Device Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device
FDA ANDA/NDA Guidance: Changes to an Approved NDA or ANDA (section 506A of the FD&C Act and 21 CFR 314.70)
FDA PMTA Rule: Premarket Tobacco Products Applications and Recordkeeping Requirements (21 CFR 1114)

76th TSRC Conference 2023, Norfolk, VA USA