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Detection and Mitigation of 2,4,6-Tribromoanisole and 2,4,6-Trichloroanisole Taints and Odors in the Pharmaceutical and Consumer Healthcare Industries

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PDA Task Force on Detection and Mitigation of 2,4,6-Tribromoanisole and 2,4,6-Trichloroanisole Taints and Odors in the Pharmaceutical and Consumer Healthcare Industries

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EXECUTIVE SUMMARY

Since December 2009, there have been multiple recalls of pharmaceutical and over the counter drug products by at least five companies for musty, moldy odor caused by trace levels of 2,4,6-Tribromoanisole (TBA) taints. Based on literature review, a bench marking survey and data made available to the PDA Task Force it was concluded that the taint was caused by trace contamination of High Density Polyethylene packaging containers with highly volatile and odorous TBA during transportation and storage on wood pallets constructed in Puerto Rico from 2,4,6-Tribromophenol (TBP)-treated lumber from South America. The moisture content of the wood was sufficient to promote fungal growth resulting in the biomethylation of the halophenol to its haloanisole.

The trace concentrations found in customer complaint samples, i.e., ppb-ppt levels, require matrix-specific sampling, pre-concentration, and gas chromatography-mass spectrometry/olfactory detection that is only suitable for analytical confirmation of taints and not routine monitoring.

Possible risk mitigation steps identified by the Task Force include not constructing pallets from TBP treated lumber, controlling the moisture content of wood to levels not conducive to fungal growth, improved supply chain awareness of haloanisole taints, other sources of halophenols and adequate environmental control and ventilation in warehouses and during transportation.

Toxicological and safety studies conducted on TBA demonstrated no mutagenicity or systemic toxicology in rodents when dosed for up to 28 days at levels a billion-fold higher than potential human exposure from the recalled product. TBA dosing produced no diarrhea or any macroscopic or microscopic pathological effects along the GI tract in rat toxicity studies. Although nausea was reported by consumers sensing the musty, moldy odor, adverse event analysis by multiple recalling companies have not established a causal relationship between TBA and gastrointestinal events. Therefore, reactions of disgust to TBA taints appears to be sensory and/or behavioral and not toxicological and therefore is not a safety risk.

Based on the high margin of safety demonstrated in toxicity studies, there is no meaningful analytical threshold that can be based on toxicity. It is therefore necessary for individual companies to consider how the odor is being perceived by their customers and the likelihood that perception to the odor could impact patient therapy, i.e. the concern is that the musty, moldy odor from these taints could increase the likelihood that patients will not take their medication.

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1.1 Scope and Purpose

The scope of this technical report covers 2,4,6-tribromoanisole (TBA) and 2,4,6-trichloroanisole (TCA) taints and odors. These particular musty, moldy taints have very low thresholds of detection, at parts per trillion (ppt), and high volatility relative to other organohalogen taints. Taints arise from an external source as opposed to off-odors or off-flavors from internal changes to a product (i.e., microbial spoilage).

The purpose of this report is to provide guidance on how to detect and mitigate TBA and TCA odors and taints. Well recognized in the food and beverage industries ***(1–4),*** the literature features knowledge from these industries regarding the origin of these odors and taints, analytical methods developed, and risk management strategies employed. In 2009, this became an issue for the pharmaceutical and consumer healthcare industries with product recalls from four companies due to the risk of product exposure to the TBA taint from tribromophenol-treated wood pallets. Recalls from additional firms continued through 2011.

This report will provide background on issues with TBA and TCA taints, highlighting:

- Uses of 2,4,6-tribromophenol (TBP) and 2,4,6-trichlorophenol (TCP) in industry
- Role of fungal halophenol methylation that generates TBA and TCA haloanisole taints
- Sensory and physiochemical properties of TBP, TCP, TBA and TCA
- Case examples from food and beverage industries with root causes and remedial actions
- Recent examples of TBA taint recalls from the pharmaceutical and consumer healthcare industries

Additionally, this report will provide guidance on signal detection from adverse event and/or product quality complaints and resulting recalls, toxicology and safety, analytical method development and use, supply chain controls, risk analysis and mitigation. Definitions of technical terms used in this report can be found in the glossary. The principles and tools used to manage these taints are also defined in this report.

1.2 Overview of the Uses of Halophenols 2,4,6-Tribromophenol (TBP) and 2,4,6-Trichlorophenol (TCP) in Industry

Multiple examples from the literature of the food and beverage industry indicate that TBP and TCP, precursors to the TBA and TCA taints, can enter the supply chain from various sources and can also form in the environment under certain conditions. Examples of these sources are highlighted below.

TBP is used as a wood preservative in various parts of the world. Although not registered for use in the United States and the European Union, TBP is known to have been used as a wood preservative in Central America, South America, Eastern Europe and Northern Asia, according to the literature ***(2, 5).*** Additionally, TBP is known to be used as fire-retardant agents in insulation (e.g., walls, ceiling tiles), epoxy resins (e.g., floor sealants), polyurethanes, plastics, paper and textiles ***(5).*** TBP has also been used in pesticides, antiseptic agents and detergents ***(6).*** It is also known that naturally occurring phenol residues in water and wood materials can be halogenated in the presence of bromine under certain conditions to form TBP *(7)*.

According to the 2005 Concise International Chemical Assessment Document No. 66 ***(8),*** TBP is reacted with sodium hydroxide to form the sodium salt of tribromophenol in water, which is used as a wood preservative. Standard application methods of pressure and vacuum impregnation, dipping, brushing, and spraying of the wood are used. The solution is very effective in controlling insects, fungi, and bacte-