# Technical Report No. 55

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

2012

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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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* PDA and the Task Force want to thank Annalisa Torrente for spending a considerable amount of time volunteering as the project manager for this Technical Report.

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ISBN: 978-0-939459-39-1



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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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