30 January 2020

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IPAC-RS Comments on Pharmacopoieal Forum stimulus article *Elastomeric Components for Inhalation Packaging/Delivery Systems*[1]

IPAC-RS is a non-profit association of companies that develop, manufacture or market orally inhaled and intranasal drug products, with the goal of advancing science-based and data-based regulations, standards, and practices for these products. A list of current members, and further information are available at http://ipacrs.org. IPAC-RS appreciates the opportunity to provide comments on the PF stimulus article *Elastomeric Components for Inhalation Packaging/Delivery Systems*

General Comments

The inclusion of the control of "special case" extractables in OINDP elastomeric components in <381> is unnecessary, as this issue is adequately addressed in the general chapter on extractables and leachables <1664.1>, and is better discussed within the context of broader philosophy and control strategies outlined in <1664.1>.

The proposal for the inclusion of specific limits for nitrosamines and PAHs in elastomeric components in <381> is not consistent with the broad principles of control of extractables and leachables outlined in <1664.1> whereby the focus of control is on the safety of leachables in the drug product. Case-by-case consideration of the correlation of extractables and leachables taking into account the mass of the components and the propensity for extractables to occur in the drug product as leachables is used to develop control strategies. This process is not facilitated by the application of control limits for elastomeric components which do not take into account product-specific considerations.

<1664.1> currently observes that these special case compounds are "typically" controlled to the limit of analytical capability, recognizing that the threshold of toxicological concern (TTC) may be inappropriate as the basis for control for compounds suspected to have unusual levels of genetoxic potential. Recent reviews of available toxicological information for nitrosamines carried out by the EMA Safety Working Party have suggested that it may now be possible to define exposure limits for these compounds from toxicological data based on ICH M7 principles. Inclusion of limits for these compounds as extractables in <381> is inconsistent with the development of this more rational approach to the control of these compounds.

Regarding PAH, the proposed limits do not take into account the potential amount in the packaging material, nor the actual exposure risk to the patient user. With regard to the amount in the device, Carbon Black (primary source of PAH) is a necessary ingredient to achieve the required functional properties of the elastomer material (as a component of the device system), including assurance to maintain those properties throughout the intended product shelf and environmental lifecycle.

Imposition of 'arbitrary' limits on PAH as an extractable in the material (without link to the actual amount of PAH migrating to the drug product, and therefore the patient) risks requiring changes to the chemical composition of the elastomer in existing marketed products, resulting in a risk to adversely impact the functional performance and safety of the finished drug product. Alternative potential

[1] PF 45(6), November 2019

approaches can include developing Permissible Daily Exposure (PDE) limits for PAHs as leachables in the drug product. Any acceptance criteria should be:

1. Based upon the appropriate sub-section of 21CFR (the reference used in the USP Stimuli paper is not appropriate for elastomer materials)

2. Based on the type of Carbon Black used (per the relevant 21CFR sub-section for elastomer materials)

3. Based upon actual safety data

Specific Comments

1. **Appropriate CFR Reference**

In the section *Polycyclic Aromatic Hydrocarbons > ACCEPTANCE CRITERIA* of the Stimuli paper, a reference for the maximum levels of PAH in Carbon Black is provided from 21CFR§178.3297(e). However, this is the chapter for colorants in polymers. Whereas, the appropriate reference for the scope of this USP<381> paper on elastomeric components should be 21CFR§177.2600.

While Carbon Black does find use in polymers as colorants, the primary (and perhaps only) intended function of Carbon Black in elastomers is as a reinforcing filler. Therefore, it is considered that 21CFR§177.2600 is the most appropriate reference to construct a proposal for acceptance criteria for PAHs.

2. Type of Carbon Black

The Stimuli paper quotes only PAH content of the type, 'high purity furnace black'. 21CFR§178.3297(e), however, lists only type channel black. Further, 21CFR§177.2600 (section (v) *Fillers*) permits the use of either channel or furnace. High-purity carbon back appears to be undefined officially in criteria for PAH level. It does appear to be a grade specifically marketed by Cabot for polymers for food contact applications.

In polymers, Carbon Black is only present at a very small quantity. Carbon Black may be <1% w/w of the colorant mixture, and the colorant mixture may be less than 3% w/w of the total polymer component. Carbon Black plays no functional role in the required physical-mechanical properties of the finished component.

However, the probability to successfully engineer an elastomer with high purity Carbon Black for inhalation applications is considered to be low because the functional role of Carbon Black in elastomers is primary. Carbon Black is typically between 40-50% w/w of the elastomer formulation. Two or more different Carbon Black types may be required in the same elastomer to achieve the required functional characteristics and durability of elastomer seals for inhalation devices and products (static sealing under high compression; elasticity to maintain sealing integrity with moving parts; aggressive propellant formulations; wide range of temperature/humidity conditions in use for up to 3 years).

Various sources of commercially available Carbon Black (furnace and channel) may contain up to 1000 (one thousand) micrograms of PAH (total) per gram of Carbon Black[2]. Extraction studies on

[2] IARC Monographs, Vol. 93. Taylor et al., 1980. Zoccolillo et al., 1984

existing elastomers (used in approved OINDP products) formulated with 40-50% Carbon Black confirms 200-300 micrograms total PAH per gram of elastomer.

In summary, the proposal of acceptance criteria for PAH based on a specific type of Carbon Black is not considered appropriate. It is also noted that existing approved inhalation applications have been approved using elastomers formulated with non-high purity Carbon Blacks (and in compliance with 21CFR§177.2600). The imposition of such criteria would require modification of the elastomer component materials, resulting in potential impact to the functional and performance safety of these products.

3. Acceptance Criteria Based upon Safety Data

The Stimuli paper proposes acceptance criteria for PAHs as extractables. An alternative approach could be for sponsors to develop Permissible Daily Exposure (PDE) limits for PAHs as leachables in the drug product, if needed, based upon risk evaluation. This is aligned with the content of the Stimuli paper, e.g., 'Limits should be based upon safety and data'.

While no PDE limits have yet been validated for PAHs, there are studies and existing exposure guidelines that companies could use. An example list is provided below, taken primarily from the Environmental Protection Agency (EPA) and the Office of Environmental Health Hazard Assessment (California). See the last page for sources, references, and abbreviations.

From this information, it may be seen that potential exists to establish data-derived limits for PDE, based upon actual risk to end-users (better assurance of public health).

There are three principal groups of data in the table below for the 17 individual PAHs:

1. Data from the Office of Environmental Health Hazard Assessment (OEHHA) providing limits for No Significant Risk Level (NSRL) in µg per day

2. Data from the Environmental Protection Agency (EPA) providing limits for Reference dose for Chronic Oral Exposure (from the NOEL, converted to µg per day from mg per kg body weight per day (for a 50kg nominal body weight))

3. Dietary intake data from the Hazardous Substances Data Bank (HSDB. US Govt National Institutes of Health)

EPA data is for studies via the oral route in mice (13 weeks) – these could thus be considered excessive. HSDB data does not infer any safe level. So, for example, stringent limits could be used to develop a PDE, although any specific approaches to deriving a PDE should be left to the sponsor.

Example Table of Reference Data

PAH	Reference Tox Limit Micrograms per Day	Reference Source
Naphtalene	5.8	OEHHA / NSRL
Benzo[a]anthracene	0.033	OEHHA / NSRL
Chrysene	0.35	OEHHA / NSRL
Benzo[b]fluoranthene	0.096	OEHHA / NSRL
Benzo[a]pyrene	0.06	OEHHA / NSRL
Dibenzo[a,h]anthracene	0.2	OEHHA / NSRL
Phenanthrene	2000	TDI, Verbruggenand van Herwijnen, 2011
Anthracene	1500	EPA / RDCOE
Fluoranthene	2000	EPA / RDCOE
Pyrene	1500	EPA / RDCOE
Acenaphthylene	3000*	EPA / RDCOE
Acenaphthene	3000	EPA / RDCOE
Fluorene	2000	EPA / RDCOE
Benzo[k]fluoranthene	0.06	HDSB/Dietary
Benzo[e]pyrene	0.17	HDSB/Dietary
Indeno[1,2,3-cd]pyrene	0.4	HDSB/Dietary
Benzo[g,h,i]perylene	1.6	HDSB/Dietary

* by reference to Acenapthene

Abbreviations

EPA	Environmental Protection Agency (USA)
OEHHA	Office of Environmental Health Hazard Assessment (California)
HDSB	Hazardous Substances Data Bank
NOEL	No Observed Effect Level
NSRL	No Significant Risk Level
TDI	Tolerable Daily Intake
RDCOE	Reference dose for Chronic Oral Exposure (from the NOEL)