EVONIK INDUSTRIES

Pharma Silica Insights

A newsletter for silica excipients for pharmaceutical formulations

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What about silica?

The pharmaceutical industry is constantly looking for (new) technologies and concepts that will allow them to improve efficiency, reduce costs, and bring their newly developed, active pharmaceutical ingredients (APIs) into therapeutically active dosage forms.

AEROSIL® colloidal silicon dioxide is a well-known excipient that helps to make pharmaceutical manufacturing processes more efficient. For 70 years now, it has been known to act as a glidant, improving the flow and processing of powders for the direct compression of tablets. Through their excellent performance, they have gained acceptance and recognition as high quality, pharmaceutical excipients.

With this newsletter we invite you to learn more about the high purity of our AEROSIL® and AEROPERL® Pharma products.

Enjoy your reading!

AEROSIL® and AEROPERL® colloidal silicon dioxide pave the way to ICH Q3D compliant formulations

After discussions for almost five years the International Conference on Harmonisation (ICH) in December 2014 agreed on guideline ICH Q3D that covers elemental impurities in pharmaceutical preparations for human use. The European and US American Pharmacopoeia have since published their timelines and policies to adopt the new purity requirements. Although the effective dates published by the pharmacopoeia are still some time ahead information on the purity levels of excipients are already important for formulators today to help them choose the excipients in their formulations. This newsletter informs on the elemental contamination of AEROSIL® and AEROPERL® Pharma products. All products have elemental impurity levels below the limits set out in the guideline for oral dosage forms. Using AEROSIL® and AEROPERL® Pharma products therefore enables pharmaceutical producers to use the facile and very convenient option 1 of the guideline to show compliance. The high purity of AEROSIL® and AEROPERL® Pharma excipients therefore guarantee future-proof pharmaceutical formulations.

Topics

Please meet us at

CPhI Worldwide
Madrid, 13–15 October 2015, Booth 7F60

AAPS Annual Meeting and Exhibition
Orlando (Fl),
25–29 October 2015
Booth 604

CPhI India
Mumbai,
1–3 December 2015

Discussions on a "Guideline for Elemental Impurities" already began in 2009 on the level of the International Conference on Harmonization (ICH) and finally led to the sign off of the ICH Q3D guideline in December 2014[1]. The guideline is not legally binding by itself but needs to be translated into relevant pharmacopoeia specifications. However, the European Pharmacopoeia (Ph. Eur.) announced to implement the new requirements for new marketing authorization applications for human medical preparations by June 2016 and for existing ones by December 2017[2]. Although the new requirements only concern human medications the agency expects pharmaceutical producers also to control the level of elemental impurities in pharmaceutical products outside the scope of the guideline such as veterinary preparations[3].

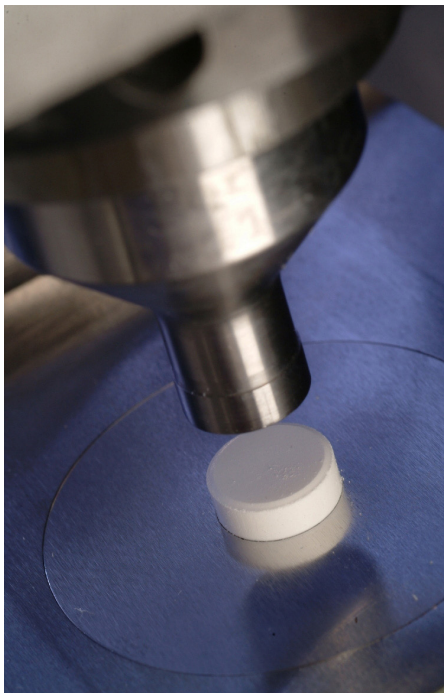
The US Pharmacopoeia (USP/NF) announced to make the metal concentration requirements binding by January 2018[4]. Revised general chapters 232 „elemental impurities – limits" (applicable to pharmaceuticals) and 2232 "elementary contaminants in dietary supplements" have already been published in the second supplement of the USP 38–NF33 edition[5].

The Japanese Pharmacopoeia has not yet announced how it plans to deal with the guideline. However, the topic has made it on the work program of the Pharmacopoeia Discussion Group with USP/NF as the coordinating pharmacopoeia and therefore also an implementation for the Japanese pharmaceutical market needs to be expected.

In the ICH guideline elemental contaminants are classified according to their toxicological profile in different groups. Permitted daily exposures (PDEs) for these contaminations are defined dependent on the way the pharmaceutical preparation will be administered. For the assessment of the risks of elemental impurities, the pharmaceutical producer additionally needs to consider the daily dosage. According to the guideline, only class 1 and class 2 a elements need to be thoroughly controlled for all dosage forms and included into the risk assessment. Class 2 b elements need to be considered across the full range of administration, but only if these elements are intentionally added in the production process. The toxicological profile of class 3 elements in oral exposure is rather low and therefore these elements can be neglected for oral dosage forms but need to be considered for inhalation and some parenteral formulations.

Table 1 Overview on ICH Q3D relevant elemental contaminations, their categorization and maximum permitted oral concentration for option 1

Class	Toxicological property	Elements	Maximum oral concentration (Option 1) [µg/g]
Class 1	Human toxicants	As	1.5
		Cd	0.5
		Hg	3
		Pb	0.5
Class 2	Route-dependent human toxicants		
• Class 2 a	– High probability of occurrence	Co	5
		V	10
		Ni	20
• Class 2 b	– Reduced probability of occurrence	Ag	15
		Au	10
		Ir	10
		Os	10
		Pd	10
		Pt	10
		Rh	10
		Ru	10
		Se	15
		Tl	0.8
Class 3	Low toxicity elements (PDE generally > 500 µg/day)	Ba	140
		Cr	1,100
		Cu	300
		Li	55
		Mo	300
		Sb	120
		Sn	600



Nevertheless, table A.2.1. of the guideline defines Permitted Daily Exposures (PDEs) for all elemental impurities in dependence of the route of administration. For the risk assessment, the elemental impurity profile of the drug product is compared against the Permitted Daily Exposure (PDE) limits defined by the guideline. To assess the concentration limits in the final dosage form, the maximum daily intake of a drug product also needs to be considered. Different approaches on how this can be done are cited in the guideline. The most convenient choice, option 1, which can be used for drug products with daily intakes of no more than 10 g, allows for a simple consideration of the known elemental impurities of each component of the drug product. If all of the components of the final dosage are below the concentration limit given in table A.2.2 of the guideline the formulation complies to the requirements.

[1] Guideline available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf.
[2] Press release by the European Directorate for the Quality of Medicines & Health Care (EDQM) of 28 April 2015, available online at https://www.edqm.eu/medias/fichiers/elemental_impurities.pdf
[3] Press release by the European Directorate for the Quality of Medicines & Health Care (EDQM) of 7 August 2015, available online at https://www.edqm.eu/medias/fichiers/ph_eur_policy_on_elemental_impurities_clarification_for_products_outside_the_scope_of_the_ich_q3d_gu.pdf
[4] Announcement on the US Pharmacopeia webpage, available at http://www.usp.org/usp-nf/key-issues/elemental-impurities#question 1
[5] Please note that USP/NF method 232 (USP 38 – NF 33, second supplement) does not list Co, Tl, Au, Se, Ag, Li, Sb, Ba, Sn as elements that need to be controlled. Special requirements are given for Class 1 elements As and Hg in terms of organic or inorganic nature of the contamination and their oxidation states.

AEROSIL® and AEROPERL® colloidal silicon dioxide in light of ICH Q3D purity requirements

Traditional inorganic excipients such as bentonite, calcium salts (USP/NF: dibasic calcium phosphate, tribasic calcium phosphate, precipitated calcium carbonate), magnesium salts (USP/NF: magnesium aluminum silicate, magnesium oxide, magnesium trisilicate, talc) and silicon dioxide (USP/NF: colloidal silicon dioxide, silicon dioxide) have recently been discussed related to the ICH Q3D guideline[6]. The authors come to the conclusion that excipients coming from mined sources may exhibit greater variations in their elemental impurity profile than those produced by chemical synthesis.

AEROSIL® and AEROPERL® Pharma colloidal silicon dioxide products are well known excipients in the pharmaceutical industry and have been used for decades as glidants for direct compression processes, pharmaceutical carriers or rheology additives for liquid and semisolid dosage forms. Apart from their well-known, reliable performance, the purity of these products has also been valued highly in the industry. AEROSIL® and AEROPERL® Pharma colloidal silicon dioxide products are not mined but synthesized by a controlled chemical process according to IPEC's GMP guideline. Unlike precipitated or gel type silica excipients[7] AEROSIL® and AEROPERL® Pharma products are formed in a gas phase process which uses silicon tetrachloride as the starting material. As silicon tetrachloride is a distillable liquid, purifying this precursor to extremely low elemental contamination levels is relatively simple and economically feasible. The high purity of the starting material in turn leads to very pure AEROSIL® and AEROPERL® Pharma products.

AEROSIL® products are used in a number of applications which require extremely low contaminant levels, e.g. the electronic industry. Therefore all AEROSIL® products including the Pharma grades have been regularly analyzed for metal contaminations and have a long history of analytical results that prove their purity.

Table 2 lists the maximum concentration of all elements mentioned in the ICH Q3D guideline. As AEROSIL® and AEROPERL® Pharma products are not recommended for use in drugs administered parenterally or by inhalation the analytical results are compared against the option 1 concentration limits for solid dosage forms.

From the data it is clear that for any formulation that employs AEROSIL® Pharma products the simplified safety assessment according to option 1 can be used. The high quality of AEROSIL® Pharma products not only will reduce the regulatory complexity for new as well as existing formulations. It also gives the formulator the assurance that their formulation work will also stand up after the changes from the ICH Q3D have been legally implemented.

Table 2 Relevant elemental contamination limits in AEROSIL® and AEROPERL® Pharma products
Data was obtained according to USP method 233 after complete dissolution of the solid samples in mineral acids by quadrupole inductively coupled plasma mass spectrometry (iCAP Q Quadrupole ICP-MS, Thermo Fisher Scientific, Bremen, Germany) or Direct Mercury Analyzer und GMP conditions.
The method was validated according to ICH guideline Q2(R1), ICH Q3D (step 4, December 2014) and USP General Method 233.

			Maximum concentration AEROSIL® and AEROPERL® Pharma products (µg/g)				
Element	**Class**	**ICH Q3D oral limit (µg/g)**	**AEROSIL® 200 Pharma**	**AEROSIL® 300 Pharma**	**AEROSIL® 300 Pharma**	**AEROSIL® R 972 Pharma**	**AEROPERL® 300 Pharma**
Cd	1	0.5	<0.1	<0.1	<0.1	<0.1	<0.1
Pb	1	0.5	<0.1	<0.1	<0.1	<0.1	<0.1
As	1	1.5	<0.3	<0.3	<0.3	<0.3	<0.3
Hg	1	3	<0.6	<0.6	<0.6	<0.6	<0.6
Co	2 A	5	<1	<1	<1	<1	<1
V	2 A	10	<2	<2	<2	<2	<2
Ni	2 A	20	<4	<4	<4	<4	<4
Tl	2 B	0.8	<0.16	<0.16	<0.16	<0.16	<0.16
Au	2 B	10	<2	<2	<2	<2	<2
Pd	2 B	10	<2	<2	<2	<2	<2
Ir	2 B	10	<2	<2	<2	<2	<2
Os	2 B	10	<2	<2	<2	<2	<2
Rh	2 B	10	<2	<2	<2	<2	<2
Ru	2 B	10	<2	<2	<2	<2	<2
Se	2 B	15	<3	<3	<3	<3	<3
Ag	2 B	15	<3	<3	<3	<3	<3
Pt	2 B	10	<2	<2	<2	<2	<2
Li	3	55	<11	<11	<11	<11	<11
Sb	3	120	<24	<24	<24	<24	<24
Ba	3	140	<28	<28	<28	<28	<28
Mo	3	300	<60	<60	<60	<60	<60
Cu	3	300	<60	<60	<60	<60	<60
Sn	3	600	<120	<120	<120	<120	<120
Cr	3	1100	<224	<224	<224	<224	<224

[6] A. Teasdale *et al.*, Pharmaceutical Technology Europe, March 2015, 12.
[7] Silica based excipients falling under USP/NF monograph "Silicon Dioxide" are produced by precipitation starting from sodium silicate solutions and mostly sulfuric acid. The elemental contamination level of these products may vary depending on the level of elemental impurities in the starting materials, the precipitation process and the work up procedures.

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