

Diatomite Filter Aid in cGMP Pharmaceutical Processing

A Regulatory Perspective

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SUMMARY

Diatomite filter aids were developed for the beverage industry in the early 1900s, when the pharmaceutical and beverage industries used similar quality standards. Consequently, conventional “Food Grade” diatomite became widely used in the pharmaceutical industry. Even after the advent of the pharmaceutical GMPs, Food Grade diatomite-components¹ continue to be widely used in the pharmaceutical industry.

This monograph summarizes widely held misconceptions on the standards of Food Grade diatomite. Several quality concerns are identified and suggestions are offered on how to resolve them.

BACKGROUND

Diatomite filter aids (*i.e.*, diatomite components), which are composed of diatoms, are widely used in cGMP pharmaceutical filtration-processes. These processes include solid-liquid separations with biologic suspensions (*e.g.*, cell broth separation), and synthetic formulations (*e.g.*, activated carbon separation from mother liquors).

There are four main facets of Food Grade diatomite that challenge standards of pharmaceutical-component quality. These are discussed in the sections that follow:

- **Compendial Standards**
- **Purity**
- **Manufacturing Process-Control**
- **Packaging**
- **Supplier Audit Considerations**

COMPENDIAL STANDARDS

“For components appearing in an official compendium, the FDA generally expects the material to be labeled and tested to the reference”. (Bobrowicz, 1999)

“Precedence is not accepted for component selection... Begin with a monograph search...and use it if it exists.” (Ianacone, 2001)

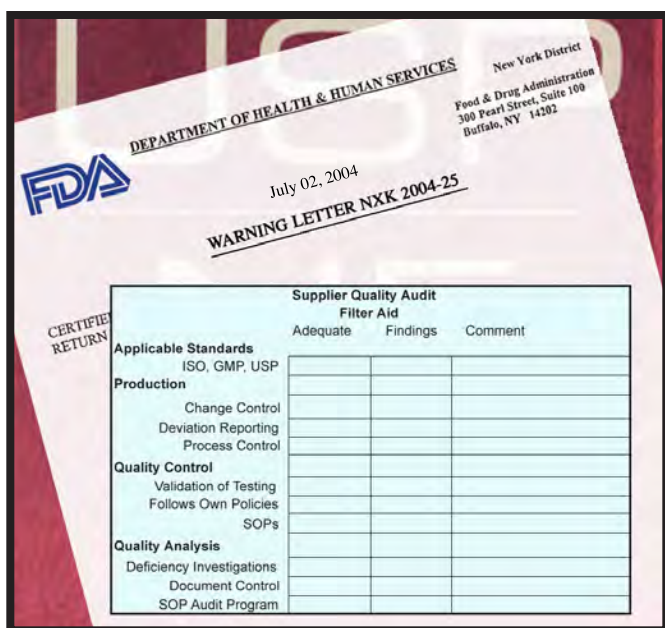
“When making an... NDA or ANDA... All substances... have to appear in this inventory, whether or not they are in the finished product. You must state the quality designation or grade for each material published by the... U.S. Pharmacopeia or National Formulary”. (*Food & Drug Letter*, July 9, 1999)

“...master production instructions...should include...a complete list of raw materials ...sufficiently specific to identify any special quality characteristics”. (*ICH Q7A, Good Manufacturing Practices for Active Pharmaceutical Ingredients*, 2001)

The above statements reflect a growing reliance on compendial standards in pharmaceutical component (*e.g.*, filter aid) selection. This reliance is based, in part, on 21CFR 211.160 (b), which states, “Laboratory controls shall include...scientifically sound and appropriate specifications, standards...to assure that components...conform to appropriate standards of...quality, and purity”.

Most pharmaceutical producers are not aware that a USP-NF monograph exists on diatomite filter aid (Table 1), which appears in the NF compendia under *Purified Siliceous Earth*.

Food Grade diatomite rarely meets USP-NF standards. Packaging aside (see Packaging), the most commonly failed USP-NF standard for diatomite is water-soluble substances, followed by acid-soluble substances and loss on drying. Drug manufacturers should be aware that USP-NF grade diatomite is now available in commercial quantities.



¹ 21CFR 210.3 (3): A component is “Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product”.

USP-NF Monograph: Purified Siliceous Earth

Parameter	Limit
Packaging	Preserve in well-closed containers
Loss on drying (731)	0.5 %
Loss on ignition (733)	2.0 %
Acid-soluble substances	2.0 %
Water-soluble substances	0.2 %
Leachable arsenic	10 mg/kg
Leachable lead	10 mg/kg
Nonsiliceous substances	50 mg (25.0 %)

Table 1. USP-NF monograph for diatomite.

There is often a misunderstanding that Food Grade Standards are adequate for pharmaceutical use. This is incorrect due to two major gaps in Food GMPs compared to pharmaceutical GMPs: (1) independence of the Quality Unit; and (2) change control. Further, an ISO 9000 Quality Management System is complementary to GMP, but not a substitute for GMP. (Moreton, 2009)

Another misconception is that conformance with the NF compendial specifications is all that is required. The General Notices of the USP-NF require that compendial products be manufactured to the appropriate standards of GMP.

PURITY

“Each component shall be tested for conformity with all appropriate written specifications for purity...”
– 21CFR 211.84 (d)(2)

“Laboratory records shall include...A statement of... how the results compare with established standards of...quality and purity for the...component...”
– 21CFR 211.194 (a) & (a)(6)

	Celpure® 300 (USP-NF Grade)	Celite Standard Super-Cel® (Food Grade)
Al	nd* (PPB)	1682 (PPB)
Ca	nd	1050
Mg	124	1010
Fe	56	400
Zn	90	210
Cu	12	16
Sb	nd	12
Mn	4	14
*(nd) Below detectable limit		

Table 2. Solubles expressed as PPB in the filtrate. Solubles extracted from 2-g samples incubated in 100-mL solutions. Solution: 10 mg/mL albumin, 50 mM sodium acetate, pH 4.3. Incubation: 4 h, 160 rpm, 50°C. Analysis by ICP-MS except for Fe (colorimetric complex with 1,10-phenanthroline).

“The applicant should summarize the actual and potential impurities most likely to arise during the synthesis, purification... This summary should be based on sound scientific appraisal of the...impurities associated with raw materials...”
– ICH Q3R, *Impurities in New Drug Substances*, 2002

“If used in a GMP setting, diatomite extractables should be well characterized. Validation of filtration extractables is a common problem in pharmaceutical manufacturing (Conn, 2000), and trends suggest that FDA investigations are focusing on filtration extractables-validation as GMP findings (Immel, 2000).

Commercially available USP-NF Grades of diatomite have much lower extractables than Food Grades (Table 2).

DEPTH FILTERS AND DIATOMITE PURITY

“...in analyzing filter extractables it is highly beneficial to study the components of the filter, rather than the entire assemblies.” (Jiang, et al., 2003)

There has been an extraordinary increase in the consumption of diatomite-based depth filters in biopharmaceutical production. All the major suppliers offer an extensive line of diatomite-based filters, including: Millipore (e.g., Millistak®), Cuno (Zeta Plus®), Pall (SUPRADisc®), and Ertel Alsop (ZETA-PAK®). Nearly every biopharmaceutical company, globally, uses one (or more) of these products.

Because of the increasing interest in the quality of individual filter ingredients (Jiang, et al., 2003), and not just the finished product, the source and quality of the diatomite in these filters will be of growing interest.

MANUFACTURING PROCESS-CONTROL

“It is also important to determine whether the company normally supplies components...to the pharmaceutical industry. Pharmaceutical company requirements are sometimes [far more stringent than the] supplier’s [main] customers. Therefore, suppliers may not be prepared to improve their standards to suit the pharmaceutical industry...” (Stephon, 2002)

Unless a diatomite component is specifically produced for pharmaceutical manufacturing, its production will likely be geared towards the food industry, which may be problematic. Drug manufacturers should look for three main potential problem areas at diatomite-manufacturing facilities:

- Process Containment
- Process Variability
- Process Change

PROCESS CONTAINMENT

“Each lot of a component...that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.”
 – 21CFR 211.84 (d)(5)

The containment standards for Food Grade diatomite manufacturing are rarely sufficient to prevent foreign matter from altering the finished product. An audit frequently reveals large open-air buildings with rail service, outdoor storage, and vermin intrusion (e.g., birds, insects). At a minimum, pharmaceutical manufacturers should insist on packaging and storage stations within a well-controlled environment.

PROCESS VARIABILITY

“Each lot of components...shall be withheld...until the lot has been released for use by the quality control unit...the amount of material to be taken from each container shall be based upon appropriate criteria such as statistical criteria for component variability...”. – 21CFR 211.84 (a & b)

Food Grade diatomite is produced using high-volume (e.g., 1,000 tons/yr./customer) standards. This can mean that diatomite specification testing is performed as infrequently as every 10,000 kg of production volume. Because this production rate exceeds more than a year’s worth of consumption for most pharmaceutical users, a greater frequency of testing (by the diatomite manufacturer) is desirable.

A more detailed certificate of analysis (Table 3) can indicate less component variability. This is increasingly relevant to process validation, where unchecked variations in diatomite can result in significant process deviations due to filtrate color, pH, and impurity profiles.

Tests Appearing on Diatomite Certificates of Analysis		
Parameters	Celpure® P1000 (USP-NF Grade)	Hyflo Super-Cel® (Food Grade)
Permeability	0.75- 1.25 darcy	0.73-1.6 darcy
Centrifuged wet-density	≤ 0.24 g/cm ³	≤ 0.35 g/cm ³
pH	≤ 8.8	*
Conductivity	≤ 15 mS/cm	*
Acid Soluble iron	≤ 5 ppm	*
Acid Soluble Aluminum	≤ 4 ppm	*
150 Mesh Screen	≤ 20%	≤ 12 %
Endotoxin	≤ 1EU/gram	*
NF Loss on Drying	≤ 0.5 %	*
NF Loss on ignition	≤ 2.0 %	*
NF Leachable arsenic	≤ 10 mg/kg	*
NF Leachable lead	≤ 10 mg/kg	*
NF Water-soluble substances	≤ 0.2 %	*
NF Acid-soluble substances	≤ 2.0 %	*
NF Nonsiliceous substances	≤ 50 mg (25 %)	*
* No release specification		

Table 3. Comparison of release specifications for USP-NF Grade and Food Grade diatomite.

PROCESS CHANGE

Drug manufacturers should verify that a diatomite producer adheres to process change agreements and that the definition of process change is relevant. With Food Grade diatomite, most aspects of process change are not monitored and therefore cannot be detected; moreover relevant batch records are mostly absent.

A typical process change agreement requires the diatomite producer to notify the pharmaceutical producer before making a change to any of the following:

- Composition of raw materials
- Source of raw materials
- Method of producing, processing, or testing
- Subcontractors used for processing
- Site of manufacture

While the site of manufacture and the use of subcontractors are usually not subject to interpretation, the other items (listed above) hold significantly different meanings for producers of Food Grade and USP-NF Grade diatomite.

More than 95% of diatomite, globally, is produced for non-pharmaceutical (e.g., beverage and industrial) filtration. While the standards of these industries are generally being met, change-control standards are substantially less rigorous than in the pharmaceutical industry. This is because the economics of diatomite production are dictated by Food Grade standards.

An example would be changing diatomite mines (i.e., diatomite type and chemistry) or testing methods. These obviously represent significant changes to the pharmaceutical industry and would require a pre-approval (Buecker, et al., 2002). The economic reality however is that companies focused on the food industry cannot afford or are not qualified to comply with the change-control requirements of drug manufacturers (Buecker, et al., 2002; Stephon, 2002).

PACKAGING

The USP-NF monograph states that diatomite packaging must be in “well-closed containers” sufficient to preserve the material. The simplest interpretation is that packaging should be sufficient to preserve component aspects covered in the USP-NF monograph. In most cases, Food Grade diatomite is packaged in paper, which absorbs water and can lead to the failure of the NF Loss on Drying Test.

Bioburden is common with paper-packaged products, especially when exposed to water and vermin in uncontrolled warehouses. If not certified to USP-NF standards, natural minerals like diatomite can contain high levels of bioburden, including pathogens (Montgomery & Manu-Tawiah, 2004).

Paper packaging is insufficient to address this problem and often supports or promotes bioburden.

Diatomite packaging should be a relatively strong, water resistant material that does not support the growth of microorganisms. At least one producer of USP-NF Grade diatomite uses plastic drums or Tyvek^{®2} bags, both of which address these issues.

SUPPLIER AUDIT CONSIDERATIONS

"...suppliers are expected to use their special knowledge to make specific value analysis recommendation about materials, processes, equipment, and assembly techniques for any products and services provided..." (Baxter Health Care Corporation, 2001).

"A company that has never supplied a customer with strict GMP standards may require re-educating from management down to the operations level...this is usually a monumental task..." (Stephon, 2002).

"FDA considers auditing to be one of the most important quality systems. Current industry practice is to audit major suppliers every 12-18 months..." (Immel, 2006).

"When it comes to controlling risk and documenting decisions related to supplier management, FDA officials expect you to balance safety and quality..." (Avellanet, 2010).

"Handle audits based on risk level, audit frequency, and the supplier rating established in a supplier profile...The audit process, related audit findings, and subsequent supplier corrective and preventive actions (CAPA) must be managed and tracked..." (Jovanis, 2009).

OPEN DIALOG

Meaningful dialog between the diatomite producer and the pharmaceutical user should be initiated with a discussion on how and why the diatomite is used (Kennedy, 2002; Stephon, 2002). Ensure that the supplier understands there are significant differences between Food Grade and pharmaceutical standards. Without this understanding an overzealous supplier may grossly overstate capabilities without realizing it.

Confusion will be most prevalent with a paper audit; it is essential that pharmaceutical companies visit the producing location, even if the diatomite is not used in a critical application. The potential for misunderstandings is so great that even "minor problems" can have substantial financial impacts (Stephon, 2002) and contaminate pharmaceutical production lines.

A relatively easy way to minimize misunderstandings is to review the supplier's marketing materials (Stephon, 2002). If you find statements like "intended for pharmaceutical use" or "USP-NF" grade, the potential for misunderstandings will be relatively low.

QUALITY CONTROL & QUALITY BY DESIGN

Make sure the supplier understands the difference between Quality Control based on "defect detection", rather than "defect prevention" (Stephon, 2002). If the diatomite is being produced at high volumes (e.g., 1,000 tons/yr./customer), QC will likely use a system based on defect detection or process capabilities (CpK) metrics. QC based on defect detection of high volume production and infrequent testing can mean the product can drift outside of specifications and still be released to customers without having been detected. Additionally, specifications can be broadened to improve CpK metrics with unknown impact on the pharmaceutical process.

ICH Q8 Pharmaceutical Development states that the purpose of pharmaceutical development is to design a manufacturing process that consistently delivers a quality product for its intended purpose. (*ICH Q8(R2), Guideline Pharmaceutical Development, 2009*)

Quality by design offers a better understanding of the materials, processes, and products than quality by inspection (*i.e.*, quality control). The guideline emphasizes understanding the sources of variability and their impact on the process.

An assessment of raw materials must extend beyond the material specifications and its direct effect on the pharmaceutical process performance to include the supplier's manufacturing processes and quality systems. The recent catastrophic experiences of heparin and melamine contamination point at the impact of improperly controlled raw materials. (Rathore, 2010)

² Tyvek is a registered trademark of DuPont.

GLOSSARY

COMPONENT

Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product, 21CFR210.3 (3).

DIATOM

See diatomite.

DIATOMITE

Obtained from diatomaceous earth, a sediment greatly enriched in biogenic silica in the form of siliceous skeletal remains of diatoms, a diverse array of microscopic, single-cell algae. Diatomite products are characterized by an inherently intricate and highly porous structure composed primarily of silica.

FILTER AID

Inorganic mineral powders or organic fibrous materials used in combination with filtration hardware to enhance filtration performance. Commonly encountered filter aids include diatomite, perlite, and cellulose. Some of these materials have been in use as filter aids for over 75 years.

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NOTES



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