Safety Assessment of Alumina and Aluminum Hydroxide as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this Tentative Safety Assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. F. Alan Andersen.

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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INTRODUCTION

This is a review of the available scientific literature relevant to assessing the safety of alumina and aluminum hydroxide as used in cosmetics. Alumina functions in cosmetics as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent; aluminum hydroxide functions as a buffering agent, corrosion inhibitor, and pH adjuster.

These ingredients have been approved by the U. S. Food and Drug Administration (FDA) for various medical devices and over the counter (OTC) drug uses. The Cosmetic Ingredient Review (CIR) believes that the cosmetic ingredients alumina and aluminum hydroxide are analogous to the alumina used in medical devices as a device color additive for bone cements and sutures and in the construction of dental and hip implants, and as aluminum hydroxide used in OTC drugs. The FDA found the safety information for those medical devices and drugs to be adequate to support safety and determined that alumina is safe for use in devices that come in contact with soft tissue, bone, and internal organs. Based on the adequacy of those data, the FDA also determined that aluminum hydroxide is generally regarded as safe (GRAS) and may be used as an antacid and as a direct food additive.

CHEMISTRY

Overview

Definitions, CAS Nos., and functions are provided in Table 1. The structures of alumina and aluminum hydroxide are provided in Figure 1.

Aluminum Hydroxide, also known as hydrated alumina, is most commonly found as the polymorph mineral gibbsite (a component of the aluminum ore known as bauxite).[1,2] This inorganic, amphoteric, solid, can also form three other polymorphs. However, the chemical formula of $Al(OH)_3$ remains the same for all four polymorphs and each one only differs by interlayer spacing and the consequential relative rates of acid/base reactions.

Alumina, also known as aluminum oxide (Al_2O_3), is dehydrated (or calcined) aluminum hydroxide.[1] Alumina is also the primary constituent of emerald, ruby, and sapphire (the colors of which come from small impurities of heavy metals). The most common naturally occurring form of alumina is corundum. Corundum is primarily composed of α-alumina, the most common phase of naturally occurring alumina. This water insoluble, but amphoteric, inorganic solid can form a number of other crystalline phases, and an amorphous form as well. Each phase has a unique crystal structure and varies in chemical properties, such rate of acid/base reactions. When synthetically dehydrated from aluminum hydroxide, a mixture of alumina phases typically forms, unless specific controls are applied.

There are four known polymorphs of crystalline aluminum hydroxide: gibbsite, bayerite, nordstrandite, and doyleite.[3] The properties of the starting materials (pH, presence of anions or salt, and mineral surfaces) are what influence the formation of crystalline aluminum hydroxide ($Al(OH)_3$) polymorphs from aluminum interlayers and/or hydroxyl-aluminum polymers. All the polymorphs of aluminum hydroxide consist of layers of aluminum octahedra with hydroxyl groups on either side that hydrogen bond the layers together with the difference being the stacking sequences of the layers. Gibbsite and bayerite represent the two ends of the spectrum of types of stacking sequences. Nordstrandite and doyleite have intermediate structures.

There is no universal standard nomenclature for aluminum oxides and hydroxides.[3] The categorization is made according to their crystallographic structures found under environmental conditions and most cited in the literature. The α-prefix is generally applied to hexagonal closepacked and related structures; these are aluminum minerals abundantly found in nature. The γ-prefix is generally applied to designate instances of polymorphism and cases of alteration or dehydration (originally to all other aluminum hydroxides and hydrolyzed aluminas). The γ-phase has cubic close-packed lattices or related structures. Comparisons of nomenclature are presented in Table 2.

Physical and Chemical Properties

Physical and chemical properties are provided in Table 3. Alumina and aluminum hydroxide are white, insoluble solids.

Method of Manufacture

Aluminum hydroxide is most commonly produced by aqueous alkaline extraction from bauxite ore, a method known as the Bayer process.[1] Alumina is then produced from the resultant aluminum hydroxide simply by strong heating to drive off the water.[4]

Impurities

Alumina balls used in artificial hips must meet the following specifications: grain size, < 5 microns and purity, > 99.7% aluminum oxide).[5] The maximum percentages for trace elements are: MgO, 0.2%; SiO_2, 0.01%; CaO, 0.03%; Na_2O, 0.02%; Fe_2O_3, 0.03%, and TiO_2, 0.01%.

When used in OTC drugs as a color additive, alumina (dried aluminum hydroxide) should contain no more than 0.5% insoluble matter in dilute hydrochloric acid. The following are the limits of impurities: lead (as Pb) ≤10 ppm, arsenic (as As) ≤ 1 ppm, mercury (as Hg), ≤ 1 ppm, and aluminum oxide (Al2O3), ≥ 50%. (21CFR 73.1010)

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 4).[6] A survey has been conducted by the Personal Care Products Council (Council) of the maximum use concentrations for alumina.[7] A survey is being conducted for aluminum hydroxide.

Alumina was reported to be used in 523 leave-on products at concentrations up to 60% (in nail products). It is reported to be used in 40 rinse-off products, including 84 products used around the eye at concentrations up to 30%, 87 lipsticks up to 6.7%, and 104 skin care preparations up to 25%.

Aluminum hydroxide was reported to be used in 572 leave-on products and 40 rinse-off products, including 80 products used around the eye, 154 lipsticks, and 6 suntan preparations.

Non-Cosmetic

Use in medical devices will be addressed below.

Aluminum salts are incorporated into some vaccine formulations as an adjuvant to enhance the immune response in the vaccinated individual.[8] The aluminum salts used in some U.S. licensed vaccines are aluminum hydroxide, aluminum phosphate, alum (potassium aluminum sulfate), or mixed aluminum salts. Aluminum hydroxide may be used in vaccines in amounts up to 25 μg/L in large volume parenteral drug products (21 CFR 201.323) and up to 1.25 μg/single dose, depending on calculation method (Table 6; 21 CFR 610.15).

The FDA considered the safety of aluminum hydroxide in OTC drugs (Table 6). The FDA recommended the oral maximum daily dose of an antacid containing aluminum hydroxide dried gel to be 8 g.(21 CFR 331.11) Chewable tablet of aluminum hydroxide;magnesium trisilicate (80:20 mg) was approved by FDA.[9] Two other chewable tablets were approved with doses of 80:20 mg and 160:40 mg.[10]

Aluminum hydroxide gel is approved for OTC skin protectant drug products as an active ingredient at 0.15% - 5% with caution to consult a doctor for children under 6 months (Table 6).(21 CFR 247.10; 21 CFR 347.50)

The safety and effectiveness of aluminum hydroxide in OTC drugs has not been established for: topical acne drug products and antidiarrheal drugs. It has been approved for digestive aid drug products and diaper rash drugs.(21 CFR 310.545)

Alumina is used as an adsorbent, desiccant, and abrasive.[11] It is used as filler for paints and varnishes. It is also used in the manufacture of alloys, ceramic materials, electrical insulators and resistors, dental cements, glass, steel, and artificial gems. It is used in coatings for metals, etc. and as a catalyst for organic reactions.

Aluminum hydroxide is considered GRAS by the FDA.[12]

ALUMINA IN MEDICAL DEVICES

Alumina has been approved by the FDA for use in medical devices. The alumina used in these devices must comply with ASTMF603-12 “Standard Specification for High-Purity Dense Aluminum Oxide for Medical application”.[13]

The FDA considered the safety of alumina when approving the following medical devices that contain this material:

- Color additive for PMMA bone cement and sutures,
- Endosseous dental implant abutments, and
- Femoral bearing head of artificial hips.

Color Additives

Colors that contain alumina (i.e., FD&C Blue #1 Aluminum Lake) are approved by the FDA to be used to color cosmetics, food, dietary supplements, drugs for internal and external use (with and without certification for use around the eyes), and medical devices (i.e., bone cement, surgical sutures). These colors are created by applying the color to an alumina substrate. All lakes are subject to certification. The name of a lake is formed from the name of the color additive combined with the name of the basic radical and the word "Lake". For example, the name of the lake prepared by extending the aluminum salt of FD&C Blue No. 1 upon alumina would be FD&C Blue No. 1 - Aluminum Lake. If a lake is prepared by extending an FD&C color additive on a substratum other than alumina, the symbol "FD&C" will be replaced by "D&C". For example, the name of the lake prepared by extending the aluminum salt of FD&C Blue No. 1 upon a substratum other than alumina would be D&C Blue No. 1- Aluminum Lake. A list of lake colors and their associated regulations are listed in Table 5.[14]

Alumina has been approved as a color additive for OTC drugs (Table 5). (21CFR 73.1010)

Ceramic Hip

The use of ceramic femoral heads (i.e., Ceramtec™ Alumina Heads, Alumina V40 Head) made up of an alumina/ceramic composite have been approved for use for hip joint replacement in humans. The material follows FDA's guideline "Guidance Document For The Preparation Of Premarket Notifications For Ceramic Ball Hip Systems".[5,15,16]

One hip replacement product was reported to be ~75% alumina, ~25% zirconia, and < 1% chromium oxide.[17]

Other Devices

Alumina has been approved for use in endosseous dental implant abutments (Table 6). (21 CFR 872.3630)

Alumina/ceramic composite is used to make internal stenting for treatment of traceomalacia.[18] These stents are inserted implanted within the trachea.

CLINICAL USE

Clinical Trials

There are multiple clinical trials of alumina-on-alumina or alumina ceramic hips, alumina/ceramic composite stents, and dental implants. There were no adverse reactions reported. None of the failures reported were due to adverse effects of the alumina but were related to mechanical or technique issues (Table 7).

In a review of four case studies of alumina ceramic hip implant failures, it was determined that all problems were due to design issues, implementation issues, or surgical issues.[19] None of the failures were attributed to any negative reactions to the alumina.

SUMMARY

Alumina functions in cosmetics as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent; aluminum hydroxide functions as a buffering agent, corrosion inhibitor, and pH adjuster.

CIR believes that the alumina and aluminum hydroxide produced for cosmetics is analogous to the materials used to color surgical sutures and in other commercial medical devices made of alumina as well as in OTC drugs and vaccines. The safety information for those medical devices and drugs was provided to the FDA in medical device and drug applications including: acute and long-term biocompatibility testing for cytotoxicity, irritation or intracutaneous reactivity, sensitization, systemic toxicity, implantation effects, and hematocompatibility. The FDA found those data to be adequate and determined that alumina and was safe and effective for use in hip and dental implants as well as to color PMMA bone cement and surgical sutures. Aluminum hydroxide is safe to be used in OTC drugs and vaccines.

In clinical trials of artificial hips, dental implants, and esophageal stents, all adverse effects were from mechanical or installation problems, not due to exposure to alumina.

DATA NEEDS

CIR is asking for information on:

- The physical and chemical properties of cosmetic grade alumina and aluminum hydroxide to confirm similarity to the medical grade.

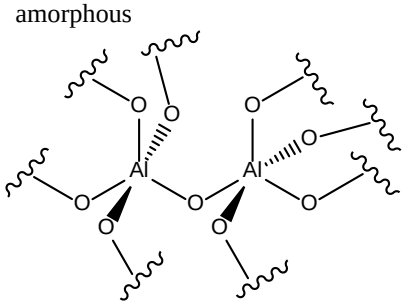
TABLES AND FIGURES

Figure 1. Formulas and idealized structures of the ingredients in this safety assessment.

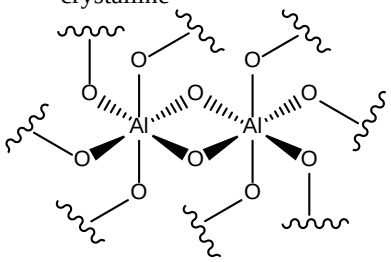
Alumina

aluminum oxide

amorphous



α-crystalline



Aluminum hydroxide

aluminum hydroxide

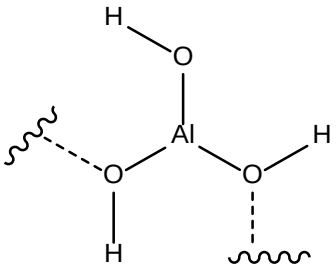


Table 1. Definitions and functions of the ingredients in this safety assessment.[20]
(The *italicized* text below represents additions made by CIR staff.)

Ingredient CAS No.	Definition	Function
Alumina 1333-84-2 (hydrate *("hydrate" in reference to Alumina often means Aluminum Hydroxide or something between Alumina and Aluminum Hydroxide); alternative CAS No. for 21645-51-2*) 1344-28-1	Alumina is an inorganic compound that conforms to the formula: Al_2O_3. *Aluminum oxide, also known as Alumina, is a mineral found as corundum, emery, ruby, sapphire, and in hydrated form (i.e., aluminum hydroxide) as bauxite or gibbsite.*	Abrasive, absorbent, anticaking agent, bulking agent, opacifying agent
Aluminum hydroxide 1333-84-2 21645-51-2	Aluminum hydroxide is an inorganic compound that conforms to the formula $Al(OH)_3 \cdot xH_2O$. *Alumina hydrates are true hydroxides (meaning they do not contain water of hydration; are often called hydrated alumina or aluminum hydroxide) and are naturally occurring as minerals including bauxite or gibbsite.*	Opacifying agent, skin protectant

Table 2. Comparison of nomenclatures for alumina and aluminum hydroxide.[3]

Mineral Name	Chemical composition	Common crystallographic designation	Past accepted crystallographic designation
Gibbsite (hydrargillite[1])[2]	Aluminum trihydroxide	α-$Al(OH)_3$	γ-$Al(OH)_3$
Bayerite	Aluminum trihydroxide	β-$Al(OH)_3$	α-$Al(OH)_3$
Nordstrandite	Aluminum trihydroxide	$Al(OH)_3$	$Al(OH)_3$
Doyleite	Aluminum trihydroxide	$Al(OH)_3$	-
Boehmite	Aluminum oxyhydroxide	γ-AlOOH	γ-AlOOH
Diaspore	Aluminum oxyhydroxide	α-AlOOH	α-AlOOH
Corundum (α-alumina)	Aluminum oxide	α-Al_2O_3	α-Al_2O_3

[1] Hydrargillite is a mineral that was named after the Greek hyder (water) and argylles (clay). The name hydrargillite was mistakenly given to describe aluminum hydroxide, but later was proven to be aluminum phosphate. However, both names are still used to describe aluminum hydroxide: gibbsite is preferred in the United States and hydrargillite is used more often in Europe.

[2] The terms in parenthesis refer to possible forms.

Table 3. Chemical and physical properties of alumina and aluminum hydroxide.

Property	Value	Reference
Alumina		
Physical Form	Solid, crystalline powder	[11,21]
Color	White	[11]
Odor	None	[21]
Molecular Weight g/mol	101.96	[11]
Density/Specific Gravity @ 20°C	4.0	[11]
Viscosity kg/(s m)@ 20°C	Solid	[21]
Vapor pressure mmHg@ 20°C	Negligible	[21]
Melting Point °C	~2000	[11]
Boiling Point °C	2980	[11]
Water Solubility g/L @ °C & pH	Insoluble	[11]
Aluminum hydroxide		
Physical Form	Amorphous powder	[11]
Color	White	[11]
Molecular Weight g/mol	78.00	[11]
Density/Specific Gravity @ °C	2.42	[11]
Melting Point °C	300	[11]
Water Solubility	Practically insoluble	[11]

Table 4. Frequency of use according to duration and exposure of alumina and sodium aluminate.[22] The Council is conducting a survey of the maximum concentrations of use for these ingredients.

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Alumina		Aluminum hydroxide	
Total/range	**563**	**0.0004-60**	**578**	**NS**
Duration of use				
Leave-on	523	0.0004-60	572	NS
Rinse-off	40	0.003-25	6	NS
Diluted for (bath) use	NR	NR	NR	NS
Exposure type				
Eye area	84	0.00075-30	80	NS
Incidental ingestion	88	0.0004-6.7	155	NS
Incidental Inhalation-sprays	7	6	6	NS
Incidental inhalation-powders	41	0.0023-5	40	NS
Dermal contact	441	0.0023-30	409	NS
Deodorant (underarm)	NR	0.004-0.01	NR	NS
Hair-noncoloring	1	NR	NR	NS
Hair-coloring	NR	1	NR	NS
Nail	30	0.0048-60	7	NS
Mucous Membrane	107	0.0004-6.7	157	NS
Baby	NR	0.0023	NR	NS

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 5. Code of Federal Regulations concerning Lake colors containing alumina.[23]

Color	Rule	Reference
FOOD, DRUGS AND COSMETICS		
FD&C Blue #1 Aluminum Lake	Color additive mixtures for food use (including dietary supplements) made with FD+C Blue No. 1 may contain only those diluents that are suitable (listed in part 73) as safe for use in color additive mixtures for coloring foods. FD+C Blue No. 1 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such other impurities may be avoided by current good manufacturing practice: • Sum of volatile matter (at 135 deg. C) and chlorides and sulfates (calculated as sodium salts) ≤ 15.0%. • Water-insoluble matter ≤ 0.2%. • Leuco base ≤ 5% percent. • Sum of *o* -,*m* -, and *p* -sulfobenzaldehydes ≤1.5%. • *N* -Ethyl, *N* -(*m* -sulfobenzyl)sulfanilic acid ≤ 0.3%. • Subsidiary colors ≤ 6.0%. • Chromium (as Cr) ≤ 50 ppm. • Manganese (as Mn) ≤ 100 ppm. • Arsenic (as As) ≤ 3 ppm. • Lead (as Pb) ≤ 10 ppm. • Total color ≥ 85.0%. FD+C Blue No. 1 may be safely used for coloring foods (including dietary supplements) generally in amounts consistent with good manufacturing practice except that it may not be used to color foods for which standards of identity have been promulgated under section 401 of the act unless added color is authorized by such standards. All batches of FD+C Blue No. 1 shall be certified in accordance with regulations in part 80 of this chapter.	21 CFR 74.101

Table 5. Code of Federal Regulations concerning Lake colors containing alumina.[23]

Color	Rule	Reference
	For ingested drugs, the color additive FD+C Blue No. 1 shall conform in identity to the requirements of 74.101(a)(1). For externally applied drugs, the color additive FD+C Blue No. 1 shall conform in identity to the requirements of 74.2101(a). Color additive mixtures for drug use made with FD+C Blue No. 1 may contain only those diluents that are suitable (listed in part 73) and generally shall conform in specifications to the requirements of 74.101(b). It shall be prepared in accordance with the requirements of 82.51 of this chapter and may be safely used for coloring drugs, including drugs intended for use in the area of the eye, in amounts consistent with current good manufacturing practice subject to the restrictions on the use of color additives in 70.5(b) and (c). All batches of FD+C Blue No. 1 shall be certified in accordance with regulations in part 80.	21 CFR 74.1101
	FD+C Blue No. 1 shall conform in specifications to the requirements of 74.101(b) and shall be prepared in accordance with the requirements of 82.51 of this chapter. It may be safely used for coloring cosmetics generally, including cosmetics intended for use in the area of the eye, in amounts consistent with current good manufacturing practice.	21 CFR 74.2101,
	The color additive FD+C Blue No. 1 shall conform in identity and specifications to the requirements of 74.101(a)(1) and (b).	21 CFR 82.101
	Any lake made by extending on a substratum of alumina, a salt prepared from one of the certified water-soluble straight colors hereinbefore listed in this subpart by combining such color with the basic radical aluminum or calcium. Specifications: • Soluble chlorides and sulfates (as sodium salts) ≤ 2.0%. • Inorganic matter, insoluble HCl ≤ 0.5%.	21 CFR 82.51
FD&C Blue #2 Aluminum Lake on alumina	Color additive mixtures for food use (including dietary supplements) made with FD+C Blue No. 2 may contain only those diluents that are suitable and that are listed in part 73 of this chapter as safe for use in color additive mixtures for coloring foods. The color additive FD+C Blue No. 2 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such other impurities may be avoided by current good manufacturing practice: • Sum of volatile matter at 135 deg. C (275 deg. F) and chlorides and sulfates (calculated as sodium salts), ≤15 percent. • Water insoluble matter ≤0.4%. • Isatin-5-sulfonic acid ≤ 0.4% percent. • 5-Sulfoanthranilic acid ≤ 0.2%. • Disodium salt of 2-(1,3-dihydro-3-oxo-7-sulfo-2*H* -indol-2-ylidene)-2,3-dihydro-3-oxo-1*H* -indole-5-sulfonic acid ≤ 18%. • Sodium salt of 2-(1,3-dihydro-3-oxo-2*H* -indol-2-ylidene)-2,3-dihydro-3-oxo-1*H* -indole-5-sulfonic acid ≤ 2%. • Lead (as Pb) ≤10 ppm. • Arsenic (as As) ≤ 3 ppm. • Mercury (as Hg) ≤ 1% ppm. • Total color ≥ 85%. The color additive FD+C Blue No. 2 may be safely used for coloring foods (including dietary supplements) generally in amounts consistent with current good manufacturing practice except that it may not be used to color foods for which standards of identity have been promulgated under section 401 of the Federal Food, Drug, and Cosmetic Act unless added color is authorized by such standards. All batches of FD+C Blue No. 2 shall be certified in accordance with regulations in part 80 of this chapter.	21 CFR 74.102
	The color additive FD+C Blue No. 2 for use in coloring surgical sutures shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice: • Sum of volatile matter at 135 deg. C (275 deg. F) and chlorides and sulfates (calculated as sodium salts) ≤ 15%. • Water insoluble matter ≤ 0.4% percent. • Isatin-5-sulfonic acid ≤0.4%. • Isomeric colors ≤18%. • Lower sulfonated subsidiary colors ≤ 5%. • Lead (as Pb) ≤ 10 ppm. • Arsenic (as As) ≤ 3 ppm. • Total color ≥ 85%. The color additive FD+C Blue No. 2-Aluminum Lake on alumina for use in bone cement shall be prepared in accordance with the requirements of 82.51. The color additive FD+C Blue No. 2 may be safely used for coloring nylon (the copolymer of adipic acid and hexamethylene diamine) surgical sutures for use in general surgery subject to the following restrictions: • The quantity of color additive ≤ 1% by weight of the suture; • The dyed suture shall conform in all respects to the requirements of the United States Pharmacopeia XX (1980); and • When the sutures are used for the purposes specified in their labeling, the color additive does not migrate to the surrounding tissues. The color additive FD+C Blue No. 2-Aluminum Lake on alumina may be safely used for coloring bone cement at a level ≤ 0.1% by weight of the bone cement. All batches of FD+C Blue No. 2 and its lake shall be certified in accordance with regulations in part 80 of	21 CFR 74.3102

Table 5. Code of Federal Regulations concerning Lake colors containing alumina.[23]

Color	Rule	Reference
	this chapter.	
	The color additive FD+C Blue No. 2 shall conform in identity and specifications to the requirements of 74.102(a)(1) and (b).	21 CFR 82.102
FD&C Red #40 and its Aluminum Lake	*Color additives for use in the area of the eye.* No listing or certification of a color additive shall be considered to authorize the use of any such color additive in any article intended for use in the area of the eye unless such listing or certification of such color additive specifically provides for such use. Any color additive used in or on any article intended for use in the area of the eye, the listing or certification of which color additive does not provide for such use, shall be considered to be a color additive not listed under parts 73, 74, and 81 of this chapter, even though such color additive is certified and/or listed for other uses. *Color additives for use in injections.* No listing or certification of a color additive shall be considered to authorize the use of any such color additive in any article intended for use in injections unless such listing or certification of such color additive specifically provides for such use. Any color additive used in or on any article intended for use in injections, the listing or certification of which color additive does not provide for such use, shall be considered to be a color additive not listed under parts 73, 74, and 81 of this chapter, even though such color additive is certified and/or listed for other uses. *Color additives for use in surgical sutures.* No listing or certification of a color additive shall be considered to authorize the use of any such color additive in any article intended for use as a surgical suture unless such listing or certification of such color additive specifically provides for such use. Any color additive used in or on any article intended for use as a surgical suture, the listing or certification of which color additive does not provide for such use, shall be considered to be a color additive not listed under parts 73, 74, and 81 of this chapter, even though such color additive is certified and/or listed for other uses.	21 CFR 70.5
	The listing of this color additive includes lakes prepared as described in 82.51 of this chapter, except that the color additive used is FD+C Red No. 40 and the resultant lakes meet the specification and labeling requirements prescribed by 82.51 of this chapter. FD+C Red No. 40 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such other impurities may be avoided by good manufacturing practice: • Sum of volatile matter (at 135 deg. C.) and chlorides and sulfates (calculated as sodium salts) ≤ 14.0%. • Water-insoluble matter ≤ 0.2%. • Higher sulfonated subsidiary colors (as sodium salts) ≤ than 1.0%. • Lower sulfonated subsidiary colors (as sodium salts) ≤ 1.0%. • Disodium salt of 6-hydroxy-5-[(2-methoxy-5-methyl-4-sulfophenyl) azo] -8-(2-methoxy-5-methyl-4-sulfophenoxy)-2-naphthalenesulfonic acid ≤ 1.0%. • Sodium salt of 6-hydroxy-2-naphthalenesulfonic acid (Schaeffer's salt) ≤ 0.3%. • 4-Amino-5-methoxy-*o*- toluenesulfonic acid ≤ 0.2%. • Disodium salt of 6,6'-oxybis (2-naphthalene-sulfonic acid) ≤ 1.0%. • Lead (as Pb) ≤ 10 ppm. • Arsenic (as As) ≤ 3 parts ppm. • Total color ≥ 85.0%. FD+C Red No. 40 may be safely used for coloring foods (including dietary supplements) generally in amounts consistent with good manufacturing practice except that it may not be used to color foods for which standards of identity have been promulgated under section 401 of the act unless added color is authorized by such standards. All batches of FD+C Red No. 40 and lakes thereof shall be certified in accordance with regulations in part 80 of this chapter.	21 CFR 74.340
	Color additive mixtures for drug use made with FD+C Red No. 40 may contain only those diluents that are suitable and that are listed in part 73 of this chapter as safe for use in color additive mixtures for coloring drugs. The listing of this color additive includes lakes prepared as described in 82.51 and 82.1051 of this chapter, except that the color additive used is FD+C Red No. 40 and the resultant lakes meet the specification and labeling requirements prescribed by 82.51 or 82.1051. FD+C Red No. 40 and FD+C Red No. 40 Aluminum Lake may be safely used in coloring drugs, including those intended for use in the area of the eye, subject to the restrictions on the use of color additives in 70.5(b) and (c), in amounts consistent with current good manufacturing practice. Other lakes of FD+C Red No. 40 may be safely used in coloring drugs, subject to the restrictions on the use of color additives in 70.5, in amounts consistent with current good manufacturing practice. All batches of FD+C Red No. 40 and lakes thereof shall be certified in accordance with regulations, in part 80.	21 CFR 74.1340
	The listing of this color additive includes lakes prepared as described in 82.51 and 82.1051, except that the color additive used is FD+C Red No. 40 and the resultant lakes meet the specification and labeling requirements prescribed by 82.51 or 82.1051. FD+C Red No. 40 may be safely used in coloring cosmetics generally, except that only FD+C Red No. 40 and FD+C Red No. 40 Aluminum Lake may be safely used in coloring cosmetics intended for use in the area of the eye. These uses are subject to the following restrictions: • The color additive may be used in amounts consistent with current good manufacturing practice. • The color additive shall not be exposed to oxidizing or reducing agents that may affect the integrity of the color additives or any other condition that may affect their integrity. All batches of FD+C Red No. 40 shall be certified in accordance with regulations in part 80.	21 CFR 74.2340
FD&C Yellow #5 Aluminum Lake	FD+C Yellow No. 5 Aluminum Lake shall be prepared in accordance with the requirements of 82.51. FD+C Yellow No. 5 Aluminum Lake may be safely used for coloring drugs intended for use in the area of	21 CFR 74.1705

Table 5. Code of Federal Regulations concerning Lake colors containing alumina.[23]

Color	Rule	Reference
	the eye, when prepared in accordance with 82.51 of this chapter.	
	FD+C Yellow No. 5 Aluminum Lake shall be prepared in accordance with the requirements of 82.51. FD+C Yellow No. 5 Aluminum Lake may be safely used for coloring cosmetics intended for use in the area of the eye, subject to the restrictions on use of color additives in 70.5(b) and (c), in amounts consistent with current good manufacturing practice.	21 CFR 74.2705
	The color additive FD+C Yellow No. 5 shall conform in identity and specifications to the requirements of 74.705 (a)(1) and (b).	21 CFR 82.705
EXTERNALLY APPLIED DRUGS AND COSMETICS (None of these colors may be used in products that are for use in the area of the eye)		
Ext. D&C Lakes	The Commissioner of Food and Drugs finds that the following lists of color additives are provisionally listed under section 203(b) of the Color Additive Amendments of 1960 (sec. 203(b), 74 Stat. 405 (21 U.S.C. 379e note)). Except for color additives for which petitions have been filed, progress reports are required by January 1, 1968, and at 6-month intervals thereafter. Specifications for color additives listed in paragraphs (a), (b), and (c) of this section appear in the respective designated sections. The listing of color additives in this section is not to be construed as a listing for surgical suture use unless color additive petitions have been submitted for such use or the Commissioner has been notified of studies underway to establish the safety of the color additive for such use. The color additives listed in paragraphs (a), (b), and (c) of this section may not be used in products which are intended to be used in the area of the eye. The color additives listed in paragraphs (a), (b), and (c) of this section are provisionally listed until the closing dates set forth therein. • Lakes (FD+C) (sec. 82.51) • Lakes (D+C) (Sec. 82.2051) • Lakes (Ext. D+C) (sec. 82.105(1))	21 CFR 81.1
	Any lake made by extending on a substratum of alumina, blanc fixe, gloss white, clay, titanium dioxide, zinc oxide, talc, rosin, aluminum benzoate, calcium carbonate, or on any combination of two or more of these: • one of the straight colors hereinbefore listed in this subpart, which color is a salt in which is combined the basic radical sodium, potassium, barium, or calcium; or • (ii) a salt prepared from one of the straight colors hereinbefore listed in this subpart by combining such color with the basic radical sodium, potassium, aluminum, barium, calcium, strontium, or zirconium. Specifications: • Ether extracts ≤ 0.5%. • Soluble chlorides and sulfates (as sodium salts) ≤ 3.0%. • Intermediates ≤ 0.2%. Each lake made as prescribed in this section shall be considered to be a straight color and to be listed therein under the name which is formed as follows: • The listed name of the color from which the lake is prepared; • The name of the basic radical combined in such color; and • The word "Lake." (For example, the name of a lake prepared by extending the color Ext. D+C Yellow No. 2 upon a substratum is "Ext. D+C Yellow No. 2--Calcium Lake," and a lake prepared by extending the barium salt prepared from Ext. D+C Red No. 2 upon the substratum is "Ext. D+C Red No. 2--Barium Lake.")	21 CFR 82.2051
	The color additive Ext. D+C Yellow No. 7 shall conform in identity with specifications to the requirements of 74.1707a(a)(1) and (b) of this chapter. Ext. D+C Yellow No. 7 is restricted to use in externally applied drugs and cosmetics.	21 CFR 82.2707
DRUGS (None of these color additives may be used in products that are for use in the area of the eye, unless otherwise indicated.).		
Alumina	Color additive mixtures for drug use made with alumina (dried aluminum hydroxide) may contain only those diluents listed in this subpart as safe and suitable for use in color additive mixtures for coloring drugs. Alumina (dried aluminum hydroxide) shall conform to the following specifications: • Acidity or alkalinity: Agitate 1 gram of the color additive with 25 milliliters of water and filter. The filtrate shall be neutral to litmus paper. • Matter insoluble in dilute hydrochloric acid ≤ 0.5%. • Lead (as Pb) ≤ 10 ppm. • Arsenic (as As) ≤ 1 ppm. • Mercury (as Hg) ≤ 1 ppm. • Aluminum oxide (Al_2O_3) ≥ 50%. Alumina (dried aluminum hydroxide) may be safely used in amounts consistent with good manufacturing practice to color drugs generally. Certification of this color additive is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification requirements of section 721(c) of the act.	21 CFR 73.1010
Aluminum hydroxide	Aluminum hydroxide gel is approved for OTC skin protectant drug products as an active ingredient at 0.15% - 5% with caution to consult a doctor for children under 6 months.	21 CFR 247.10; 21 CFR 347.50
MEDICAL DEVICES		
FD&C Blue #2 Aluminum lake on alumina	The color additive FD+C Blue No. 2 shall conform in identity to the requirements of 74.102(a)(1). The color additive FD+C Blue No. 2 for use in coloring surgical sutures shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice: • Sum of volatile matter at 135 deg. C (275 deg. F) and chlorides and sulfates (calculated as sodium	21 CFR 74.3102

Table 5. Code of Federal Regulations concerning Lake colors containing alumina.[23]

Color	Rule	Reference
	salts) ≤ 15%. • Water insoluble matter ≤ 0.4%. • Isatin-5-sulfonic acid ≤ 0.4%. • Isomeric colors ≤ 18%. • Lower sulfonated subsidiary colors ≤ 5%. • Lead (as Pb) ≤ 10 ppm. • Arsenic (as As) ≤ 3 ppm. • Total color ≥ 85%. The color additive FD+C Blue No. 2-Aluminum Lake on alumina for use in bone cement shall be prepared in accordance with the requirements of 82.51. The color additive FD+C Blue No. 2 may be safely used for coloring nylon (the copolymer of adipic acid and hexamethylene diamine) surgical sutures for use in general surgery subject to the following restrictions: • The quantity of color additive does not exceed 1% by weight of the suture; • The dyed suture shall conform in all respects to the requirements of the United States Pharmacopeia XX (1980); and • When the sutures are used for the purposes specified in their labeling, the color additive does not migrate to the surrounding tissues. The color additive FD+C Blue No. 2-Aluminum Lake on alumina may be safely used for coloring bone cement at a level not to exceed 0.1% by weight of the bone cement. All batches of FD+C Blue No. 2 and its lake shall be certified in accordance with regulations in part 80.	

Table 6. Regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

Device/Drug	Rule	Reference
Endosseous dental implant abutment		
	An endosseous dental implant abutment is a premanufactured prosthetic component directly connected to the endosseous dental implant and is intended for use as an aid in prosthetic rehabilitation. Class II (special controls). The guidance document entitled "Class II Special Controls Guidance Document: Root-Form Endosseous Dental Implants and Endosseous Dental Implant Abutments" will serve as the special control. (See 872.1(e) for the availability of this guidance document.)	21 CFR 872.3630
Hip joint metal/ceramic/polymer semi-constrained cemented or nonporous uncemented prosthesis		
	(a) A hip joint metal/ceramic/polymer semi-constrained cemented or nonporous uncemented prosthesis is a device intended to be implanted to replace a hip joint. This device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. The two-part femoral component consists of a femoral stem made of alloys to be fixed in the intramedullary canal of the femur by impaction with or without use of bone cement. The proximal end of the femoral stem is tapered with a surface that ensures positive locking with the spherical ceramic (aluminum oxide, $A1_2 0_3$) head of the femoral component. The acetabular component is made of ultra-high molecular weight polyethylene or ultra-high molecular weight polyethylene reinforced with nonporous metal alloys, and used with or without bone cement. (b)*Classification.* Class II.	21 CFR 888.3353
	(a) A hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis is a two-part device intended to be implanted to replace the articulating surfaces of the hip while preserving the femoral head and neck. The device limits translation 888.3410 and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across the joint. This generic type of device includes prostheses that consist of a femoral cap component made of a metal alloy, such as cobalt-chromium-molybdenum, or a ceramic material, that is placed over a surgically prepared femoral head, and an acetabular resurfacing polymer component. Both components are intended for use with bone cement (888.3027). (b) *Classification* . Class III. (c) *Date PMA or notice of completion of a PDP is required* . A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before January 3, 2005, for any hip joint metal/polymer or ceramic/polymer semiconstrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976, or that has, on or before January 3, 2005, been found to be substantially equivalent to a hip joint metal/polymer or ceramic/polymer semiconstrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976. Any other hip joint metal/polymer or ceramic/polymer semiconstrained resurfacing cemented prosthesis must have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.	21 CFR 888.3410

Table 6. Regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

Device/Drug	Rule	Reference
Injections		
	Sec. 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition. (a) The aluminum content of LVP) drug products used in TPN therapy must not exceed 25 µg/L. (b) The package insert of LVP's used in TPN therapy must state that the drug product contains no more than 25 µg/L aluminum. This information must be contained in the "Precautions" section of the labeling of all large volume parenterals used in TPN therapy. (c) Except as provided in paragraph (d) of this section, the maximum level of aluminum present at expiry must be stated on the immediate container label of all SVP drug products and PBPs used in the preparation of TPN solutions. The aluminum content must be stated as follows: "Contains no more than __ µg/L of aluminum." The immediate container label of all SVP's and PBP's that are lyophilized powders used in the preparation of TPN solutions must contain the following statement: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than __ µg/L." This maximum level of aluminum must be stated as the highest of: (1) The highest level for the batches produced during the last 3 years; (2) The highest level for the latest five batches, or (3) The maximum historical level, but only until completion of production of the first five batches after July 26, 2004. (d) If the maximum level of aluminum is 25 µg/L or less, instead of stating the exact amount of aluminum as required in paragraph (c) of this section, the immediate container label may state: "Contains no more than 25 µg/L of aluminum." If the SVP or PBP is a lyophilized powder, the immediate container label may state: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L". (e) The package insert for all LVP's, all SVP's, and PBP's used in TPN must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling. The warning must state: WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/L/kg/d accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. (f) Applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to the Food and Drug Administration validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment under 314.60 or 314.96 of this chapter.	21 CFR 201.323
	(a)*Ingredients, preservatives, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed: (1) 0.85 milligrams if determined by assay; (2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or (3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in 600.2 of this chapter). (b)*Extraneous protein; cell culture produced vaccines.* Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000. (c)*Antibiotics.* A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines. (d) The Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research may approve an exception or alternative to any requirement in this section. Requests for such exceptions or alternatives must be in writing.	21 CFR 610.15

Table 6. Regulations for medical devices, drugs, and other regulated uses of alumina and aluminum hydroxide.

Device/Drug	Rule	Reference
OTC Drugs		
	(a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses: (1)*Topical acne drug products.* (3)*Antidiarrheal drug products* --(i)*Approved as of May 7, 1991* . (8)*Digestive aid drug products* --(i)*Approved as of May 7, 1991*. (iii)*Diaper rash drug products.*	21CFR310.545
	(a) Aluminum-containing active ingredients: (1) Basic aluminum carbonate gel. (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated). (3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid. (4) Aluminum phosphate gel when used as part of an antacid combination product and contributing at least 25 percent of the total acid neutralizing capacity; maximum daily dosage limit is 8 grams	21CFR331.11
	Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. (a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses: Topical acne drug products and antidiarrheal drugs.	21 CFR 310.545
	The labeling of the product contains the following information for anorectal ingredients identified in 346.10, 346.12, 346.14, 346.16, 346.18, and 346.20, and for combinations of anorectal ingredients identified in 346.22. Unless otherwise specified, the labeling in this subpart is applicable to anorectal drug products for both external and intrarectal use. (H) "Temporarily relieves the symptoms of perianal skin irritation." (iv)*For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5).* "For the temporary relief of itching associated with moist anorectal conditions." *For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5).* "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area."	21 CFR 346.14
	Listing of specific active ingredients (a) Aluminum-containing active ingredients: (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).	
	Permitted combinations of active ingredients. (a)*Combinations of skin protectant active ingredients.* (1) Any two or more of the ingredients identified in 347.10(a), (d), (e), (i), (k), (l), (m), and (r) may be combined provided the combination is labeled according to 347.50(b)(1) and provided each ingredient in the combination is within the concentration specified in 347.10. (2) Any two or more of the ingredients identified in 347.10(a), (d), (e), (g), (h), (i), (k), (l), (m), and (r) may be combined provided the combination is labeled according to 347.50(b)(2) and provided each ingredient in the combination is within the concentration specified in 347.10. (b)*Combination of ingredients to prepare an aluminum acetate solution* . Aluminum sulfate tetradecahydrate may be combined with calcium acetate monohydrate in powder or tablet form to provide a 0.13 to 0.5 percent aluminum acetate solution when the powder or tablet is dissolved in the volume of water specified in "Directions."	21 CRF 347.10
Food Packaging		
	Aluminum hydroxide is among the list of substances that may be a component of cellophane as a food packaging substance.	21 CFR 177.1200
	Aluminum hydroxide is included in the list of fillers of rubber articles intended for repeated use may be safely used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21CFR177.2600

LVP - large volume parenteral; PBP – pharmacy bulk packages; SVP - small volume parenteral; TPN - total parenteral nutrition

Table 7. Clinical trials of medical devices containing alumina.

Study	Results	Reference
Artificial Hips		
Alumina-on-alumina (n = 88 subjects; 107 hips) and alumina ceramic bearing (n = 65; 71 hips) followed for an average of 6.84±1.49 years and 7.73±1.60 years.	No adverse effects from exposure to alumina.	[24]
Two alumina hips compared, with and without alumina grit blasted finish (n = 14, 18) followed for 12 months and compared for complications.	Alumina particles on the surface of prostheses has a histologically observable impact on surrounding tissues and leads to surface wear in vivo, This was considered mechanical and not a reaction to alumina.	[25]
Alumina-on alumina (n = 849; 930 hips) followed for an average of 5.9 years for adverse events, 10 years for survivorship.	All adverse event/complications were of mechanical origin, not from exposure to alumina. Survival[1] of the hips at 10 years was 96.8%.	[26]
Fine-grained alumina ceramic hips, with and without zirconium oxide added (n = 29 women, 35 men and 21 women, 24 men) followed for an average of 73 (26-108) and 72 (31-98) months.	Survivorship was 95% and 93% at 6 years, respectively. There were no cases of osteolysis in the first group and 1 case in the second. No adverse effects attributed to alumina were reported.	[17]
Alumina-on-alumina hips (n = 77, 82 hips) were retroactively followed for 8 years.	8 year survival was 90.7% with no revisions, 94.4% with revisions. All issues were attributed to mechanical issues and not from exposure to alumina.	[27]
Alumina ceramic hips (n = 301) were followed for at least 10 years.	Survival was 98% (confidence interval 94.2%-99.6%) at 10 years. All adverse effects were due to mechanical issues.	[28]
Dental Implants		
Alumina ceramic attachment (> 95% alumina) to hold dentures (n = 20) were followed for 1 year.	No adverse effects from exposure to alumina.	[29]
Single crystal alumina endosteal dental implants (n = 29) followed for 5 years.	5 implants removed from study due to mechanical issues, infection, or patient discomfort. No adverse effects from exposure to alumina.	[30]
Single crystal alumina endosteal dental implants (n = 23; 15 subjects) followed for 10 years. 6 weeks after implantation, the implants served as abutments for fixed prostheses.	After 10 years 2l baseline implants were still in place, I7 were fully functional (81% survival). All adverse events were mechanical and not due to exposure to alumina.	[31]
Glass infiltrated alumina crowns (n = 5a; 21 subjects) followed for 5 years.	All adverse events were mechanical and not related to exposure to alumina.	[32]
Other Devices		
Retrospective study (n = 12) of internal alumina/ceramic composite stents inserted for treatment of traceomalacia were followed.	None of the complications were due to the materials. In an assessment of biocompatibility, the authors concluded that there were no foreign body reactions, the inserts were stable, and were a long-term solution with proper suturing technique	[18]

[1] Survival refers to how long the prosthesis is functional.

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