

## Review Article

ISSN CODE: 2456-1045 (Online)

(ICV-MDS/Impact Value): 2.31

(GIF) Impact Factor: 1.272

Copyright@IJF 2016

Journal Code: ARJMD/MDS/V-7.0/I-1/C-11/NOV-2016

Website: [www.journalresearchijf.com](http://www.journalresearchijf.com)

Received: 28.11.2016

Accepted: 04.12.2016

Date of Publication: 08.12.2016

Page: 67-78



Name of the Authors:

**Vani Mamillapalli<sup>1</sup>,**  
**Padma Latha Khantamneni<sup>2</sup>**  
**Yakkali Hanumanth Madhuri<sup>1</sup>**  
**Atmakuri HLB Sravya<sup>1</sup>**

<sup>1</sup>Department of Pharmacognosy and Phyto Chemistry, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Viayawada, Pin: 521108, Krishna District, Andhra Pradesh, (India)

<sup>2</sup>Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Viayawada, Pin: 521108, Krishna District, Andhra Pradesh, (India)

### Citation of the Article

Mamillapalli V; Khantamneni P.L; Madhuri Y.H, Sravya AHLB; (2016, December 8). Bio compatible materials used in medical practice. *Advance Research Journal of Multidisciplinary Discoveries*. Vol. 7.0, C11, PP.67-78, Nov. 2016. ISSN-2456-1045. from <http://www.journalresearchijf.com/>

### ABSTRACT

Medical implants are products that have to satisfy functionality demands defined by the human body as working environment. The choice of material used for designing a medical implant is governed by biocompatibility. The development of this area attracts commercial utility. Focus of this contribution is on metallic, ceramic and polymeric biomaterials and laws regulating their use in modern medical applications. Further studies relating to long-term effects of materials on biological tissues are necessary, and are likely to lead to an increased understanding of the biocompatibility of materials in the future.

### KEY WORDS:

Medical implants,  
 biocompatible,  
 biomaterials

### I. INTRODUCTION

The development of medical implants utilizing new materials continues to attract considerable academic and commercial interest. The development of new biomaterials involves a complicated mix of materials science and cell biology. Collaboration of various experienced specialists such as material scientists, metallurgists, traumatologists, orthopedists, chemists, mechanical engineers, pharmacists and others in order to achieve better results in research, development and implementation of the extracted knowledge into the practice is of essential importance. Biomaterials are nonviable materials used in a medical devices intended to interact with biological systems (Ratner et al., 2004) and cover several classes of materials, such as metallic, ceramic, and polymeric materials. Medical implants are products that have to satisfy functionality demands defined by the human body as working environment. Ideally, they should have biomechanical properties

comparable to those of autogenous tissues without any adverse effects and are regulated in order to ensure safety and effectiveness. The choice of material used for designing a medical implant is governed by biocompatibility, bioadhesion, bio functionality corrosion resistance etc. To better understand implant material-biological organism interaction most of the studies are directed into the releases of particles from the material and offer screens for genotoxicity, carcinogenicity, cytotoxicity, irritation, sensitivity and sterilization agent residues (Balazic et al., 2007) Focus of this contribution is on metallic, ceramic and polymeric biomaterials and laws regulating their use in modern medical applications.

**1.1 TYPES OF BIOMATERIALS:**

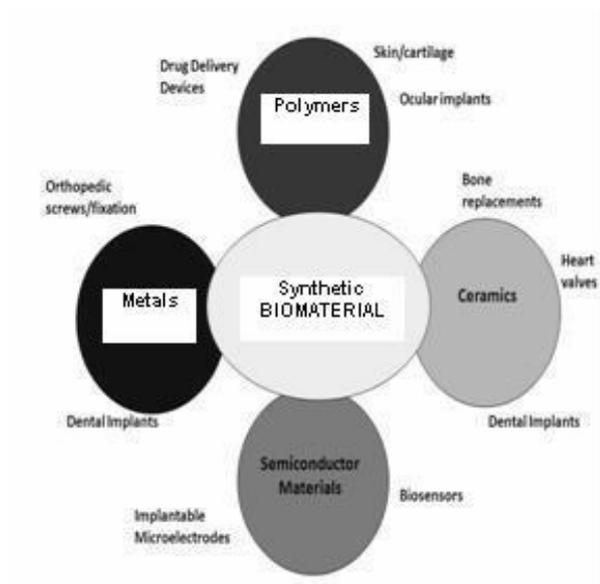
Biomaterials are divided into following subgroups (Fig. 1).

1.1.1 Metallic biomaterials: Stainless steel, Cobalt alloys, Titanium alloys

1.1.2 Ceramic biomaterials: Aluminium oxide, Zirconia, Calcium phosphates

1.1.3 Polymeric biomaterials:

- Synthetic polymers- Silicones, polyethylene, polyvinyl chloride, polyurethanes.
- Natural polymers- Collagen, gelatin, elastin, silk, polysaccharide.



**Fig. 1: Main types of biomaterials in humans**

**1.1.1 METALLIC BIOMATERIALS**

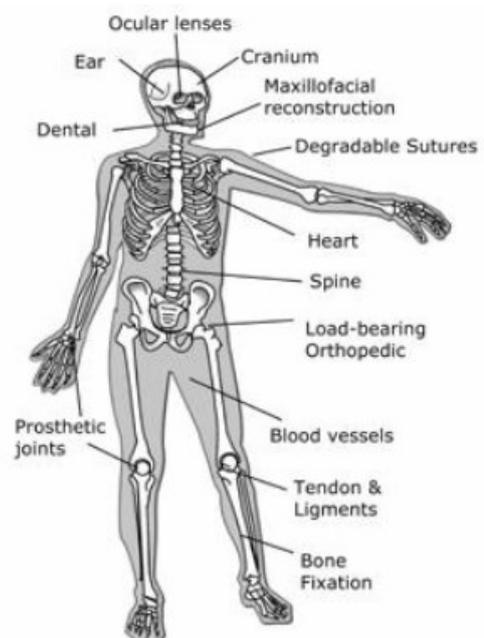
Metallic biomaterials are often used to support and/or replace components of the skeleton. They are used e.g. as artificial joints, bone plates, screws, intramedullary nails, spinal fixations, spinal spacers, external fixators, pace maker cases, artificial heart valves, wires, stents, and dental implants. They possess greater tensile strength, fatigue strength, and fracture toughness when compared to polymeric and ceramic materials. Most widely used metallic

biomaterials for implants devices are 316L stainless steels, cobalt alloys, commercially pure titanium, and Ti-6Al-4V alloys (Sumita M et al., 2004; Annual book of ASTM standards 1999; Williams 1993; Breme et al., 1998). Originally, these materials were developed for industrial purposes.

**Table 1: Mechanical characteristics of metal alloys used in medicine**

Characteristics	Stainless steel	Cobalt alloys	Titanium alloys
Stiffness	High	Medium	Low
Strength	Medium	Medium	High
Corrosion Resistance	Low	Medium	High
Biocompatibility	Low	Medium	High

The corrosion resistance, which results in very small release of harmful toxins when exposed to bodily fluids, is the main reasons for these materials can be left inside the body for a longer period of time and are therefore appropriate for medical uses. In Table 1 some mechanical and biological characteristics of stainless steel, cobalt and titanium alloys are presented. As additional information let us mention that production of metallic-based medical devices in general involves cutting operations (turning, milling, drilling etc.); forming operations (pressing, hydroforming, forging etc.) and other alternative machining operations (laser and waterjet cutting, different layer-by-layer sintering techniques such as direct metal laser sintering, selective laser melting, selective laser sintering, electron beam melting and laser engineered net shaping) (Bombac et al 200).



**Fig. 2: Biocompatible materials in the human body**

The broad spectrum of biocompatible materials for use within the human body (Figure 2). Titanium is widely used for implants, surgical instruments and pacemaker boxes. Titanium hip prostheses are well known and have been used for more than 30 years. Contemporary sheaths accelerating titanium adhesion to adjacent bone are already accessible.

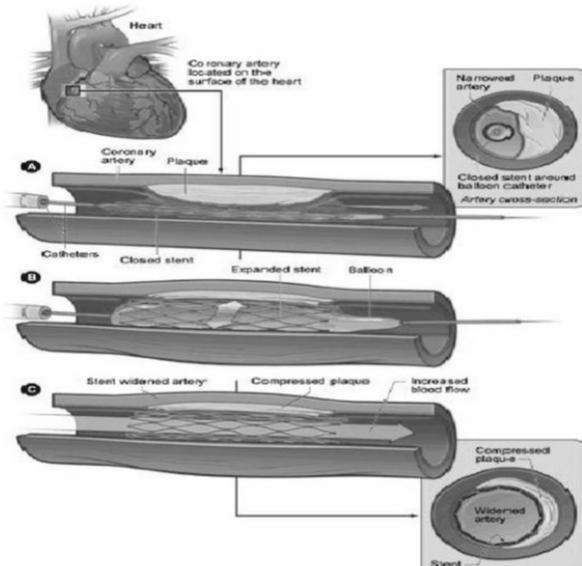
✓ **METALLIC BIOCOMPATIBLE MATERIALS USED IN MEDICAL PRACTICE:**

**Stent implantation:** Stent implantation is a stage in the development of invasive cardiology. The concept of intravascular stent implantation was developed by Dotter in 1964, but it was not introduced into practice until 1985, when Sigwart implanted the first intravascular stent, a self-expandable Wallstent, in a human iliac artery.



**Figure 3: Cardio vascular Stent**

Routine stent use into practice has significantly reduced the incidence of complications, restenosis and repeat revascularization after coronary angioplasty (Fig. 3 & 4). A great number of study results, including these from 8 and 10 year follow-ups of patients, have shown the superiority of coronary stent placement over cardio surgical revascularization. However, the tendency to prevalent recurrent complaints and repeat revascularization is still observed in patients with stents. A possible decision of this problem is the introduction of drug-eluting stents. These are stents, loaded with a specific drug, usually a cytostatic agent, which inhibits the endothelial and fibro muscular excessive proliferation, induced by the presence of a foreign body in the blood vessel.



**Fig. 4: Coronary stent implantation**

Presently, in the world, as well as in Bulgaria, an increasing number of interventions is performed in other than the coronary arteries – carotid artery stenting, endoaortic prosthesis, laser atherectomy and rotablation, angioplasty of peripheral, visceral and renal arteries, closure of atrioventricular fistulas, vascular embolisation (for example, in tumors of vascular origin), insertion of inferior vena cava filters in cases of pulmonary thromboembolism, super selective fibrinolysis in cases of pulmonary thromboembolism, percutaneous mitral and aortic valvuloplasty etc. (Praveen kumar GVP 2008; Kumar GVP 2008; Kumar GVP 2010).

- Ocular lenses

Contact lenses are the second widespread means for correction of visual disturbances, due to deviations in the ocular optical system (hyperopia, myopia, astigmatism, keratoconus). Contact lenses are also used with cosmetic purposes for accentuating or changing the eye colour (colour contact lenses), protection of the eyes from radiation, enhanced healing of corneal lesions etc. Depending on material, there are three main types of contact lenses:

- Rigid lenses from plexiglass (PMMA). These lenses are in fact outdated and are rarely used.
- Soft lenses from gel-like plastic materials. These lenses are a little bit larger than the iris and find the most common application.
- GP lenses, known as rigid gas permeable (RGP) lenses, produced of rigid, hydrophobic plastic materials and recommended in presbyopia and severe astigmatism. Usually, these lenses have a diameter of about 8mm and are smaller than the iris.
- Silicone-hydrogel lenses, a type of soft contact lenses, known also as “breathing” lenses and produced of a silicone polymer. Silicone-hydrogel lenses are increasingly implemented into practice and are considered to be one of the best achievements in contactology.

**Intraocular lenses**

Cataract is a condition of loss of transparency of the lens of the eye or of its capsule, varying in degree from slight to complete opacity. This may result in gradual reduction of vision to complete obstruction of the passage of light and images to the retina. The most effective and common treatment of a cataract is the surgical, i.e. removal of the lens and its replacement with a suitable artificial lens (an implant), which results in restoration of patient’s vision and quality of life. The surgical intervention consists of breaking and removing the cloudy natural lens with a miniature probe through a very small incision (of about 2-2.5mm). After then, an artificial lens is implanted through the same incision and the visual function of the eye is restored. The intervention is bloodless and suture less. Usually, the cataract extraction takes 20 or some more minutes and the majority of patients return quickly and easily to their normal rhythm of life. This is due to the artificial intraocular lens (IL) implanted into the eye during the final stage of the surgical intervention. The intraocular

lens (Figure 5) is an artificial lens, which replaces the cloudy cataract and restores the visual function of the eye.

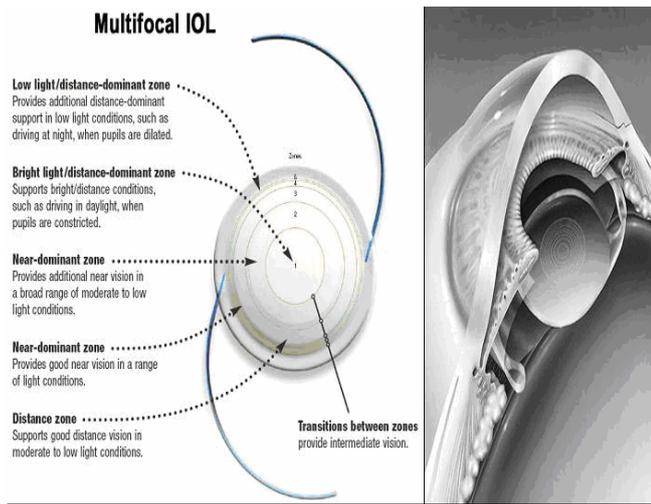


Fig. 5: An Intraocular lens

The traditional method of cataract surgery includes the insertion of a monofocal lens, which corrects hyperopia and avoids the necessity of wearing glasses for myopia and correction of the existing astigmatism. The new generation of artificial lenses aims at correcting some refraction anomalies, such as astigmatism, myopia and hyperopia. Besides, the improved design of the lens surface protects the eye (retina) from the ultraviolet spectrum of the daylight and improves vision in unfavourable light conditions (in foggy weather or at dusk).

#### Types of intraocular lenses:

- Intraocular implants with one focus and a filter for UV and blue light.
- Intraocular implants with more than one focus.
- Multifocal lenses, correcting hyperopia and myopia.

**Artificial cornea :** In March 2004, Dr. Ming Wang entered in the history of medicine as the first surgeon in the world who succeeded in implanting an artificial cornea (alphacor). This revolutionary surgical intervention can help people who have lost their vision due to corneal damage and who have been irresponsive to other treatment methods. Alphacor is an artificial cornea made of a biocompatible, flexible, hydrogel material, relative to the material used for soft contact lenses. It consists of a central transparent zone with refractive properties and a periphery, which stimulates the restoration of the eye onto the foreign body (Lighe B 2002; Marilyn 2010; Mascai 2006).

**Dental implants :** Being an artificial substitute of the lost tooth, the dental implant is used in dental prosthetics as a support of bridges and crowns. There are several types of dental implants, generally classified as Osseo integrated and fibro integrated implants. Presently, the most commonly used and successful implants are the Osseo integrated titanium screw implants (Fig. 6), which are based on the fundamental inventions of the Swedish Professor Per-Ingvar Brånemark, who put the basis of contemporary implantology 30 years ago. He has proved experimentally

that the intraosseously implanted titanium is surrounded by a newly formed bone, adhering to it – a phenomenon, called “osseointegration”. This is a remarkable, rarely observed in the nature process – namely, the creation of a bond between the living tissue (bone) and the foreign body (titanium/metal). Thus, the structural and functional relationships between the bone and implant are formed, making the bone-implant complex a complete unit.

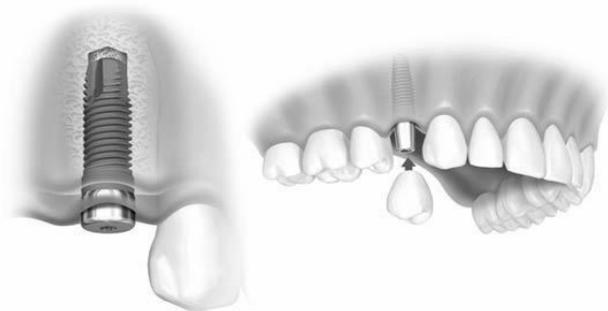


Fig. 6: Commonly used dental implants

After the rise of implantology, the variety of implants and implant systems is difficult to be described. Different criteria for implant classification are used. According to their shape, 98% of the modern implants are helical. According to the material of which they are made, titanium implants are mostly used, although there are some implants made of ceramics. In fact, the wide variety of implants is due to their most important part, the surface of the implant. For creating a maximum strong bone-implant bond and a large contact surface, the specialists test different types of implant surfaces and coatings. There are implants with various threads, specifically grooved apices and various coatings – hydroxyapatite or triphosphorous complexes, acid- or laser roughened surface (Godfredsen K 2001; Sykara SN 2000).

#### 1.1.2 CERAMIC BIOMATERIALS

In order to avoid the problems associated with random dissolution which include uncontrolled physical degradation, particulate release and long-term durability, the materials need to remain essentially soluble only to be removed by specific cell activity. Ceramic biomaterials have been developed that not only act as suitable substrates for bone mineralization by osteoblasts but are essentially insoluble in biological media and are resorbed when acted upon by osteoclasts (Lngstaff 2001).

#### ✓ CERAMIC BIOMATERIALS USED IN MEDICAL PRACTICE

##### Zirconium dioxide or zirconia ceramics (ZrO<sub>2</sub>):

It is a bioinert nonresorbable metal oxide which has a good chemical and dimensional stability, and a high strength and toughness (Piloni 1999). Currently, zirconia ceramic is being recognized for its high strength and surface finish, making this material potentially suitable for the highly loaded environments found in joint replacement. Biomedical grade Zirconia was introduced approximately 20 years ago to solve the problem of

alumina brittleness and the consequent potential failure of implants (Christel et al., 1988). Its color and excellent biocompatibility and mechanical properties have made it attractive for dental applications (Ahmad 1998; Meynberg 1995; Fritzsche 2003; Tinschert 2001; Glauser 2004). A prerequisite for successful bone implant integration is direct bone apposition which was observed at bone-zirconia interfaces in histological (Akagawa 1998; Akagawa 1993; Scarano 2003) and ultrastructural (Albrektsson 1985) studies suggesting that ZrO<sub>2</sub> may also be a suitable implant material. On the one hand, biomedical grade Zirconia exhibits the best mechanical properties of oxide ceramics: this is the consequence of phase transformation toughening, which increases its crack propagation resistance. The stress induced phase transformation involves the transformation of meta stable tetragonal grains to the monoclinic phase at the crack tip, which, accompanied by volume expansion, induces compressive stresses (Garvie 1975). On the other hand, due to this meta-stability, zirconia is prone to ageing in the presence of water (Lawson 1995). Up to date clinical reports appear to be again somewhat opposite where some results show excellent behavior of some femoral heads after several years in vivo (Caton 2004) while others show poor follow up results (Allain 1999) with severe wear and osteolysis around the implant. Few case studies report surface degradation of zirconia implants, which could be related to ageing (Haraguchi 2001; Catledge 2003).

#### **Alumina ceramics (Al<sub>2</sub>O<sub>3</sub>):**

Alumina ceramics have been used for implants and prostheses for several decades now (Hulbert 1970). The material is characterized by its excellent biocompatibility (Griss 1980) and high strength, hardness and fracture resistance (Green 1998; Munz 1999). The resultant high wear resistance is of particular interest for implant components with articulating surfaces like artificial joints. The outstanding wear resistance is the major reason for the predominant use of this material for the femoral joint head (Willmann 1998). A common material pairing used for hip arthroplasty is a femoral joint head made of alumina and an acetabular liner made of UHMWPE. Inauspiciously alumina is not suitable for 486 Bombac, D., Brojan, M., Fajfar, P., Kosel, F., Turk, R. RMZ-M&G 2007, 54 implant components with bone contact, because the material is bio inert and thereby no bony on growth, and subsequently loosening of the implant occurs (Fischer et al., 2005). No difference between the biocompatibility of zirconia and that of alumina ceramics has been found in the biological reaction in vivo. Furthermore, the wear factor of UHMWPE against zirconia ceramic is 40-60 % less than that against alumina ceramic counter faces and 10-20 % less than that against SUS 316L metal counter faces (Yen et al., 2001).

#### **Hydroxyapatite ceramic (HAC) granules:**

Hydroxyapatite ceramic (HAC) granules are used successfully world-wide as a bone substitute material because of their high biocompatibility. In an orthotropic site, such as a bony defect, bone formation occurs on ceramic surfaces. This newly formed bone bonds tightly to the ceramic surface without any mechanical interlock (Holtgrave et al., 1995).

#### **Bioactive glasses:**

Bioactive glasses have been used in many medical applications. However, due to their poor mechanical properties, these glasses cannot be used in load-bearing applications, whereas metallic alloys are still the materials of choice. It was recognized early on that one of the main applications of bioactive glasses could be coatings for prosthetic metallic implants.

#### **These coatings serve two purposes:**

Improving the osseointegration of the implants, and protecting the metal against corrosion from the body fluids and the tissue from the corrosion products of the alloys. Unfortunately, most of the attempts to coat metallic implants with bioactive glasses have had limited success due to poor adhesion of the coating and/or degradation of the glass properties during the coating procedure, typically enamelling, or flame or plasma spray coating (Lopez-Esteban et al., 2003). In recent years, transition metal nitrides like TiN, ZrN, TiAlN, NbN, TaN and VN were successfully used as protective coatings against wear and corrosion in order to increase the life expectancy of surgical implants and prosthesis (Braic 2005; Leng et al., 2001; Hubler et al., 2001).

#### **1.1.3 POLYMERIC BIOMATERIALS**

Polymeric biomaterials are used as a substitute for metal alloys in trauma and orthopaedic implant devices or as an aid at surgical procedures.

#### **✓ POLYMERIC BIOMATERIALS USED IN MEDICAL PRACTICE:**

##### **Ultra-high molecular weight polyethylene (UHMWPE):**

First polymeric material, used in medicine since the 1960s, was ultra-high molecular weight polyethylene (UHMWPE). It is a thermoplastic with extremely long chains and molecular weight numbering between 2 and 6 million. The longer chain serves to transfer load more effectively to the polymer backbone by strengthening intermolecular interactions. UHMWPE is highly resistant to corrosive chemicals, with exception of oxidizing acids and has extremely low moisture absorption, very low coefficient of friction, characteristic of self lubrication and high resistance to abrasion. The mechanical and tri-biological properties of UHMWPE favour its use as a bearing material in many joint replacement devices. UHMWPE is used in buttons to resurface the patella in total knee arthroplasty, in sleeves to permit semi-constrained rotation in elbow and wrist arthroplasty designs, and in counterfaces inserted into the glenoid in shoulder arthroplasty. However, for the purposes of this review we will focus on the most common uses of UHMWPE in medical devices, those of tibial bearings in knee arthroplasties and of acetabular bearings in hip arthroplasties (Kurtz et al., 1999). UHMWPE was first used clinically in 1962 and emerged as the dominant bearing material for total hip and knee replacements in the 1970s.

Since the 1980s UHMWPE is successfully used for spine implants (Kurtz SM 2004). Thus, even though UHMWPE components are typically in no imminent danger of wearing through during a patient's lifetime, the generation of particulate debris from the articulating surface has been associated with osteolysis and loosening of implants (Lewis G 1997; Schmalzried et al., 1992; Xenos et al., 1995; Livingston et al., 1997). To address these problems a highly cross linked UHMWPE materials were clinically introduced in 1998 and has rapidly become the standard of care for total hip replacements (LI et al., 1994; Premnath et al., 1996; Sauer et al., 1998; Mckellop 1998; Eyerer et al., 1990; Fischer et al., 1991; Klein et al., 19991). Another important medical advancement for UHMWPE in the past decade has been the increase in use of fibers for sutures, where maximum strength and minimum weight are required. It is ideal for orthopaedic implants, for example, as it allows smaller implants to be used, and is flexible and resistant to abrasion. Similarly, its strength can be used for surgical instruments for minimally invasive procedures ([www.dsm.com](http://www.dsm.com)).

### Polymethyl methacrylate (PMMA)

PMMA is the synthetic polymer of methyl methacrylate and is in field of medical technologies and implants used because of its good degree of compatibility with human tissue. In orthopaedics, PMMA bone cement is used to affix implants and to remodel lost bone. It is supplied as a powder with liquid methyl methacrylate (MMA). When mixed these yield dough like cement that gradually hardens. Surgeons can judge the curing of the PMMA bone cement by pressing their thumb on it. Although PMMA is biologically compatible, MMA is considered to be an irritant and a possible carcinogen and therefore PMMA has also been linked to cardiopulmonary events in the operating room due to hypotension (Ellis et al., 1974; Gresham et al., 1971; Hornsy et al., 1971; Philips et al., 1971; Orsini et al., 1987; Kaufmann et al., 2002). Bone cement acts like a grout and not so much like a glue in arthroplasty. Although sticky, it does not bond to either the bone or the implant, it primarily fills the spaces between the prosthesis and the bone preventing motion. A big disadvantage to this bone cement is that it heats to quite a high temperature while setting and because of this it kills the bone in the surrounding area. It has a Young modulus between the one of cancellous bone and the one of cortical bone, thus it is a load sharing entity in the body not causing bone re-sorption (Miller 2004). Dentures are often made of PMMA, and can be colour matched to the patient's teeth and gum tissue. In cosmetic surgery, tiny PMMA microspheres suspended in some biological fluid are injected under the skin to reduce wrinkles or scars permanently. PMMA also is used for replacement intraocular lenses in the eye when the original lens is removed in the treatment of cataracts. Hard contact lenses are frequently made of this material. Soft contact lenses are often made of a related polymer, where acrylate monomers containing one or more hydroxyl groups make them hydrophilic (Olson et al., 1998; Oshika et al., 1998; Kruger et al., 2000; Findl et al., 2005).

### Polyetheretherketone (PEEK):

Another polymeric material used as biomaterial for trauma, orthopaedic and spinal implanting is polyetheretherketones (PEEK). The remarkable mechanical, chemical resistance and biocompatible properties offered by Peek-Optima™ LT polymer, compounds and long fibre composites make it an attractive material to be considered for implant use. In consequence, these materials are undergoing evaluation for a variety of different implant applications. Developments are in progress in nearly every area of application where titanium is presently being used. The most important activities are based on orthopaedic applications for structural implants: in joint replacement systems and in spine surgery (especially for cages used in vertebral fusion surgery). Other developments are ongoing in cardiovascular applications, like heart valves and pacemakers, in dental implants for fixation of artificial teeth, housings for electronic devices, sensor housings and others (Victrex PEEK-OPTIMA™ Product Guide).

## II. LEGAL REGULATIONS IN THE EUROPEAN UNION

Medical devices and dental materials and are subject to legal specific regulations in EU. All these regulations deal with biocompatibility and effectiveness of the medical materials and devices. Everyone in the working in the field of medicine should be informed about the regulations and their responsibilities imposed by them (including adverse effect reporting).

### Definitions

According ISO 13485, medical device is "Any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices, providing information for medical purposes by means of in vitro examination of specimens derived from the human body and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means" (International standard organisation 2003). According to European Union Medical Devices Directive (MDD), "medical device" means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease

diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, control of conception and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means; 'accessory' means an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device (Directive 2001/83/EC, Regulation (EC) No 726/2004). Because the intended main function of dental materials is generally to replace lost tissue, these materials fall by definition into the jurisdiction of the MDD.

### Legal regulations

In the European Union (EU), a number of regulations must be followed for materials and devices used in medical and dental practice. The most important regulations are the MDD (Regulation (EC) No 726/2004) and the European Chemical Regulation for Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) (Regulation (EC) No 1907/2006). Besides the EU directive for medical devices, other directives are also applicable, including the following:

- Cosmetics (Cosmetics Regulation (EC) No 1223/ 2009, 2013), which comprises, among other things, oral hygiene products (Regulation (EC) No 1223/2009).
- Drugs the requirements and procedures for the marketing authorisation for medicinal products for human use, as well as the rules for the constant supervision of prodhttpucts after they have been authorised, are primarily laid down in Directive 2001/83/EC and in Regulation (EC) No 726/2004 (Directive 2001/83/EC, Regulation (EC) No 726/2004). The European Parliament adopted amendments to the proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009;
- Active, implantable medical devices such as heart pacemakers (Directive 2007/47/EC)
- In vitro diagnostics (98/79/EEC)

There are also regulations concerning waste disposal, environmental protection, and occupational safety. The directive 93/42/EEC on medical devices (MDD) was adopted on 14 June 1993 (Directive 2001/83/EC, Regulation (EC) No 726/2004 ). Directives of the EU are equivalent to laws and must be turned into national legislation within the given time limit by all member countries of the EU. Directives, like laws, are periodically amended. The MDD was amended in 2007 Directive 2007/47/EC of the European Parliament and of the Council amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and

Directive 98/8/EC concerning the placing of biocidal products on the market, with "Revision of the medical device directives", 2013. Retrieved 15 June 2014 (Directive 98/79/EC ; Revision of the medical device directives, 2013). Available standards (such as those of the International Organization for Standardization, or ISO) are used in most cases and presently are of high importance for fulfilling the essential requirements.

### How Medical Devices are Segmented in Europe

The MDD applies to a great variety of more than 400,000 different medical devices. Therefore, a classification system is necessary. This classification into four classes is based on the intended application of the products and the risk potential associated with each individual product (Schmalz G 1995). Essentially, all devices fall into four basic categories:

- Non-invasive devices
- Invasive medical devices
- Active medical devices
- Special Rules (including contraceptive, disinfectant, and radiological diagnostic medical devices)

Devices are further segmented into the classes noted below:

**Class I** – Provided non-sterile or do not have a measuring function (low risk).

**Class I** – Provided sterile and/or have a measuring function (low/medium risk)

Examples in dentistry include non-invasive products, such as adhesive bandages for small wounds; invasive products (for transient contact with the body, such as impression materials and materials for bite registration); reusable surgical instruments.

**Class IIa** (medium risk)

Examples in dentistry include surgically invasive products (for longer than transient contact with the body), such as pit and fissure sealants and filling materials and syringes and needles for dental anesthetic cartridges; active therapeutic products without potential risk, such as dental hand pieces; active diagnostic products, such as appliances for determining pulp vitality.

**Class IIb** (medium/high risk)

Examples in dentistry include dental implants; Contraceptives; condoms; active therapeutic appliances with potential risk, such as electrosurgical devices; ionizing radiation.

**Class III** (high risk)

Examples include products for life-maintaining functions; products with drug like effect. In general, class I is associated with low health risk, and class III devices carry the highest risk. The type of testing and the extent of individual requirements depend on the classification of the medical device. For instance, in contrast to class IIb devices, no clinical tests are mandatory for class IIa devices; clinical testing of class IIa devices is required only when clinical assessment cannot provide the necessary

information (Wachenhausen H 2002). Dental materials are usually classified under class IIa; exceptions include dental implants (class IIb) and root canal filling materials containing active pharmaceutical ingredients (class III). This category of materials must fulfil the relevant requirements of the drug directive.

According to the MDD, the responsibility for performance, safety, and quality of a medical device – that is, fulfilment of the essential requirements – always lies with the manufacturer. Importers may be responsible for products imported from countries outside the European Economic Area. In general, the manufacturers define the indications for use of their medical devices. A medical device that is in compliance (conformity) with the essential requirements of the MDD receives the CE label and can be launched on the market within the area of MDD jurisdiction. The respective process is therefore called conformity assessment. Various possibilities for such a conformity assessment are described in the MDD, depending on the class to which the individual medical device belongs.

**- Conformity assessment for class I devices:** This applies, for instance, to impression materials. Devices of class I can be assessed for conformity by the manufacturers themselves. The manufacturer, however, needs to have all information available for a clinical assessment of its devices.

**- Conformity assessment for class II and class III devices:** Medical devices of classes II and III must be assessed together with an external authority (“notified body”). Class II and class III devices are assessed for conformity by different processes. The manufacturer always uses the CE label at its own responsibility when all essential requirements are met and the stipulated conformity assessments have been successfully performed. In the case of class IIa products, either the manufacturer or one of its products can be certified by the notified body. If a manufacturer has been certified (complete quality assurance system), then the manufacturer can place the CE label on the devices it manufactures with no further involvement of a notified body. This policy is preferred by most manufacturers of dental materials of class II (e.g., restorative materials and alloys). For medical devices that contain pharmaceutically active agents (class III), a statement by the legal authority responsible for drugs is necessary during the conformity assessment. The execution of clinical studies is regulated in a specific paragraph of the MDD. Each clinical study has to be registered with the appropriate agency, and a number of requirements (such as approval by an ethics committee) have to be met before such a study can be initiated. These regulations are meant to protect patients who participate in these studies. The legal regulations of the MDD do not release dentists from their responsibility to inform patients independent of the manufacturer’s interest and to define the indications for each individual case within the scope of the specifications set by the manufacturer. Furthermore, a patient will most likely contact the dentist first if he or she has a problem with a material. In addition, it has been found in the past that various filling materials were labelled with CE (without clinical examination) but subsequently caused problems in patients (pain, tooth fractures). Therefore, if any doubt

exists, one should not just rely on the CE label but should critically question the statements associated with the material’s label. If a medical device is not applied by the dentist according to the manufacturer’s specifications (for example, use of an expired product or application of a product outside the range of indications), then this qualifies as malpractice. In this case, the injured person can claim compensation. Since June 2007, the new European regulation on registration, evaluation, and authorization of chemicals (REACH) has been in force (Council Directive 67/548 EEC ; Regulation (EC) No 1907/2006 ; Directive 1999/45/EC ). Its main purpose is a high level of protection of human health for consumers, workers, and the environment. It is directed at chemical elements and their compounds, preparations (mixtures or solutions composed of two or more substances), and articles (objects of special design) that mainly determines their functions. The responsibility for safe use lies with the manufacturer of the substances. Manufacturers and importers of chemicals have until 2018 to use a stepwise approach to register with the European Chemicals Agency (ECHA) in Helsinki all new and currently available (presently, approximately 30,000 marketed substances) chemicals that have a production volume of >1 ton (1,000 kg) per year. Particularly dangerous substances must pass an authorization procedure. Related legislation (such as that regarding product safety, construction products, and the health and safety of workers who handle chemicals) and other legislation that regulates chemicals (such as in cosmetics and detergents) are not replaced by REACH and will continue to apply. REACH has been designed not to overlap or conflict with other chemical legislation ( Regulation (EC) No 1907/2006;Regulation (EC) No 1907/2006). Medical doctors, dentists and dental laboratories belong mainly to the group of “downstream users” as long as they do not synthesize chemicals themselves. For them, it is important that scenarios of chemical exposure in dentistry be addressed in the basic documents for the substances. Therefore, the manufacturers of such substances must declare that, for these substances, the exposure scenarios in dentistry have been taken into account. Information for the downstream user is provided by information such as the safety data sheet. Safety data sheet are required also for dental materials (material safety data sheets - MSDS), and they can be requested from the manufacturer or obtained from the Internet (refer to the manufacturer’s Web site). These data sheets are an important source of information concerning the components of a material and its biocompatibility. However, because this is a shortcut standard information format, other information sources, such as the scientific literature, are still necessary.

**Labeling** of a substance, preparation, or medical device (including dental materials) serves as a tool for risk communication from the manufacturer to the user. Within the EU, a labelling system for chemicals is laid down in directives 67/548/EEC (substances) (Council Directive 67/548 EEC and 1999/45/EC)(preparations) (Directive 1999/45/EC). The latter regulation is obligatory in some EU countries (e.g., in Scandinavia) to be used for dental materials; in others, it is used by certain manufacturers.

A central aspect of these regulations is the use of specific symbols to visualize risks. These symbols are placed on the device together with "R-phrases" to further specify the risk. "S-phrases" describe safety advices for the material. The formulations of these sentences are standardized and have to be selected by the manufacturer according to the directive's defined procedure. If a dental material includes a danger label, the dentist should consult the safety data sheet for further information, especially concerning safety advice. After about 10 years of effort, a new regulatory body was developed by the United Nations and adopted in 2003: the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). The GHS will enter in the EU into force in 2008. It includes criteria for classifying health, physical, and environmental hazards, and it furthermore specifies which information should be included on labels of hazardous chemicals and on safety data sheets.

### III. CONCLUSION

A variety of different materials and processing technologies are available for medical applications, Which material should be used depends on the type of injury. Medical implants used for temporary healing should be made of conventional metallic biomaterials. The question of the long-term effects of bio-metal, on patients is very important. Further studies relating to long-term effects of materials on biological tissues are necessary, and are likely to lead to an increased understanding of the biocompatibility of materials in the future.

### REFERENCES

- [i]. Ahmad I. Yttrium-partially stabilized zirconium dioxide posts: an approach to restoring coronally compromised non vital teeth. *International Journal of Periodontics & Restorative Dentistry*. 1998; 18(5): 454-465.
- [ii]. Akagawa Y, Hosokawa R, Sato Y, Kamayama K. Comparison between free standing and tooth-connected partially stabilized zirconia implants after two years function in monkeys: a clinical and histologic study. *Journal of Prosthetic Dentistry*. 1998; 80(5): 551-558.
- [iii]. Akagawa Y, Ichikawa Y, Nikai H, Tsuru H. Interface histology of unloaded and early loaded partially stabilized zirconia endosseous implant in initial bone healing. *Journal of Prosthetic Dentistry*. 1993; 69(6):599-604.
- [iv]. Albrektsson T, Hansson HA, Ivarsson B. Interface analysis of titanium and zirconium bone implants. *Biomaterials*. 1985; 6(2):97-101.
- [v]. Allain J, Le Mouel S, Goutallier D, Voisin M C. Poor eighth year survival of cemented
- [vi]. Annual Book of ASTM Standards. Section 13 - Medical Devices and Services: Medical Devices, 1999.
- [viii]. Balazic M, Brojan M, Bombac D, Caram R Jr, Kosel F, Kopac J. Titanium and titanium alloy applications in medicine. *Surface Engineered Surgical Tools and Medical Devices*. Editors: Jackson J, Ahmed W, Springer, 2007; ISBN: 978-0-387-27026-5.
- [ix]. Balazic M, Brojan M, Bombac D, Caram R Jr., Kosel F, Kopac J. Titanium and titanium alloy applications in medicine. *Surface Engineered Surgical Tools and Medical Devices*. Editors: Jackson J, Ahmed W, Springer, 2007; ISBN: 978-0-387-27026-5.
- [x]. Bombac D, Brojan M, Krkovic M, Turk R, Zalar A. Characterization of titanium and stainless steel medical implants. 2007.
- [xi]. Braic M, Balaceanu M, Braic V, Vladescu A, Pavelescu G, Albulescu M. Synthesis and characterization of TiN, TiAlN and Technology TiN/TiAlN biocompatible coatings. *Surface and Coatings*. 2005; 200(1-4):1014-1017.
- [xii]. Breme J, Biehl V. *Metallic biomaterials. Handbook of Biomaterials Properties*. Editors: Black J, Hastings G, Springer, ISBN: 978-0-412-60330-3. 1998.
- [xiii]. Breme J, Biehl V. *Metallic biomaterials. Handbook of Biomaterials Properties*. Editors: Black J, Hastings G, Springer, 1998; ISBN: 978-0-412-60330-3.
- [xiv]. Catledge SA, Cook M, Vohra Y, Santos E M, Mc Clenny M D, Moore K D. Surface crystalline phases and nanoindentation hardness of explanted zirconia femoral heads. *Journal of Materials Science: Materials in Medicine*. 2003; 14(10):863-867.
- [xv]. Caton J, Bouraly JP, Reynaud P, Merabet Z. Phase Transformation in Zirconia Heads after THA Myth or Reality. *Proceedings of the Ninth BIOLOX Symposium*. 2004; 26-27: 73-74.
- [xvi]. Christel P, Meunier A, Dorlot JM, Crolet JM, Witvoet J, Sedel L, Boutin P. Biomechanical compatibility and design of ceramic implants for orthopedic surgery, *Bioceramics: material characteristics versus in vivo behaviour*. *Annals of the New York Academy of Sciences*. 1988; 523: 234-256.
- [xvii]. coatings for orthopedic metallic implants. *Journal of the European Ceramic Society*. 2003; 23(15): 2921-2930.
- [xviii]. Commission Regulation (EU) No 895/2014 of 14 August 2014 amending Annex XIV to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
- [xviii]. Council Directive 67/548 EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities*. 1967; P 196, 1-98.
- [xix]. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. *Official Journal of the European Communities*. L 169, 36:1-43 (12 July 1993); Directive 2001/83/EC, Regulation (EC) No 726/2004.
- [xx]. Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. <http://eurlex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31999L0045>

- [xxi]. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market. *Official Journal of the European Communities*. L 247, vol. 50 (21 Sep 2007)
- [xxii]. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. *Official Journal of the European Communities*. 1998; L 331(41) :1-37.
- [xxiii]. Ellis RH, Mullvein J. The cardiovascular effects of methylmethacrylate. *Journal of Bone and Joint Surgery*. 1974; 56(1): 59-61.
- [xxiv]. Eyerer P, Ellwanger R, Federolf HA, Kurth M, Madler H. Polyethylene. *Concise encyclopaedia of medical and dental materials*. Editors: Williams, D., Cahn, R., Pergamon, Oxford, 1990; ISBN: 978-0-080-36194-9.
- [xxv]. Findl O, Buehl W, Menapace R, Sacu S, Georgopoulos M, Rainer G. Long-term Effect of Sharp Optic Edges of a Polymethyl Methacrylate Intraocular Lens on Posterior Capsule Opacification: A Randomized Trial. *Ophthalmology*. 2005; 112(11): 2004-2008.
- [xxvi]. Fischer H, Niedhart C, Kaltenborn N, Prange A, Marx R, Niethard FU, Telle R. Bioactivation of inert alumina ceramics by hydroxylation. *Biomaterials*. 2005; 26(31):6151-6157.
- [xxvii]. Fisher J, Dowson D. Tribology of total artificial joints. *Proceedings of the Institution of Mechanical Engineers, Part H*. 1991; 205(2):73-79.
- [xxviii]. Fritzsche, J. Zirconium oxide restorations with the DCS precedent system. *International Journal of Computerized Dentistry*. 2003; 6(2):193-201.
- [xxix]. Garvie RC, Hannink RHJ, Pascoe RT. Ceramic Steel?. *Nature*. 1975; 258:703-704.
- [xxx]. Glauser R, Sailer I, Wohlwen A, Studer S, Schibli M, Schärer P. Experimental zirconia abutments for implant supported single-tooth restorations in esthetically demanding regions: 4-year results of a prospective clinical study. *The International Journal of Prosthodontics*. 2004; 17(3): 285-290.
- [xxxi]. Godfredsen K, Berglundh T, Lindhe J: Bone reactions adjacent to titanium implant with different surface characteristic subjected to static load A study in the dog *Clinical oral Implants Research* 2001; 12:196-2019
- [xxxii]. Green DJ. *An Introduction to the Mechanical Properties of Ceramics*. Cambridge University Press, 1998. ISBN: 978-0-521-59913-9.
- [xxxiii]. Gresham GA, Kuczyński A, Rosborough D. Fatal fat embolism following replacement arthroplasty for transcervical fracture of femur. *British Medical Journal*. 1971; 2 (5762):617-619.
- [xxxiv]. Griss P, Werner E. Aluminac ceramic, bioglass and silicon nitride. A comparative biocompatibility study. *Mechanical Properties of Biomaterials*. Editors: Hastings G W, Williams, D F, John Wiley, 1980. pp. 217-225, ISBN: 978-0-471-27761-3.
- [xxxv]. Haraguchi K, Sugano N, Nishii T, Sakai T, Yoshikawa H, Ohzono K. Phase transformation of a zirconia ceramic head after total hip arthroplasty. *Journal of Bone and Joint Surgery*. 2001; 83 (7): 996-1000.
- [xxxvi]. Holtgrave EA, Donath H. Response of odontoblast-like cells to hydroxyapatite ceramic granules. *Biomaterials*. 1995; 16(2):155-159.
- [xxxvii]. Homsy CA, Tullos HS, Anderson MS, Diferrante NM, King JW. Some physiological aspects of prosthesis stabilization with acrylic polymer. *Clinical Orthopaedics and related research*. 1972; 83:317-328.
- [xxxviii]. Hübler R, Cozza A, Marcondes TL, Souza RB, Fiori FF. Wear and corrosion protection of 316-L femoral implants by deposition of thin films. *Surface and Coatings Technology*. 2001; 142-144:1078-1083.
- [xxxix]. Hulbert SF, Young FA, Mathews R S, Klawitter JJ, Talbert CD, Stelling FH. Potential of ceramic materials as permanently implantable skeletal prostheses. *Journal of Biomedical Materials Research*. 1970; 4(3): 433-456.
- [xl]. International Standard Organisation. ISO 13485:2003
- [xli]. Kaufmann TJ, Jensen ME, Ford G, Gill LL, Marx WF, Kallmes DF. Cardiovascular Effects of Polymethylmethacrylate Use in Percutaneous Vertebroplasty. *American Journal of Neuroradiology*. 2002; 23(4): 601-604.
- [xlii]. Klein PG, Gonzalez-Orozco J A, Ward I M. Structure and morphology of highly oriented radiation cross linked polyethylene fibres. *Polymer*. 1991; 32(10):1732-1736.
- [xliii]. Kruger A J, Schauersberger J, Abela C, Schild G, Amon M. Two-year results: sharp vs. rounded optic edges on silicone lenses. *Journal of Cataract & Refractive Surgery*. 2000; 26(4): 566-570.
- [xliv]. Kumar GVP, Mathew L. "Effects of Stent Design Parameters on the Aortic endothelium". 13th International Conference on Biomedical Engineering, Singapore, 3-6 December 2008. 23. pp. 1539-42.
- [xlv]. Kumar GVP, Mathew L. "New Stent Design for Percutaneous Aortic Valve Replacement". *International Journal of Cardiovascular Revascularization Medicine* 10 (2): 121-4.
- [xlvi]. Kurtz SM. *The UHMWPE Handbook: Ultra-High Molecular Weight Polyethylene in Total Joint Replacement*. Academic Press, New York, 2004. ISBN: 978-0-124-29851-4.
- [xlvii]. Langstaff S, Sayer M, Smith T J N, Pugh S.M. Resorbable bioceramics based on stabilized calcium phosphates. Part II: evaluation of biological response. *Biomaterials*. 2001; 22(2):135-150.
- [xlviii]. Lawson, S. Environmental degradation of zirconia ceramics. *Journal of the European Ceramic Society*. 1995; 15(6): 485-502.
- [xlix]. Leng YX, Sun H, Yang P, Chen Y, Wang J, Wan GJ, Huang N, Tian X B, Wang LP, Chu PK. Biomedical properties of tantalum nitride films synthesized by reactive magnetron sputtering. *Thin Solid Films*. 2001; 398-399: 471-475.
- [l]. Lewis G. Polyethylene wear in total hip and knee arthroplasties. *Journal of Biomedical Materials Research*. 1997; 38(1):55-75.

- [li]. Li S, Burstein A H. Ultrahighmolecular weight polyethylene. The material and its use in total joint implants. *Journal of Bone and Joint Surgery*. 1994; 76 A(7):1080-1090.
- [lii]. Lighe B: Soft lens materials. In Kfron, ed. *Contact Lens Practice*. Oxford: Butterworth-Heinemann, 2002: 81.
- [liii]. Livingston BJ, Chmell MJ, Spector M, Poss R. Complications of total hip arthroplasty associated with the use of an acetabular component with a Hylamer liner. *Journal of Bone and Joint Surgery*. 1997; 79 A(10):1529-1538.
- [liv]. Lopez-Esteban S, Saiz E, Fujino S, Oku T, Suganuma K, Tomsia A P. Bioactive glass.
- [lv.] Macsai et al. Visual outcomes after accommodating intraocular lens implantation. *J Cataract Refract Surg*. 2006; 32(4): 628-33.
- [lvi]. Marilyn Haddrill. "Crystalens & Accommodating Intraocular Lenses for Cataract Surgery". *All About Vision*. Retrieved 2010-05-11.
- [lvii]. Mc Kellop A. Wear assessment The adult hip Editors: Callaghan, JJ, Rosenberg AG, Rubash HE, Lippincott-Raven Publishers, Philadelphia, 1998; ISBN: 978-0-397-51704-6.
- [lviii]. Meyenberg K H, Luthy H, Schärer P, Zirconia Posts: New All-Ceramic Concept for Nonvital Abutment Teeth. *Journal of Esthetic Dentistry*. 1995; 7(2):73-80.
- [lix]. Miller, M.D. *Review of Orthopaedics* 4th Edition. W.B. Saunders Company, 2004. ISBN: 978-0-721-60364-3, 129.
- [lx]. Munz D, Fett T. *Ceramics: Mechanical Properties, Failure Behaviour, Materials Selection* 1st Review of materials in medical applications 499 RMZ-M&G 2007, 54Ed., Springer Verlag, 1999. ISBN: 978-3-540-65376-9.
- [lxi]. Olson RJ, Crandall AS. Silicone vs polymethylmethacrylate intraocular lenses with regard to capsular opacification. *Ophthalmic Surgery and Lasers*. 1998; 29(1): 55-58.
- [lxii]. Orsini EC, Byrick RJ, Mullen J B M, Kay JC, Waddell J P. Cardiopulmonary function and pulmonary microemboli during arthroplasty using cemented or 494 Bombač, D., Brojan, M., Fajfar P, Kosel F, Turk R. *RMZ-M&G* 2007, 54 non-cemented components. *Journal of Bone and Joint Surgery*. 1987; 69(6): 822-832.
- [lxiii]. Oshika T, Nagahara K, Yaguchi S. Three-year prospective, randomized evaluation of intraocular lens implantation through 3.2mm and 5.5 mm incisions. *Journal of Cataract & Refractive Surgery*. 1998; 24(4): 509-514.
- [lxiv]. Phillips H, Cole PV, Lett in *AWF Cardiovascular effects of implanted acrylic bone cement*. *British Medical Journal*. 1971; 3(5772): 460-461.
- [lxv]. Piconi C, Maccauro G. Zirconia as a ceramic biomaterial. *Biomaterials*. 1999; 20(1):1-25.
- [lxvi]. Praveen Kumar GVP, Mathew L. "Design for Percutaneous Aortic Valve Stent". *International Conference on Biotechnology Proceedings*, VIT University, Feb 8, 2008. pp. 139-40.
- [lxvii]. Premnath V, Harris WH, Jasty M, Merrill EW. Gammasterilization of UHMWPE articular implants: an analysis of the oxidation problem. *Biomaterials*. 1996; 17(18):1741-1753.
- [lxviii]. Ratner BD, Schoen F, Hoffman A, Lemons J. *Biomaterials Science: An Introduction to Materials in Medicine*. Elsevier Science & Technology Books, 2004; ISBN: 978-0-125-82463-7.
- [lxix]. Ratner, B.D., Schoen, F., Hoffman, A., Lemons, J. (2004): *Biomaterials Science: An Introduction to Materials in Medicine*. Elsevier Science & Technology Books, ISBN: 978-0-125-82463-7.
- [lxx]. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (Text with EEA relevance). *Official Journal of the European Union*. L 342/59 (22 Dec 2009).
- [lxxi]. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. *Official Journal of the European Union*. L 396, vol. 49/1 (30 Dec 2006).
- [lxxii]. Revision of the medical device directives, 2013, Retrieved 15 June 2014, [http://ec.europa.eu/health/medical-devices/documents/revision/index\\_en.htm](http://ec.europa.eu/health/medical-devices/documents/revision/index_en.htm)
- [lxxiii]. Sauer WL, Anthony M E. Predicting the clinical wear performance of orthopaedic bearing surfaces. *Alternative bearing surfaces in total joint replacement*. Editors: Jacobs JJ, Craig, TL, American Society for Testing and Materials, West Conshohocken. 1998; ISBN: 978-0-803-12490-5.
- [lxxiv]. Scarano A, Di Carlo F, Quaranta M, Piattelli A. Bone response to Zirconia ceramic implants: An experimental study in rabbits. *Journal of Oral Implantology*. 2003; 29(1):8-12.
- [lxxv]. Schmalz G. *Biological Evaluation of Medical Devices: A Review of EU Regulations, with Emphasis on In Vitro Screening for Biocompatibility*. *ATLA*. 1995; 23:469-473.
- [lxxvi]. Schmalzried TP, Kwong LM, Jasty M, Sedlacek RC, Haire TC, O'Connor DO, Bragdon CR, Kabo JM, Malcolm AJ, Harris WH. The mechanism of loosening of cemented acetabular components in total hip arthroplasty. Analysis of specimens retrieved at autopsy. *Clinical Orthopaedics and related research*. 1992; 274: 60-78.
- [lxxvii]. Sumita M, Hanawab T, Teoh SH. Development of nitrogen containing nickel-free austenitic stainless steels for metallic biomaterials - review. *Materials Science and Engineering*. 2004; 24(6-8):753-760.
- [lxxviii]. Sumita, M., Hanawab, T., Teoh, S.H. (2004): *Development of nitrogen containing nickel-free austenitic stainless steels for metallic biomaterials- review*. *Materials Science and Engineering: C*; Vol. 24, No. 6-8, pp. 753-760.
- [lxxix]. Sykara S N, Lacopino AM, Marker VA, Triplett RG, Woody RD. *Implant material, designs and surface topographies: Their effect on osseointegration Literature Review*. *Oral Maxillofac Implants*. 2000; 15(5):675-690.

[lxxx]. Tinschert J, Natt G, Mautsch W, Spiekermann H, Anusavice K J. Marginal fit of alumina and zirconia-based fixed partial dentures produced by a CAD/CAM system. *Operative dentistry*. 2001; 26(4): 367-374.

[lxxxi]. Wachenhausen H. [Legal requirements for clinical testing.] [in German] *Medizinprodukte Journal*. 9, 80 (2002).

[lxxxii]. Williams, D.F. (1993): Volume 14: Medical and Dental Materials. *Materials Science and Technology: A Comprehensive Treatment*. Editors: Cahn, R.W., Haasen, P., Kramer, E.J., Wiley-VCH, ISBN: 978-3-527-26825-2.

[lxxxiii]. Williams, D.F. Volume 14: Medical and Dental Materials. *Materials Science and Technology: A Comprehensive Treatment*. Editors: Cahn RW, Haasen P, Kramer E J, Wiley-VCH, ISBN: 978-3-527-26825-2.1993.

[lxxxiv]. Willmann, G. Überlebensrate und Sicherheit von keramischen Kugelköpfen für Hüftendoprothesen (Survival rate and reliability of ceramic femoral heads for total hip arthroplasty). *Materialwissenschaft und Werkstofftechnik*. 1998; 29(10):595-604.

[lxxxv]. [www.dsm.com/en\\_US/html/hpf/dyneema\\_purity.htm](http://www.dsm.com/en_US/html/hpf/dyneema_purity.htm).

[lxxxvi]. Xenos JS, Hopkinson WJ, Callaghan JJ, Heekin RD, Savory CG. Osteolysis around an uncemented cobalt chrome totalhip arthroplasty: Polyethylene wear. *Clinical Orthopaedics and related research*. 1995; 317:29-36.

[lxxxvii]. Yen SK, Guo MJ, Zan HZ. Characterization of electrolytic ZrO<sub>2</sub> coating on Co-Cr-Mo implant alloys of hip prosthesis. *Biomaterials*. 2001; 22(2): 125-133.

[lxxxviii]. Zirconia-polyethylene total hip replacements. *Journal of Bone and Joint Surgery*. 1999; 81(5): 835-842.

**Address for Correspondence** : Mrs. Mamillapalli Vani, Dept. of Pharmacognosy & Phytochemistry, Viaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Viyawada-521108, Andhra Pradesh, India. Mobile no. 9704625782. [vanimamillapalli@yahoo.co.in](mailto:vanimamillapalli@yahoo.co.in)

\*\*\*\*\*