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Biomaterials Evaluation: Conceptual Refinements and Practical Reforms

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Abstract

Regarding the widespread and ever-increasing applications of biomaterials in different medical fields, their accurate assessment is of great importance. Hence the safety and efficacy of biomaterials is confirmed only through the evaluation process, the way it is done has direct effects on public health. Although every biomaterial undergoes rigorous premarket evaluation, the regulatory agencies receive a considerable number of complications and adverse event reports annually. The main factors that

challenge the process of biomaterials evaluation are dissimilar regulations, asynchrony of biomaterials evaluation and biomaterials development, inherent biases of postmarketing data, and cost and timing issues. Several pieces of evidence indicate that current medical device regulations need to be improved so that they can be used more effectively in the evaluation of biomaterials. This article provides suggested conceptual refinements and practical reforms to increase the efficiency and effectiveness of the existing regulations. The main focus of the article is on strategies for evaluating biomaterials in US, and then in EU.

Keywords

biomaterials evaluation, safety, performance, premarket evaluation, postmarket surveillance

Introduction

Biomaterials: Definition, Classification and Applications

Although there are several instances that have historically demonstrated the use of man-made structures as artificial organs in ancient times, the science and engineering of biomaterials has only a half-century history.[1] There is not a consensus over the definition of biomaterials among authors. In the past, biomaterials were defined as “non-vital materials used in medical devices, intended to interact with biological systems.” In this definition, biomaterials were considered as a structural component of medical devices and their evaluation was a part of the evaluation process of medical devices. In the newer definition, biomaterial is any material (other than drugs) that interacts with living tissues and performs a “particular function” without causing adverse effects.[2,3] Particular functions intended for biomaterials include (1) measurement of biomarkers and diagnosis of diseases, (2) enhancement of tissue functions, and (3) total/partial substitution of a damaged tissue or organ. In this definition, biomaterials are considered as an independent category of medical devices that require the accurate recognition of their types, features, and applications to allow appropriate evaluation.

Traditionally, biomaterials have been classified based on their chemical composition into metallic, polymeric, ceramic, and composite biomaterials.[4] This kind of classification is simple, but it is neither all-encompassing nor technically beneficial. Merely limiting the widespread scope of biomaterials to metallic, polymeric, ceramic, and composite will lead to ignorance of the definitive characteristics of these diverse and ever-growing classes of medical devices. In general, because of the direct contact of biomaterials with living tissues, characteristics that describe the type and duration of the biomaterial-tissue interactions should be considered in their classification.

In the past, biomaterials were mainly used for substitution of tissues damaged by disease or traumas. Nevertheless, in the last 2 decades, advances in fabrication and characterization of materials on one hand, and the evolution of regenerative strategies in medicine alongside with groundbreaking successes in cellular and molecular biology and genetics on the other hand, provided a substrate in which new classes of biomaterials with innovative applications were developed. The emerging biomaterials are not only intended to restore the structure and function of damaged tissues but also to regenerate them via active and targeted interactions. Tissue engineering scaffolds, injectable hydrogels, and delivery vehicles for cells, genes, and drugs are examples of emerging biomaterials.[5,6]

Biomaterials Evaluation

Biomaterials evaluation encompasses the assessment of their safety and performance. As stated in FDA's Medical Device User Fee Act (MDUFA) and EU Regulation on Medical Devices, safety and performance of medical devices are of equal importance and should be taken into account concurrently and conjointly.[7,8]

The safety of a biomaterial should be viewed from a risk management perspective, and its complete life span should be considered in order to analyze its associated risks. Generally, not only the biomaterial but also its potential degradation products and sterilization residuals should not cause any harmful local or systemic effects in host tissues. A wide range of in vitro and in vivo tests may be used to evaluate cytotoxicity, genotoxicity, pyrogenicity, local effects following implantation, hemocompatibility, sensitization potential and systemic toxic effects of biomaterials. If further information on the carcinogenicity or reproductive/developmental toxicity is published, they will also be considered. In very rare cases, additional tests are also carried out if required by regulators.[9]

Several methods have been developed and standardized to study each of the above-mentioned potential effects of biomaterials. For example, hemocompatibility is assessed via hemolysis, medical device–mediated complement activation and thrombogenicity. Furthermore, there are several ways to perform a special test. For instance, hemolytic properties of (bio)materials could be tested according to the guidelines of ASTM F 756-00. However, some researchers believe that ASTM F 756-00 is developed to test the hemolytic properties of specific materials, so blood compatibility of whole medical devices cannot be evaluated merely via this standard. These researchers suggest to implement ASTM F756-00 as a starting point to develop a protocol for hemolysis test.[10,11]

Among different available approaches, ISO 10993 standards provide a framework of guidelines for biological safety assessment of medical devices. ISO 10993 is composed of 20 parts. Table 1 summarizes the title and the last version of each parts.

Table 1. ISO 10993 Series of Standards for Evaluating Biological Safety of Medical Devices.

Part Number	Title	Last Updated Version	Reference
1	Evaluation and testing within a risk management process	2009	12
2	Animal welfare requirements	2006	13
3	Tests for genotoxicity, carcinogenicity, and reproductive toxicity	2014	14
4	Selection of tests for interactions with blood	2002	15
5	Tests for in vitro cytotoxicity	2009	16
6	Tests for local effects after implantation	2016	17
7	Ethylene oxide sterilization residuals	2008	18
8	Selection and qualification of reference materials for biological tests	2001	19
9	Framework for identification and quantification of potential degradation products	1999	20
10	Tests for irritation and skin sensitization	2010	21
11	Tests for systemic toxicity	2006	22
12	Sample preparation and reference materials	2012	23
13	Identification and quantification of degradation products from polymeric medical devices	1998	24
14	Identification and quantification of degradation products from ceramics	2001	25
15	Identification and quantification of degradation products from metals and alloys	2000	26
16	Toxicokinetic study design for degradation products and leachables	1997	27
17	Establishment of allowable limits for leachable substances	2002	28
18	Chemical characterization of materials	2005	29
19	Physicochemical, morphological, and topographical characterization of materials	2006	30
20	Principles and methods for immunotoxicology testing of medical devices	2006	31
22	Guidance on nanomaterials	2017	32
33	Guidance on tests to evaluate genotoxicity—Supplement to ISO 10993-3	2015	33

On the other hand, every biomaterial is manufactured for a specific purpose. The clinical effectiveness of a biomaterial is proved only when it can produce the intended effect(s) for the relevant medical condition. To demonstrate the claimed performance of a biomaterial, its technical functions should be verified as well. For instance, in parts 2 and 3 of ISO 5840, material properties and mechanical features that affect the performance of heart valve substitutes are declared.[34,35] Guidelines on test methods and acceptable values for each of the functional attributes are also given in these standards.

Biomaterials Evaluation Procedures

The evaluation of biomaterials is performed in accordance with the process used to evaluate medical devices. That is why sometimes biomaterials and medical devices are used as interchangeable terms in the following.

Biomaterials evaluation process divides into premarket evaluation and postmarket surveillances. US and EU, as the largest biomaterials markets, implement somewhat different routes for biomaterials evaluation.

Premarket evaluation

The Food, Drug, and Cosmetics Act (FD&C Act) has established FDA regulations for medical devices to ensure their safety and performance. Generally, for a given biomaterial to be sold in US, whether it has been manufactured in US or not, a marketing application is submitted to be reviewed by Center for Devices and Radiological Health (CDRH).[36] FDA evaluates biomaterials based on their level of risk (Table 2).

Table 2. FDA's Risk-based Classification of Medical Device.[37]

Class	Level of Risk	Description	Approval Requirements	Examples
I	Low	Simple, well established, with minimal controls for user	General controls	Wound dressing, zinc oxide-eugenol dental cement
II	Medium	Simple to medium complexity, with existing products on the market	General controls and special controls	Nonabsorbable surgical suture, Gutta Percha
III	High	New technology or life-supporting	General controls and premarket approval	Aortic stent, drug-containing bone grafting materials

Concisely,

- Almost all class III biomaterials are subject to premarket approval (PMA) application.
- If "substantial equivalence" is available for a class II biomaterial, a 510(k) notification should be submitted. Substantial equivalence means that the safety and performance of the new medical device is similar to a device that is already on the market (a predicate device). In other words, it is possible for a newer version of an existing biomaterial to enter the market in a less cumbersome way via 510(k) submission. The 510(k) does not mandate manufacturers to perform clinical trials; thus, it is a less stringent process than PMA evaluation.
- Most of the biomaterials in class I are exempt from premarket evaluation. However, the safety of all biomaterials must be established in any case. In the case of in vitro diagnostic devices, biocompatibility assessment is not required. Because they do not directly or indirectly contact the body.[38,39]

The European Medical Device Regulation was implemented in May 2017. In the EU, local private for-profit organizations called Notified Bodies are responsible for the evaluation of medical devices. Regulation of biomaterials (and medical devices) in Europe is based on Medical Device Directives (MDDs), including Active Implantable Medical Device Directive (AIMDD 90/385/EE), Medical Device Directive (MDD 93/42/EEC), and In Vitro Diagnostic Medical Device Directive (IVDMDD 98/79/EC).[8]

The main criterion of a biomaterial to be approved in the EU is that its benefits outweigh its risks, and it possesses the claimed performance.[40] Once a biomaterial is approved, it can hold a CE (Conformity European) mark, and only in this case can it be available in the European market.

In the EU, the selection of the appropriate procedure to evaluate a biomaterial is determined based on the biomaterial's class of risk. There are some differences between classification of biomaterials in US and EU. The EU classification has determined that class I refers to "low risk" biomaterials which are non-invasive and have no interaction with body tissues. Class IIa and IIb are the biomaterials with "medium risk." The level of invasiveness of the biomaterials in the Class IIb are higher, thus they are subject to more special controls. Biomaterials in the Class III are high risk and scientific review of their safety and performance is required during their premarket approval procedure (Table 3). The conformity assessment of Class III biomaterials is similar to class IIb, except their approval is dependent on the submission of design documents and relevant technical files to be completely reviewed by the Notified Bodies.[40,41]

Table 3. Conformity Assessment Route and the Related Annexes of the Directive 93/42/EEC, as Amended for the Assessment of Different Classes of Biomaterials in EU.[41]

	Biomaterial's Class					
Related Annexes	I	I Sterile	I Measure	IIa	IIb	III
II (– section 4)		•	•	•	•	
II (+ section 4)						•
III					•	•
IV		•	•	•	•	•
V		•	•	•	•	•

VI		•	•	•	•	
VII	•	•	•	•		

Generally, for medical devices requiring full PMA, EU evaluations require less time than FDA processes. In 2012, California Healthcare Institute and Boston Consulting Group conducted a comparative study on 46 medical devices approved through PMA. The study revealed that evaluations in EU last on average 3 years less than the US. However, the approval lag time between US and EU is much less for 510(K) and class I devices.[42]

Postmarket surveillances

After the release of biomaterials in the American or European markets, postmarket surveillances are performed to assess their long-term safety. Because clinical trials are not mandatory for the approval of all biomaterials, postmarket surveillances are of great importance in long-term evaluations of safety and performance. Another reason to perform postmarket surveillances is because clinical trials inherently cannot detect some "adverse events" because of the limited number of enrolled subjects or the limited time that could be allocated for clinical trials.[43]

One among many examples that illustrates the need to perform biomaterials postmarket surveillances is "very late stent thrombosis (VLST)" of drug-eluting coronary stents. VLST is a catastrophic event that could lead to the patient's death. It occurs at least one year after the implantation of the biomaterial via percutaneous coronary intervention; thus, it is unlikely to be demonstrated with premarket evaluation.[44]

In the US, based on Section 522 of the Federal Food, Drug and Cosmetic Act, FDA has the authority to mandate manufacturers to perform postmarket surveillances if their products belong to class II or III and meet any of the following conditions:

1. The failure of the device could cause severe health consequences.
2. The device is planned to be implanted in the body for at least 1 year.
3. The device has a significant use in kids.
4. The device is a "life-sustaining" or "life-supporting" device and is used outside a device user facility.[43]

Special programs are developed to facilitate the postmarket surveillance of medical devices in the US. Manufacturers and consumers of medical devices report adverse events by Medical Device Report and Med Watch programs, respectively.[45,46] When postmarket surveillances find potential complications in a device, safety alerts are issued by the FDA to patients and clinicians. If the studies reflect systemic concerns about a device, the manufacturer must conduct a recall. According to FDA, "A recall is an action taken to address a problem with a medical device that violates FDA law. Recalls occur when a medical device is defective, when it could be a risk to health, or when it is both defective and a risk to health."[47]

Recalls do not necessarily mean that the device should not be used anymore; rather it could simply indicate the device needs to be checked, adjusted, or fixed.

To better perform postmarket surveillances, device manufacturers are required to mark the devices with a unique device identifier (UDI). UDI facilitates the traceability of devices and accelerates the identification of devices with adverse events. Information about devices that hold UDI are available via the Global UDI Database (GUDID).[48]

In the EU, after a biomaterial's safety and performance is approved by a Notified Body, its postmarket surveillances is conducted under the supervision of a Competent Authority (CA). The basic principles to perform postmarket surveillances are outlined by Medical Device Directives. Further details and templates for collecting data and reporting adverse events are provided by Non-Binding European Commission guidance documents. Recall data and adverse event reports gathered by CAs are submitted to the European Databank on Medical Devices (EUDAMED). EUDAMED enables information transfer between CAs and the European Commission's Enterprise and Industry Directorate General.[49]

In order to reduce the risk of death or to avoid endangering the patient's health, manufacturers take Field Safety Corrective Actions (FSCAs) in the case of the defective approved devices. Based on the level of the risk caused by device malfunction, appropriate actions (varied from changes in labeling to complete removal from the market) will be taken.[50]

Examples of Why Biomaterials Evaluation Processes Need to Be Improved

In March 2010, French Agency for the Safety of Health Products (AFSSAPS) removed breast implants manufactured by Poly Implant Prothèse (PIP) from the market. Further investigations revealed that PIP implants were made of a nonmedical silicone gel without "biocompatibility" assessment of the material. The PIP scandal was not publicized until a middle-aged recipient of PIP died of an infrequent cancer called Anaplastic Large-Cell Lymphoma (ALCL). The number of PIP implant recipients estimated 30,000, in France alone.[51,52]

In August 2010, Articular Surface Replacement (ASR) hip implants produced by DePuy were recalled from the market. The number of ASR implants sold previously was more than 93,000 units. This was despite the several individual and organizational reports that have declared complications related to ASR implants earlier. For example, the Australian National Joint Replacement Registry report in 2007 indicated that the revision rate of ASR implants was higher than the expected rate for hip arthroplasty revisions (5.16% to 1%, respectively).[53,54]

The above examples occurring in the same year reveal that pre- and postmarket vigilance of biomaterials need to be improved.

Challenges in Biomaterials Evaluation

Evaluation of medical devices in general, and biomaterials in particular, is a challenging process. The following are the current challenges of biomaterials evaluation:

1. **Asynchrony of biomaterials evaluation and biomaterials development:** Evaluation of biomaterials has not kept pace with the development of new biomaterials. According to the "Innovation or Stagnation" report issued by FDA in 2004: "Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated."[55]

2. **Dissimilar regulations:** Approval requirements for a specific biomaterial are not the same in different regulatory systems. For example, the minimum clearance criterion of FDA for GuardWire—a coronary guidewire with an elastomeric balloon used in angioplasty—was a multicenter randomized controlled trial performed on 800 patients.[56] Meanwhile, the European Regulator required PercuSurge, the manufacturer of Guardwire, to perform a 22-patient study with no control group.[57] Dissimilar regulations for a specific product makes development of biomaterials a costly and time-consuming process. Recent ISO refinements, particularly in biological assessment of medical devices, has increased the consistency between ISO and FDA guidelines. However, there is still not an overall standard approach covering all classes of medical devices. Remaining inconsistencies in evaluation procedures is still the main source of confusing and inefficient assessment processes.[58]
3. **Inherent biases of postmarketing data:** There is no guarantee that the data provided to the regulatory agencies by health associate professionals or manufacturers are free of bias. Adverse events may not be reported transparently and accurately. Therefore, it is better not to rely on this information unconditionally. FDA uses Medical Device Reporting (MDR) to collect information and assess the risks associated with marketed devices. According to the FDA: "Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use."[59]
4. **Costs and timing:** There is no doubt that improving the quality of human life is dependent on innovative medical solutions. The evaluation of biomaterials should be not only accurate but also agile and economically beneficial. In 2010, the data from a survey of over 200 American companies in the field of medical technology showed that the approximate cost for a low- to moderate-risk medical device to be cleared via 510(k) was US$31 million. The average cost to bring a high-risk device "from concept to clearance" via PMA was approximately US$94 million. The participants also claimed that they should experience a 31-month review time for their new products from the first communication to clearance.[60] Regarding the significant approval costs and prolonged delays in FDA compared to the corresponding processes in the EU, FDA critics argue that the US will no longer be able to compete in global medical device markets.[61]

   Costs and timing-related issues do not only decelerate the development of new biomaterials, but also hinder the availability of new drugs. Developing new antiviral vaccines requires an average of 8 to 12 years and US$2 billion.[62] This demonstrates that global health is not prepared to confront the emerging threats.

Discussion

In order to improve biomaterials evaluation, the following conceptual refinements and practical reforms are suggested:

Conceptual refinements: An inclusive classification of biomaterials is essential to cover key aspects and provide profound insights about the completely different types and interactions of

biomaterials with surrounding tissues. In other words, the inclusive classification is one of the prerequisites to establish efficient regulations for biomaterials evaluation. In Table 4, a number of criteria to classify the biomaterials is suggested, which provides a broad overview of classic and emerging biomaterials. For instance, classification based on structural integrity divides biomaterials into porous biomaterials and nonporous biomaterials. These 2 classes of biomaterials have distinctive interactions with surrounding tissues. For example, it has been well demonstrated that in porous implants with pore diameters ≥100 μm, bone ingrowth facilitates implant fixation. On the contrary, in nonporous implants and implants with smaller pores, a loose fibrous capsule forms at the interface, which increases the risk of failure. Therefore, in porous biomaterials, porosimetry analysis should be used to measure pore parameters including volume, size, interconnectivity, and distribution.[63]

Table 4. Classification of Biomaterials.

Classification Basis	Classes of Biomaterials
Chemical composition	Metallic, polymeric, ceramic, composite
Origin	Natural, synthetic, hybrid (semisynthetic)
Dimensions	Macrometric, micrometric, nanometric
Interaction with living tissues	Bioinert, bioactive
Biodegradability	Biostable, biodegradable
Structural integrity	Porous, nonporous
Aim of application	Diagnostic, therapeutic, preventive, restorative, regenerative
Site of application	Extracorporeal, intracorporeal
Duration of contact with body	Limited (≤1 d), prolonged (>1 d and <30 d), permanent (>30 d)

The left column is the basis used for the classification of biomaterials and the right column is the classes of biomaterials regarding the classification basis indicated in the adjacent column.

Following the revolutionary advancements in biomaterial science and technology in the last 2 decades, it seems that the definitions of some of the key concepts should be updated in a unified manner.

One of the key concepts that indicates the biological safety of biomaterials is biocompatibility. In 1980s, biocompatibility was defined as “the ability of a material to perform with an appropriate host response in a specific application.”[64] This ambiguous and imprecise definition is not practically useful and does not distinguish between different classes of biomaterials with diverse natures of interactions and durations of contact with host tissues.

It had been demonstrated in early 1973 that the biological reactions to poly(2-hydroxyethyl methacrylate) in its porous and solid form are completely different. The surrounding tissue isolates the solid polymer by fibrotic avascular capsule formation, while the tissue integrates to the polymer with 30- to 40-μm pores with a much less fibrosis and much more vascularization. Recently, Buddy D. Ratner[65] addressed an important question about these 2 completely different biological reactions: “The only word that we have for these two tissue reactions is biocompatible. The healing reactions are so different. How can we call both biocompatible?”

Consequently, he proposed 2 definitions based on the biological reactions to the implanted materials: “Biotolerability is the ability of materials to reside in the body for long periods of time with only low

degrees of inflammatory reaction.…Biocompatibility is the ability of materials to locally trigger and guide normal wound healing, reconstruction, and tissue integration."

From Ratner's point of view, the majority of existing biomaterials that are approved routinely by regulatory agencies are biotolerable, while the emerging biomaterials that are able to integrate with tissues via rigorous vascularization are biocompatible.[65]

Concisely, the assessors of biomaterials should be thoroughly aware of unique and distinctive aspects of biomaterials. On the other hand, since it seems that biomaterial innovation is in its heyday, the assessors should also be able to refurbish their knowledge on biomaterial innovation and advancements quickly and continuously. Although it is not easy to be synchronized with the ever increasing innovations in the field of biomaterials, establishing closer links between universities, research centers, and assessors would facilitate knowledge transfer and help the assessors to update their knowledge through periodic training courses.

Regardless of the reactions of scientific communities, these suggestions are considered to be invaluable and thought-provoking because they provide a more accurate and discriminative view about the biomaterials.

Practical Reforms

1. **Integration and harmonization of regulations**: In order to overcome the difficulties caused by dissimilar regulations, the Global Harmonization Task Force on Medical Devices (GHTF) was formed. GHTF covers all classes of medical devices, including biomaterials, and aims to speed up coordination and convergence of international regulations.[66] In addition to partnerships between relevant organizations, it seems that the political will of the major players of the biomaterial market is also needed to establish a global evaluation system and to accelerate the processes that lead to the uniformity of treatment.
2. **Innovators-regulators close collaborations:** Patients need to reach the most innovative medical products and solutions in a timely manner. Collaborations between the innovators and the regulators should be optimized in order to address this demand. In 2011, FDA designed the Innovation Pathway to "shorten the time and reduce the costs from concept to commercialization for innovative medical devices."[67] Regional hubs for innovation and evaluation that would operate based on harmonized regulatory procedures could facilitate the approval processes of new biomaterials. These centers might be established by mutual investment of neighboring countries.
3. **Universal Biomaterials Databases (UBDs)**: During the last 2 decades, biomaterials have attracted great interest from researchers. Nowadays, vast amounts of scientific knowledge are available to describe different types of biomaterials, their properties and applications. Building up and developing universal databases to gather data and results from previously published and ongoing scientific publications that address the interactions of different materials with living tissues is an efficient way to drive biomaterials evaluations faster and in a more economically beneficial way. Knowledge from prior research could accelerate ongoing studies by avoiding redundancy.[68] It could also be beneficial for manufacturers by reducing product development costs and time. Obviously, the transfer of knowledge and experience between researchers and manufacturers can be more effective when it becomes a reciprocal process.

However, manufacturers may not be willing to share their knowledge because of market competition. This barrier can be eliminated by respecting intellectual property rights and providing financial incentives for manufacturers. Clearly, active participation of all involved parties expedite the process of biomaterials research and development.

Conclusion

The number and variety of biomaterials on the market has increased dramatically in recent years. These innovative products have improved life quality of patients all over the world. However, evaluation of biomaterials according to the existing medical device assessment regulations faces challenges that needs to be addressed. To remove these challenges, conceptual refinements and practical reforms are necessary. It can be concluded that improvement of biomaterials evaluation principally requires a collaborative effort between all interested parties including researchers, manufacturers and regulators.

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Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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