BIOMATDB

ADVANCED DATABASE FOR BIOMATERIALS WITH DATA ANALYSIS AND VISUALISATION TOOLS EXTENDED BY A MARKETPLACE WITH DIGITAL ADVISORS

Grant Agreement: 101058779

D2.1 Knowledge Compilation and Structural Material Collection

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Deliverable

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Executive Summary

This deliverable represents a compiled knowledge on classifications, ontologies, labels, actors, tools and other types of data sources and structures in the field of biomaterials. Special emphasis in the process of data collection is put on the DEBBIE project as it constitutes the basis for all following activities. Additionally, to identify capability gaps in the field this document aims to provide a market overview, a collection of already existing similar databases and marketplaces, as well as a compilation of technical solutions and relevant initiatives. Based upon the above-mentioned actions the deliverable constitutes an essential resource for all the next steps and related development activities in the BIOMATDB project – the creation of a biomaterials database and a biomaterials marketplace and label of biocompatibility. In this context, the following actions and related outcomes are comprehensively described. Several definitions of biomaterials are outlined and a glossary with explanations of important terms in the field of biomaterials is presented. Next, the biomaterials landscape is sketched out, an overview of the current biomaterials market is given and possible future developments in the biomaterials market are discussed. To ensure that the project's technical solutions deliver information, which is up-to-date with relevant regulatory frameworks, policies and standards, deliverable D2.1 reviews regulatory requirements in the field of biomaterials and biomaterial-based medical devices including relevant ISO standards. Further, important sources of information on biomaterials are outlined including journal and clinical trial repositories, raw data collections and patent databases, already existing ontologies for biomaterials and biomaterials databases and other relevant material databases that are not specialised on medical biomaterials. Additionally, the document seeks to elaborate how intelligent data processing platforms and technical approaches have been designed and applied in the biomaterials field to date. To achieve this, the consortium provides an overview of already existing marketplaces for biomaterials, and related products such as medical devices based on biomaterials. As one of the focal points of the BIOMATDB project, the document explains how decision support processes (digital advisors) can enhance marketplaces, and a number of marketplaces that already use such tools are presented. Last but not least, to highlight the possibility of exploiting existing developments in the field, the deliverable presents projects, in which members of the BIOMATDB consortium were involved as well as initiatives, which were carried out by external consortia and with which the BIOMATDB project would like to collaborate.

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Acronyms & Abbreviations

Term	Description
AAL	Ambient Assisted Living
API	Application Programming Interface
ATMP	Advanced Therapy Medicinal Products
Ctry.	Country
D	Deliverable
DEBBIE	Database of Experimental Biomaterials and their Biological Effect
EMA	European Medicines Agency
EUDAMED	European database on medical devices
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICIJ	International Consortium of Investigative Journalists
IMDD	International Medical Devices Database
ISO	International Organisation for Standardisation
ISSN	International Standard Serial Number
KPIs	Key Performance Indicators
MDACS	Medical Device Administrative Control System
MDR	European Medical Device Regulation
NLP	Natural Language Processing
NLTK	Natural Language Toolkit
PPP	PowerPoint Presentation
PMS	Post-market surveillance system
Ref.	Reference
SJR	SCImago Journal Rank
SMEs	Small and medium-sized enterprises
T	Task
UIMA	Unstructured Information Management Architecture
USPTO	U.S. Patent and Trademark Office
WIPO	World Intellectual Property Organization
WP	Work Package

1 Introduction

1.1 Overview

As a multidisciplinary field, the design and development of new biomaterials, devices, implants or Advanced Therapy Medicinal Products (ATMPs) and their commercialization involves the collection and analysis of many types of data, ranging from physicochemical properties, pre- and post- clinical data, regulatory information and even market data. All these combine to form a vast amount of "biomaterials data" from a wide variety of sources, that makes it difficult to compare the performance of different biomaterials or select a biomaterial for a specific medical application.

The aim of this deliverable is to provide a wide overview of relevant information and actors in the biomaterials field and of tools to obtain information about biomaterials at different levels. With regard to the planned outcomes of the BIOMATDB project, a biomaterials database and a biomaterials marketplace, this deliverable provides a market overview, a collection of already existing similar databases and marketplaces, as well as a compilation of technical solutions and relevant projects to identify the gaps in this field.

In summary, Deliverable 2.1 provides a compilation of existing knowledge, classifications, ontologies, data sources and structures in the context of biomaterials and related disciplines and insights from former projects covering related materials, especially from the DEBBIE project as the basis for all following activities. This document will be a source of relevant data to be employed in the upcoming sections of the BIOMATDB project.

1.2 Relation to other tasks and deliverables

This deliverable is related to the following other BIOMATDB tasks and deliverables:

Receives inputs from:

Table 1. D2.1 Input from other tasks and deliverables

Deliverable	Due Date	Input for D2.1
D1.1	31.07.2022	Kick-off meeting report: Workshop session about stakeholders and categorisation

Provides outputs to:

Table 2. D2.1 Output for other tasks and deliverables

Deliverable	Due Date	Output from D2.1
D2.2	31.01.2023	Information on the biomaterial landscape and stakeholders for the survey creation
D2.3	31.01.2023	Existing knowledge to be used for the definition of meta use cases and label specifications
D2.4	31.05.2024	Information on the biomaterial landscape and stakeholders for the survey creation

D2.5	30.09.2024	Knowledge compilation as a starting point for the data collection
D3.1	28.02.2023	Inputs for the conception of the BIOMATDB database and marketplace

As this deliverable serves as a compilation of knowledge, data, and other sources of information available in the field of biomaterials, its content will not only serve as a basis for the deliverables listed above, but essentially for all following developments within the BIOMATDB project and future deliverables as well as all tasks related to the development of the project's solutions, the biomaterials database, marketplace, and the label of biocompatibility.

1.3 Structure of the deliverable

This deliverable is structured as follows: Chapter 1 outlines the overall purpose and aim of this deliverable. Chapter 2 describes the tools, processes, and strategies the consortium has used to compile a comprehensive set of information sources and resources which have been summarised in this report to provide an overview of the biomaterials landscape. Chapter 3 summarises important facts, figures, and requirements from the field of biomaterials:

- Definitions of biomaterials are outlined and a glossary with explanations of important terms in the field of biomaterials is presented.
- The biomaterials landscape is sketched out, an overview of the current biomaterials market is given and possible future developments in the biomaterials market are discussed.
- Regulatory requirements in the field of biomaterials and biomaterial-based medical devices are reviewed.
- Relevant ISO standards in the field of biomaterials are outlined.

Chapter 4 provides an overview of important sources of information on biomaterials. These include general resources such as journal and clinical trial repositories, raw data collections and patent databases, already existing ontologies for biomaterials and biomaterials databases, and other relevant material databases that are not specialised in medical biomaterials.

Chapter 5 outlines how Intelligent Data Processing platforms and technical approaches have been designed and applied in the biomaterials field to date.

In chapter 6, an overview of already existing marketplaces for biomaterials, and related products such as medical devices based on biomaterials, is given. In addition, as this will be one of the focal points of the BIOMATDB project, it explains how decision support processes (digital advisors) can enhance marketplaces, and describes a number of marketplaces that already use such tools.

Chapter 7 presents on the one hand, projects in which members of the BIOMATDB consortium were involved and from whose results and experiences the BIOMATDB project can benefit and, on the other hand, projects that were carried out by external consortia and with which the BIOMATDB project would like to collaborate.

Last but not least, chapter 8 analyses the existing knowledge and tools to identify gaps & limitations that the BIOMATDB project aims to fill in. Finally, chapter 9 summarises the results in the conclusion section.

2 Approaches to the structured knowledge compilation and material collection

As already mentioned above, the objective of D2.1 “Knowledge compilation and structural material collection” of the BIOMATDB project is to compile a comprehensive baseline report containing knowledge about the biomaterials landscape and market as well as knowledge relevant to the creation of the biomaterials database and marketplace. This includes biomaterial terminologies and definitions, classifications of biomaterials, existing ontologies and (technical) approaches in the context of (bio)materials databases, marketplaces and digital advisors. In order to fulfil the requirements of D2.1 it was essential to utilise the combined resources and experiences of the partners as well as an elaborate literature and online research to establish a large collection of existing knowledge and materials.

To facilitate a structured collection of knowledge and materials, the consortium utilised a set of tools to structure and monitor the progress of the collection. These tools and strategies consisted of the definition of clear search foci and starting points for the search as well as the provision of spreadsheets to collect knowledge and resources in a structured way and to monitor the progress of the search of each consortium member. These tools and strategies are presented in the following sections.

2.1 Definition of search foci: segmentation of stakeholders, entities and materials

As a first step, the search was broken down into different segments aimed at getting an overview of the biomaterials landscape, the biomaterials market as well as project-relevant knowledge and resources. These subcategories, entities and stakeholders that we wanted to search for in particular, consisted of demanders and suppliers of biomaterials, enablers, events, investors in the field, marketplaces, and online platforms, products, publications such as journals, books or whitepapers and the research community (see Table 3).

It is important to note that this segmentation was done at the very beginning of the project. The naming of the different groups must therefore be taken with caution. For example, based on the state of knowledge at the beginning of the project, we considered on the side of the suppliers, biomaterials or medical device manufacturers and companies, the biomedical engineering industry, the smart healthcare/tech sector, SMEs, and start-ups and on the demander side hospitals, physicians, medical procurers or procurement groups. Additionally, we assigned researchers and the scientific community to a separate group as they represent an essential stakeholder group, especially with regard to the biomaterials database. In the course of the stakeholders, knowledge and material collection we later noticed that the distinction between demanders and suppliers is not always straightforward. Depending on which requirements the BIOMATDB solutions (the biomaterials database and the biomaterials marketplace) will fulfil in the end and which biomaterials in which stage of development they will contain, the classification may change. This challenge can be explained by the following example: at the moment, the collection of products contains raw biomaterial products as well as medical devices made out of biomaterials. Similarly, the collection of suppliers contains companies providing raw biomaterials as well as medical device manufacturers. At this stage, the project can still develop in several directions, especially regarding the marketplace. For the marketplace, the focus will either be placed on offering raw biomaterials or on offering biomaterial-based medical devices. If raw

biomaterials are offered, the classification of medical device manufacturers as suppliers will no longer be correct - rather, they will have to be assigned to the demanders group. However, for the purpose of the knowledge collection for this deliverable, we worked with the segmentation as outlined in Table 3.

Table 3. Segmentation of stakeholders, entities and materials

Entities	Description	Examples
Demanders	Demanders are stakeholders that are potentially interested in buying biomaterials-based products and in using the solutions provided by the biomaterials marketplace and advanced database. Potential demanders are, for example, hospitals, hospital groups or associations, purchasing networks, central purchasing bodies, public organisations, physicians, nursing homes, universities or others.	RESAH, Texas A&M University College of Engineering, ORPEA Group, Ramsay Health Care
Suppliers	Suppliers are manufacturers, developers and/or vendors of products or services, in the context of biomaterials. This group includes companies that develop, manufacture and/or sell raw biomaterials or biomaterial-based products, such as medical devices, prostheses, implants or components of medical devices. Other suppliers would be companies that provide contract manufacturing services (CMS), companies or laboratories that offer testing solutions (e.g. biocompatibility testing) or other relevant entities.	formlabs, Orchid Orthopaedic Solution, Stryker, Resorba Stratasys, Sagemax, Biomomentum
Products	The list of products contains a collection of biomaterials. They can be medical devices (made of, or containing biomaterials), therapies based on biomaterials such as ATMP, components of medical devices, raw or shaped biomaterials and others.	OSTENE Bone Hemostasis Material, 4Degra® resin-inks, SafeSept®, PERLE™ by GCA, A2® Short Stem, TheraPEA™
Enablers	Enablers create economic opportunities through the involvement in the process between the exchange of demanders and suppliers. In other words, enablers exist to keep the different stakeholders connected as well as to connect new stakeholders through events such as fairs. Potential enablers could be biomaterials societies, associations, foundations, and networks in the context of biomaterials or others.	European Society for Biomaterials, IUSBSE, SSB+RM, MedTech Europe, AO CMF
Events	Events could be conferences, expositions or similar occasions connected to medical devices or biomaterials.	International Conference Bioceramics32, 12th World Biomaterials Congress (WBC)
Projects	Projects related to BIOMATDB, similar to BIOMATDB, and projects relevant in the project context (e.g., for possible collaborations).	TBMED, SAFE-N-MEDTECH, MDOT, ENANOMAPPER
Marketplaces + Online Platforms	The list of marketplaces collects platforms that sell biomaterials products or services from multiple suppliers or mediate contacts between suppliers and demanders in order to sell biomaterials products or services (B2B). Furthermore, platforms where information about biomaterials can be	MD+DI, Medical EXPO, The Biomaterial Store, GUDID, Wound Reference

	found or databases in the context of biomaterials should be added to this list as well.	
Publications	Within the publications table, biomaterials journals, books and other publications (e.g., presentations, …) will be collected.	Regenerative Biomaterials (journal), Acta Biomaterialia (journal), Biopolymers and Biomaterials (book)
Research community	Collection of universities, institutions, departments, and researchers, who may be interested and could use the BIOMATDB project tools.	Texas A&M University College of Engineering, Department of Biomedical Engineering, Isaac Adjei
Investors	Collection of individuals, companies or other entities who invest money in biomaterials or medical device companies, the development of biomaterials or other causes relevant in the context of the BIOMATDB project.	DSW Ventures
Policy makers & Regulators	Public bodies, public administrations, governmental, regulation & standardisation bodies, certifiers, policy stakeholders and policy makers involved in the regulation and certification of biomaterials as well as in the approval of medical devices.	EUDAMED EMA FDA

To collect all of this information in a structured way, collection sheets were created to be filled in by all of the partners. The collection sheets were stored within a Google Drive Folder accessible by all the partners (see Figure 1). The collection sheets will be described in the next section and the collected results within these spreadsheets will be made available as part of D2.5, later in the project.

Figure 1. Folder structure - Collection & Mapping Sheets

2.2 Overview sheet as central orchestration element

The central orchestration element of the structured knowledge, material and stakeholder collection was the **BIOMATDB Collection overview** sheet (see Figure 2. BIOMATDB Collection overview sheet). This tool was created to coordinate the collection and to track the status of the collection. All the individual collection sheets for the different search segments could be accessed via the links in the overview sheet. The consortium was asked to regularly update their progress in the different collection sheets (number of entries) in the respective row and column of the overview sheet. This practice of

monitoring the progress of the search has not only proven to be a helpful motivation for the partners in previous projects of the Coordinator SYNYO, it can also ensure that the KPIs promised in the proposal can be reached.

NO.	ACRONYM	COUNTRY	COLLECTED	Suppliers	Entries	Demanders	Entries	Enablers	Entries	Products	Entries	Projects	Entries	Events	Entries	Research Community (Institutions)	Entries	Research Community (Researchers)	Entries	Investors	Entries	Policy makers & Regulators	Entries	Marketplaces & Online Platforms	Entries	Publications	Entries	META	Entries
1	SYNYO	Austria	9	TO DO	0	TO DO	0	TO DO	0	IN PROGRESS	5	IN PROGRESS	4	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0
2	BSC	Spain	15	IN PROGRESS	2	IN PROGRESS	4	TO DO	0	TO DO	0	TO DO	0	IN PROGRESS	4	IN PROGRESS	5	IN PROGRESS	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0
3	UIO	Norway	575	DONE	10	DONE	4	DONE	7	DONE	1	DONE	1	DONE	1	DONE	8	DONE	0	DONE	8	DONE	11	DONE	0	DONE	520	DONE	2
4	UPC	Spain	539	DONE	100	DONE	100	DONE	9	NO COLLECTION	0	DONE	1	NO COLLECTION	0	DONE	116	DONE	116	NO COLLECTION	0	NO COLLECTION	0	DONE	25	DONE	29	DONE	43
5	TAU	Finland	62	DONE	7	IN PROGRESS	5	DONE	6	DONE	19	DONE	1	DONE	1	IN PROGRESS	13	TO DO	0	IN PROGRESS	2	DONE	3	IN PROGRESS	1	DONE	4	NO COLLECTION	0
6	ZUT	Poland	66	IN PROGRESS	10	IN PROGRESS	4	IN PROGRESS	2	IN PROGRESS	8	IN PROGRESS	8	IN PROGRESS	4	IN PROGRESS	10	IN PROGRESS	10	TO DO	0	IN PROGRESS	3	TO DO	0	IN PROGRESS	6	IN PROGRESS	1
7	M&S	Austria	365	IN PROGRESS	121	IN PROGRESS	35	IN PROGRESS	18	IN PROGRESS	17	IN PROGRESS	10	IN PROGRESS	17	IN PROGRESS	7	IN PROGRESS	51	IN PROGRESS	12	IN PROGRESS	2	IN PROGRESS	12	IN PROGRESS	26	IN PROGRESS	35
8	CECCCIC	Portugal	306	IN PROGRESS	0	IN PROGRESS	0	IN PROGRESS	0	IN PROGRESS	306	IN PROGRESS	0	IN PROGRESS	0	IN PROGRESS	0	IN PROGRESS	0	IN PROGRESS	0	IN PROGRESS	0	IN PROGRESS	0	NO COLLECTION	0	NO COLLECTION	0
9	CLUSTER	Italy	352	DONE	95	DONE	22	DONE	19	DONE	43	DONE	20	DONE	19	DONE	22	DONE	41	DONE	20	DONE	12	DONE	2	DONE	30	DONE	7
10	NUIG	Ireland	26	IN PROGRESS	12	IN PROGRESS	0	IN PROGRESS	12	IN PROGRESS	1	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	IN PROGRESS	1
11	FHUNJ	Spain	157	DONE	18	DONE	57	DONE	3	DONE	8	DONE	2	DONE	1	DONE	21	DONE	21	IN PROGRESS	0	DONE	12	DONE	1	DONE	13	IN PROGRESS	0
12	ECHA	Ireland	244	DONE	15	DONE	107	DONE	5	DONE	16	DONE	5	DONE	2	DONE	2	NO COLLECTION	0	NO COLLECTION	0	DONE	92	NO COLLECTION	0	NO COLLECTION	0	NO COLLECTION	0
13	OSNAT HAKIMI	Israel	28	IN PROGRESS	2	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0	IN PROGRESS	13	IN PROGRESS	13	TO DO	0	TO DO	0	TO DO	0	TO DO	0	TO DO	0
14	YANNIS MISSIRLIS	Greece	27	IN PROGRESS	8	TO DO	0	TO DO	0	TO DO	0	TO DO	0	IN PROGRESS	2	IN PROGRESS	5	TO DO	0	TO DO	0	TO DO	0	TO DO	0	IN PROGRESS	12	TO DO	0
15	CARLA FUENTESLÓPEZ	UK & Mexico	34	IN PROGRESS	4	TO DO	0	IN PROGRESS	1	DONE	10	TO DO	0	DONE	11	IN PROGRESS	4	TO DO	0	IN PROGRESS	4	TO DO	0	TO DO	0	TO DO	0	TO DO	0
			2803		404		338		82		434		52		64		226		252		46		135		41		640		89

Figure 2. BIOMATDB Collection overview sheet

The overview sheet was also used as a tool to find useful **starting points** for the searches. As can be seen in Figure 3, the BIOMATDB consortium consists of 12 partners from 8 different countries. In addition, the contracted expert partners were from Israel, Greece, and from the United Kingdom and Mexico.

NO.	ACRONYM	COUNTRY
1	SYNYO	Austria
2	BSC	Spain
3	UIO	Norway
4	UPC	Spain
5	TAU	Finland
6	ZUT	Poland
7	M&S	Austria
8	CECCCIC	Portugal
9	CLUSTER	Italy
10	NUIG	Ireland
11	FHUNJ	Spain
12	ECHA	Ireland
13	OSNAT HAKIMI	Israel
14	YANNIS MISSIRLIS	Greece
15	CARLA FUENTESLÓPEZ	UK & Mexico

Figure 3. Breakdown by country

Since the international composition of the consortium represents a valuable asset of the BIOMATDB project, the consortium was asked to start the search by focusing on their country of origin, before later expanding the search globally on countries not covered by any of the partners. This search strategy has the advantage that overlapping results (e.g., two partners find the same supplier twice) can be reduced, while at the same time covering as large a geographical area as possible. Furthermore, the overview sheet contained a “Keywords” tab with useful keywords for the searches (see Figure 4). These keywords provided not only the advantage of serving as starting points for the searches, but they were also a tool to facilitate the search in different languages, since the consortium members could provide translations of the keywords.

Category	Keyword (EN)	Keyword (DE)	Keyword (ES)	Keyword (NO)	Keyword (FI)	Keyword (PL)	Keyword (PT)	Keyword (IT)	Keyword (IE)	Keyword (IL)	Keyword (GR)
Suppliers	medical device manufacturers							produttori di dispositivi medici			
	medical device suppliers							fornitori di dispositivi medici			
	biomaterials companies							aziende di biomateriali			
	biocompatibility testing							test di biocompatibilità			
	contract manufacturing services ANI							Servizi di produzione a contratt			
Demanders	hospital groups							gruppi ospedalieri			
	hospital associations							ospedale			
	central purchasing bodies AND medi							casa di riposo			
	purchasing networks AND medical d							università			
								reti di acquisto AND dispositivi			
								centrali committenze AND disp			
Enablers	biomaterials AND societies OR assoc							biomateriali AND società OR as			
	biomedical engineering AND societie							ingegneria biomedica AND soci			
	tissue engineering AND societies OR							Ingegneria tissutale AND societ			
	medical technology AND societies O							tecnologia medica AND società			
Products	implants							impianti			
	prostheses							protesi			
	heart valves							valvole cardiache			
	implantable devices							dispositivi impiantabili			
	medical dressings										
	haemostatic dressings										
	osteosynthesis devices							dispositivi di osteosintesi			
	prosthetic dentistry							odontoiatria protesica			
	biomaterials							biomateriali			

Figure 4. Keywords Tab - BIOMATDB Collection overview sheet

As mentioned previously, the overview sheet provided access to the **individual collection** sheets for the different search foci via links. The individual spreadsheets were named based on the segments presented in Table 3. Segmentation of stakeholders, entities and materials. The individual collection sheets will be explained in the next section of this deliverable.

2.3 Individual Collection sheets

For a most comprehensive collection of stakeholders, materials, and knowledge, we defined various search segments. For each search segment, a Google spreadsheet was created to collect the relevant information. To ensure the quality of the knowledge and information collection, a unified and collective approach to the search was necessary. Therefore, the partners were provided with guides explaining how to use the individual collection spreadsheets, the monitoring tool in the form of the overview sheet, and the do's and don'ts for the collection. Most importantly, the guides also displayed Table 3. Segmentation of stakeholders, entities and materials to clearly define and explain the different search segments for the consortium members. Additionally, the consortium was provided with a detailed PowerPoint presentation on how to use the individual collection sheets accurately. Excerpts from these guides and the presentation can be seen in the screenshots in Figure 5 and Figure 6.

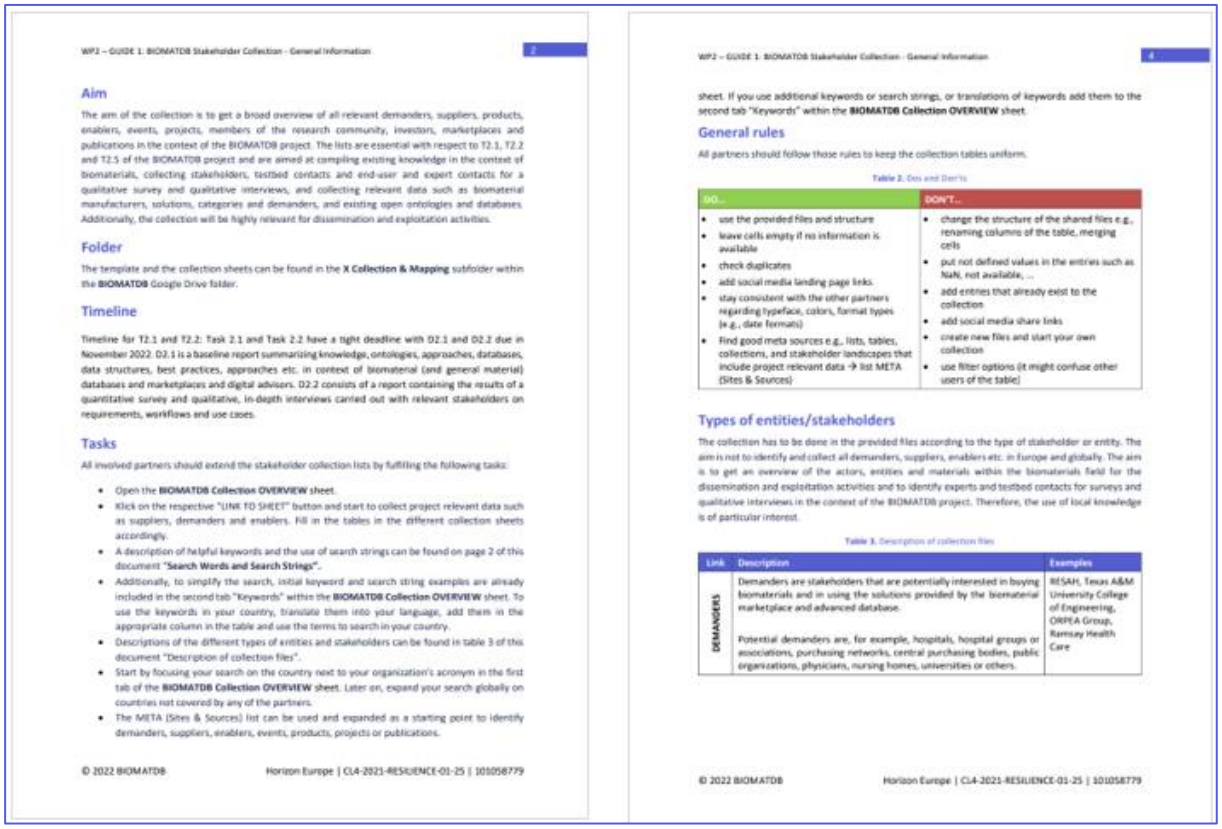


Figure 5. Screenshots of the General Collection Guide

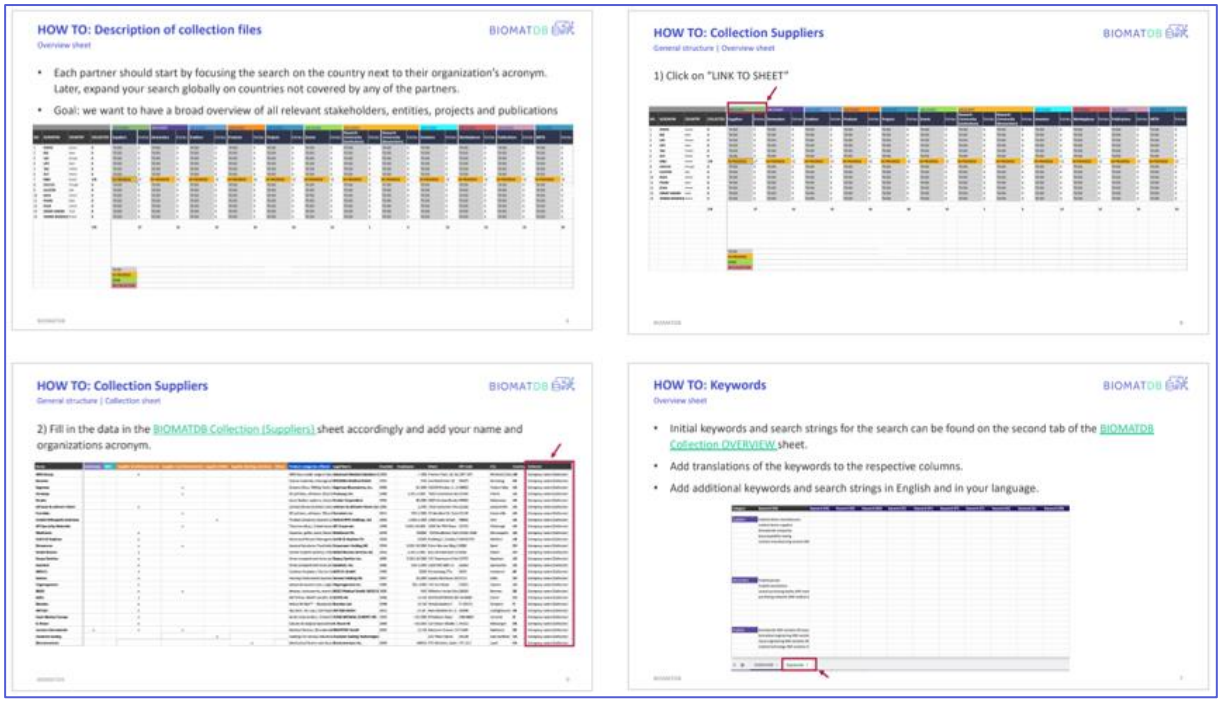
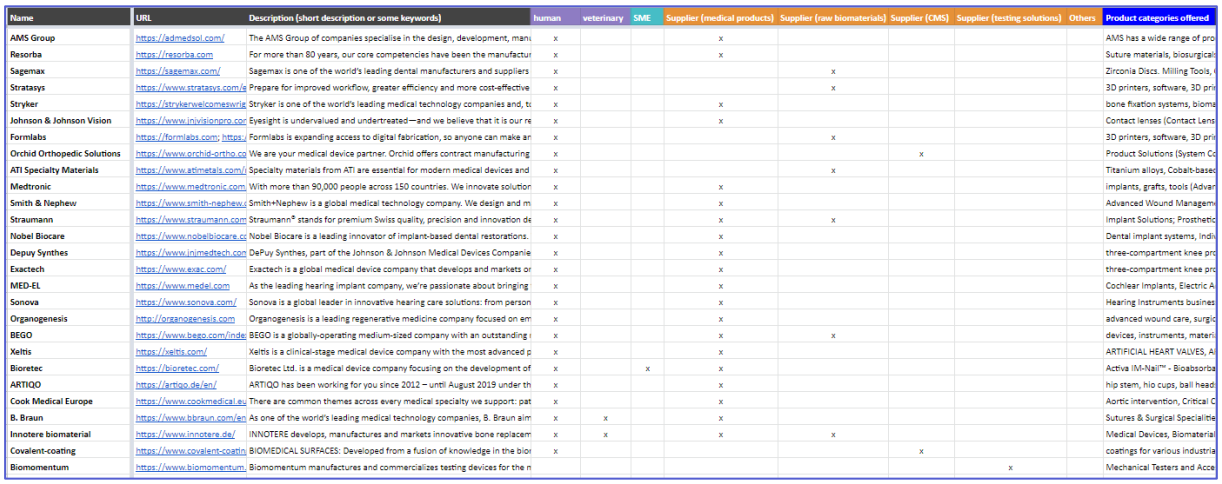


Figure 6. Screenshots of the Power Point Collection Guides

As already mentioned, for each of the stakeholders, entities, or materials a Google spreadsheet was created for the collection. In the following screenshots an overview of the individual collection sheets as well as some relevant statistics are provided.

The **Suppliers collection sheet** (Figure 7) contains information about companies that manufacture, develop, and/or sell products or services in the context of biomaterials. This group includes companies that develop, manufacture, and/or sell raw biomaterials or biomaterial-based products, such as medical devices, prostheses, implants or components of medical devices. Additionally, the consortium has collected companies that provide contract manufacturing services (CMS) or companies or laboratories that offer testing solutions (e.g., biocompatibility testing) within the Suppliers collection sheet.



Name	URL	Description (short description or some keywords)	human	veterinary	SME	Supplier (medical products)	Supplier (raw biomaterials)	Supplier (CMS)	Supplier (testing solutions)	Others	Product categories offered
AMS Group	https://admedsol.com/	The AMS Group of companies specialise in the design, development, manu	x			x					AMS has a wide range of pro
Resorba	https://resorba.com	For more than 80 years, our core competencies have been the manufactur	x			x					Suture materials, biosurgicals
Sagemax	https://sagemax.com/	Sagemax is one of the world's leading dental manufacturers and suppliers	x				x				Zirconia Discs. Milling Tools,
Stratasys	https://www.stratasys.com/e	Prepare for improved workflow, greater efficiency and more cost-effective	x				x				3D printers, software, 3D pri
Stryker	https://strykerwelcomeswrig	Stryker is one of the world's leading medical technology companies and, t	x			x					bone fixation systems, bioma
Johnson & Johnson Vision	https://www.inivisionpro.cor	Eyesight is undervalued and undertreated—and we believe that it is our re	x			x					Contact lenses (Contact Lens
Formlabs	https://formlabs.com; https:/	Formlabs is expanding access to digital fabrication, so anyone can make an	x				x				3D printers, software, 3D pri
Orchid Orthopedic Solutions	https://www.orchid-ortho.co	We are your medical device partner. Orchid offers contract manufacturing	x					x			Product Solutions (System Co
ATI Specialty Materials	https://www.atimetals.com/i	Specialty materials from ATI are essential for modern medical devices and	x				x				Titanium alloys, Cobalt-based
Medtronic	https://www.medtronic.com	With more than 90,000 people across 150 countries. We innovate solution	x			x					Implants, grafts, tools (Advan
Smith & Nephew	https://www.smith-nephew.(	Smith+Nephew is a global medical technology company. We design and m	x			x					Advanced Wound Managem
Straumann	https://www.straumann.com	Straumann® stands for premium Swiss quality, precision and innovation de	x			x	x				Implant Solutions; Prosthetic
Nobel Biocare	https://www.nobelbiocare.co	Nobel Biocare is a leading innovator of implant-based dental restorations.	x			x					Dental implant systems, Indi
Depuy Synthes	https://www.inimedtech.con	DePuy Synthes, part of the Johnson & Johnson Medical Devices Companie	x			x					three-compartment knee pro
Exactech	https://www.exac.com/	Exactech is a global medical device company that develops and markets or	x			x					three-compartment knee pro
MED-EL	https://www.medel.com	As the leading hearing implant company, we're passionate about bringing	x			x					Cochlear Implants, Electric A
Sonova	https://www.sonova.com/	Sonova is a global leader in innovative hearing care solutions: from person	x			x					Hearing Instruments busines
Organogenesis	http://organogenesis.com	Organogenesis is a leading regenerative medicine company focused on em	x			x					advanced wound care, surgic
BEGO	https://www.bego.com/inde	BEGO is a globally-operating medium-sized company with an outstanding	x			x	x				devices, instruments, materi
Xeltis	https://xeltis.com/	Xeltis is a clinical-stage medical device company with the most advanced p	x			x					ARTIFICIAL HEART VALVES, A
Bioretec	https://bioretec.com/	Bioretec Ltd. is a medical device company focusing on the development of	x		x	x					Activa IM-Nail™ - Bioabsorba
ARTIQO	https://artiqo.de/en/	ARTIQO has been working for you since 2012 – until August 2019 under th	x			x					hip stem, hip cups, ball head
Cook Medical Europe	https://www.cookmedical.eu	There are common themes across every medical specialty we support: pat	x			x					Aortic intervention, Critical C
B. Braun	https://www.bbraun.com/en	As one of the world's leading medical technology companies, B. Braun aim	x	x		x					Sutures & Surgical Specialitie
Innotere biomaterial	https://www.innotere.de/	INNOTERE develops, manufactures and markets innovative bone replacem	x	x		x	x				Medical Devices, Biomaterial
Covalent-coating	https://www.covalent-coatin	BIOMEDICAL SURFACES: Developed from a fusion of knowledge in the bio	x					x			coatings for various industria
Biomomentum	https://www.biomomentum.	Biomomentum manufactures and commercializes testing devices for the n							x		Mechanical Testers and Acce

Figure 7. Suppliers collection sheet

As of now, the consortium collected 404 suppliers in total (Figure 8). 64.9 % of those suppliers can be considered as manufacturers of medical devices, 18.4 % of the collected companies produce or sell raw biomaterials, and 6.4 % provide Contract Manufacturing Services (CMS) and perform one or more steps for the production or distribution of a biomaterial product on behalf of another company. 5.4 % of the collected companies offer services in the form of testing solutions, such as mechanical testing or biocompatibility testing, and 4.9 % of the collected entities fall in neither of those categories. In addition, the consortium indicated for each company if they provide products for the human or veterinary product sector (Figure 8). 90.4 % of the companies that were collected so far produce for the human sector, 5.8 % for the veterinary sector. In 3.7 % of the cases, it was not indicated whether the products belong to the human or veterinary sector, either because this information was not available, or because this distinction did not make sense for the offered products.

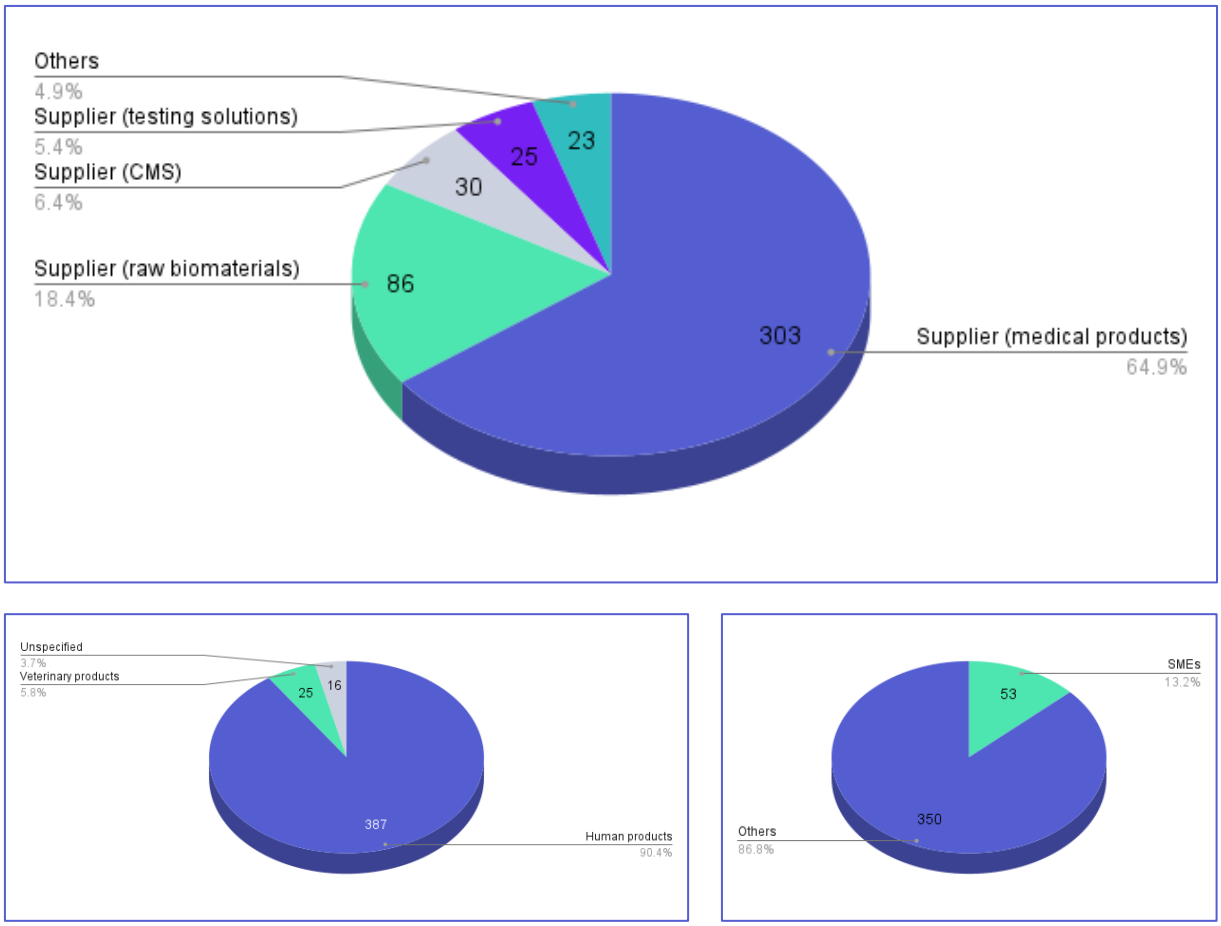


Figure 8. Statistics - Suppliers collection sheet

The **Demanders collection sheet** (Figure 9) collects stakeholders that are potentially interested in buying biomaterials-based products and in using the solutions provided by the biomaterials marketplace and advanced database. Potential demanders are, for example, hospitals, hospital groups or associations, purchasing networks, central purchasing bodies, public organisations, physicians, nursing homes, universities, or others. It is important to consider, that in this definition of demanders, manufacturers of medical devices are not considered to be demanders, as they have been collected together with the manufacturers of raw materials in the suppliers list (for more information see Definition of search foci: segmentation of stakeholders, entities and materials).

Name	URL	Hospital (operators)	Purchasing Networks (Cent	Universities	Others	Description (short description or	Country	Type	Founded	Employees
Réseau des Acheteurs Hospitaliers (RESAH)	http://www.resah.fr/		x			Created in 2007, RESAH is a public	FR	public, non-profit	2007	51-200
Texas A&M University College of Engineering -	https://engineering.tamu.edu/b			x		We are making advances in biome	US		1972	501-1.000
ORPEA Group	https://www.orpea-group.com/	x			x	Deeply rooted in France through i	FR	for profit	1989	68 800
AMGROS - Danish Critical Supply Agency	http://www.amgros.dk/en		x			Together with other healthcare st	DK	for profit	1990	51-200
San Donato Hospital Group	https://www.gsdinternational.c	x				Being the No 1 hospital group in t	IT	private	1957	10.001
MercurHosp	https://www.mercurhosp.be/		x			MercurHosp is a central purchasir	BE	non-profit	2013	1-10
Sykehusinnkjøp	http://sykehusinnkjop.no		x			Sykehusinnkjøp HF is a public non	NO	public, non-profit	2015	300
Ramsay Health Care (Ramsay) global	https://www.ramsayhealth.com	x				Ramsay Health Care (Ramsay) pro	AU	private	1964	86,000
Massachusetts Institute of Technology	https://dmse.mit.edu/			x		DMSE is home to the world's pren	US		1974	
National Health Service (NHS)	https://www.england.nhs.uk/		x			From 1 April 2019, NHS England a	UK	governmental	2012	)01-10.000
Netherlands Federation of University Medical	http://www.nfu.nl/		x			The Netherlands Federation of Un	NL	public	2004	11-50
NHS Commercial Solutions	https://www.england.nhs.uk/		x			From 1 April 2019, NHS England a	UK	governmental	2012	)01-10.000
Ramsay Health Care Australia	https://www.ramsayhealth.com	x				Ramsay Health Care (Ramsay) pro	AU	private	1964	
Ramsay Health Care United Kingdom	https://www.ramsayhealth.co.u	x				Ramsay Health Care (Ramsay) pro	UK	private	1964	
Ramsay Santé France	https://www.ramsaysante.fr/	x				Ramsay Health Care (Ramsay) pro	FR	private	1964	
RHÖN-KLINIKUM	https://www.rhoen-klinikum-ag	x				Founded in 1973 with 66 employe	DE	private		10.001+
Sana Kliniken	https://www.sana.de/	x				The care of patients in our hospita	DE	private	1976	
SCR Piemonte	http://www.scr.piemonte.it/cms		x			SCR Piemonte is the central purch	IT	public	2007	
SPMS	http://spms.min-saude.pt/		x			SPMS is a public enterprise create	PT	public	2010	
Stanford University	https://mse.stanford.edu/			x		Materials Science and Engineering	US			501-1.000
Styrelsen for Forsyningssikkerhed / Danish Crit	https://sfos.dk/english/		x			SFOS (Styrelsen for Forsyningssikk	DK	governmental	2020	51-200
The Pennsylvania State University	http://www.mri.psu.edu/			x		Penn State's MRI is a catalyst for r	US		1992	
The Pennsylvania State University	https://www.huck.psu.edu/			x		The Huck isn't easy to explain. It c	US		1996	
The Pennsylvania State University	https://www.bme.psu.edu/			x		The Penn State Department of Bic	US			
Universidade do Porto	https://www.i3s.up.pt/			x		Health Research in a single and so	PT		2015	
University of Pittsburgh	https://mirm.pitt.net/			x		To realize the vast potential of tiss	US			
Vienna University of Technology (TU Wien)	https://www.tuwien.ac.at/insti			x		The Institute for Materials Science	AT	public	2004	

Figure 9. Demanders collection sheet

Up to now, the consortium collected 338 entities in the Demanders collection sheet (Figure 10). 60.3 % of those entities are hospitals, hospital groups or hospital operators. 12.6 % are Purchasing Networks such as Central Purchasing Bodies, Group Purchasing Organisations, Governmental or Public Purchasing Organisations or Public Companies specialised in acquiring biomaterial-based medical devices. 7.6 % are universities with Biomedical Engineering or Tissue Engineering departments and 19.5 % are possible demanders of biomaterial-based products that do not exactly fit into the categories mentioned above.

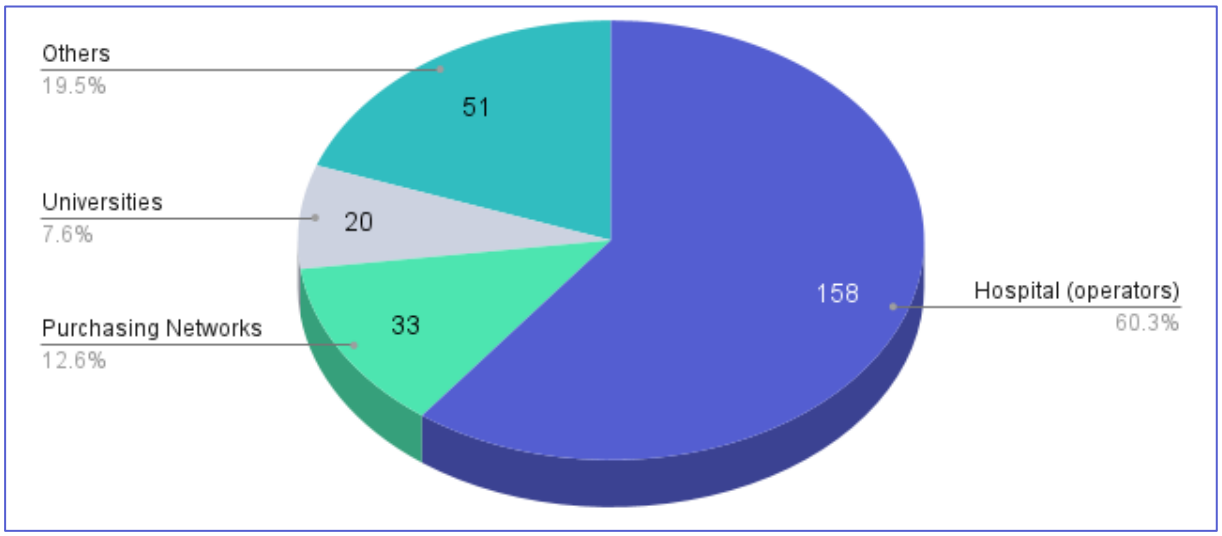


Figure 10. Statistics - Demanders collection sheet

The **collection sheet for products** (Figure 11) contains a collection of biomaterials or biomaterial-based products. This includes, for example, medical devices (made of, or containing biomaterials), therapies based on biomaterials such as ATMPs, components of medical devices, or raw or shaped biomaterials. Due to the abundance of biomaterial products this list is mainly useful to get a rough overview of the different product types that are relevant for the biomaterials market. At this point the collection includes 434 entries (Figure 2. BIOMATDB Collection overview sheet).

Product Name	Product URL	Medical Application	Biomaterial/Device constituents	Manufactured object	Description (short description or some keywords)	Supplier Name
FLOSEAL Hemostatic Matrix	https://advancedsurgery.baxter.com/f	Biosurgical (hemostasis)	bovine-derived Gelatin, human-der	Surgical implant (matrix/glue)	thrombin reacts with fibrinogen of the patient	Baxter
TISSEEL Fibrin Sealant	https://advancedsurgery.baxter.com/t	Biosurgical (hemostasis, sealing)	fibrin	Bioadhesive, Surgical implant (r	TISSEEL is a fibrin sealant indicated for use as an adji	Baxter
TACHOSIL® Fibrin Sealant Patch	https://advancedsurgery.baxter.com/t	Biosurgal (hemostasis, mild to moderati	human fibrinogen, human thrombi	Surgical implant (patch)	TachoSil® is a fibrin sealant patch indicated for use v	Baxter
COSEAL Surgical Sealant	https://advancedsurgery.baxter.com/c	Biosurgical (sealing, vascular reconstruc	two synthetic polyethylene glycols	Bioadhesive, Surgical implant (I	COSEAL is indicated for use in vascular reconstructio	Baxter
PREVELEAK Surgical Sealant	https://advancedsurgery.baxter.com/p	Biosurgical (sealing, vascular and cardia	provided in a double-barreled syrir	Bioadhesive	PREVELEAK Surgical Sealant (PREVELEAK) is a sealan	Baxter
OSTENE Bone Hemostasis Material	https://advancedsurgery.baxter.com/p	bone bleeding in orthopedic and cardio	sterile mixture of water-soluble alk	Bone Hemostasis Material	Control of bone bleeding in orthopedic and cardioth	Baxter
4Degra® resin-inks	https://4dbiomaterials.co.uk/pipeline/	diverse	polycarbonate-urethane based resi	Bioink	4Degra® resin-inks are available now in both standai	4DBiomaterials
SafeSept®	https://www.pressure-products.com/s	left atrial access	Nitinol	wire	The very sharp tip of the SafeSept® requires less forc	Pressure Products
Impella RP heart pump	https://www.heartrecovery.eu/produc	right heart failure	Nickel-Titan Alloy, coated in polym	heart pump	The Impella RP heart pump provides temporary, circ	Abiomed
Dual Lumen Gastrointestinal Tubes	https://www.cardinalhealth.co.uk/en_	enteral feeding and removal of fluids ar	synthetic Polymer (PVC)	tube	The Dual Lumen Gastrointestinal Tubes are a sterile,	Cardinal Health
PERLE™ by GCA	https://www.gcaesthetics.com/produc	breast implant	Emunomic™ Breast Tissue Dynamic	breast implant	Round, smooth opaque breast implant with (R)evolu	GC Aesthetics
Carillon Mitral Contour System®	https://cardiacdimensions.com/physic	Heart Failure and Functional Mitral Reg	Nitinol, Titan	coronary vein implant	Our Carillon Mitral Contour System® is a groundbrea	Cardiac Dimensions
Acron PEEK Interbody system	https://www.acron-medical.com/de/	interbody fusion in osteoporotic patient	Polymer, (otpional) metal coat	implant (spine)	The Acron PEEK Interbody system is the new gold sta	Acron Medical
A2® Short Stem	https://artiqo.de/en/products/hip-ste	hip protheses	titan, titan alloy, accelerated osteoi	hip stem	Short stems are being used more and more frequent	ARTIQO
4-motion® knee joint	https://artiqo.de/en/products/4-motic	knee protheses	tibia compnent (Ti6Al4V), Inlay (XL	knee joint	With the development of the 4-motion® knee joint,	ARTIQO
Absorv™ – Bioabsorbable Extrusions	https://www.zeusinc.com/products/bi	diverse (dental, orthopedical, surgery, ..	Bioabsorbables	scaffold	novel bioabsorbable polymers to meet precise degra	ZEUS
Aeos™ ePTFE Suture Monofilament	https://www.zeusinc.com/products/bi	diverse (anamastosis, hernia, ...)	suture monofilament	suture monofilament	permanently implantable and non-absorbable sutur	ZEUS
Aeos™ ePTFE	https://www.zeusinc.com/products/bi	diverse (dental, giber optics,...)	diverse	material composed of a numbe	ePTFE is composed of a number of solid nodes interc	ZEUS
Bioweb™	https://www.zeusinc.com/products/bi	PTFE and PU into polymeric nanofibers	PTFE and PU into polymeric nanofi	implantable stent and scaffold	non-woven composite membrane produced by elect	ZEUS
Linear Hyaluronic Acid	https://www.iralab.it/en/medical-devi	Intra-articular treatment for pain and/o	injectable, non-pyrogenic, reabsorl	colorless gel contained in a pre-	Intra-articular injections of hyaluronic acid to promo	IRA Istituto Ricerch
PerSorb®	https://www.aferetica.com/en/therap	Ex vivo perfusion	resin with beads of polystyrene-div	sorbent cartridge	PerSorb® allows adsorption of inflammation mediati	Aferetica
CytoSorb®	https://www.aferetica.com/en/therap	Septic shock in intensive care, vasoplegi	resin with beads of polystyrene-div	sorbent cartridge	CytoSorb® allows blood purification in clinical condit	Aferetica
Hyalomatrix®	https://anika.com/medical/products/h	management of wounds	Single-layered: HYAFF matrix (a der	sterile, biodegradable, flexible a	The matrix provides a 3-D scaffold for cellular invasic	Anika
Tactoset®	https://anika.com/medical/products/t	bone marrow lesions, insufficiency fract	synthetic, biocompatible, hyaluron	Injectable Bone Substitute	The device provides an injectable, self-setting, osteo	Anika

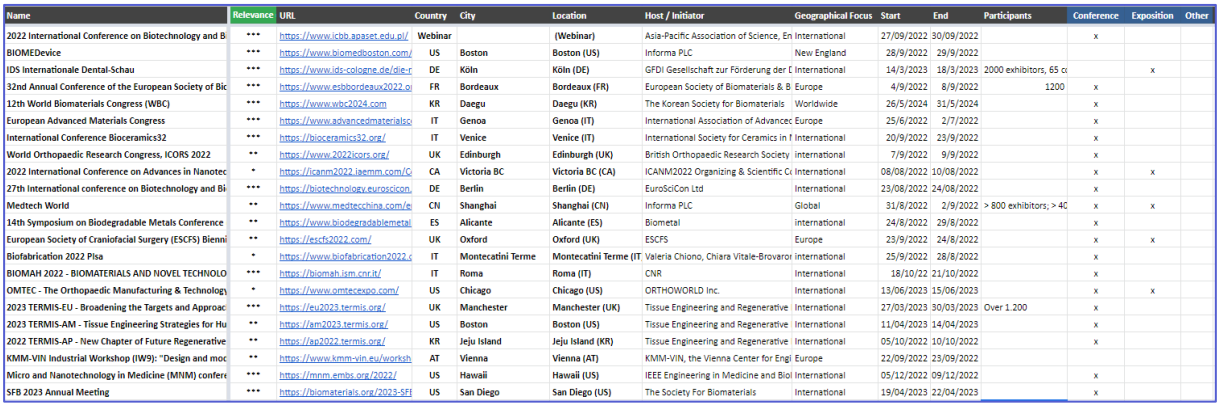
Figure 11. Products collection sheet

As described in Table 3. Segmentation of stakeholders, entities and materials above, enablers create economic opportunities through the involvement in the process between the exchange of demanders and suppliers. Enablers are entities that help to connect the different stakeholders. In the case of biomaterials, we collected biomaterials societies as well as associations, foundations and networks in the context of biomaterials in the **Enablers collection sheet** (Figure 12). So far, the consortium collected 82 enablers (Figure 2) from at least 24 different countries, in the Middle east, the Asian & Pacific region, Europe, North America, South/Latin America and Africa. Those enablers have regional, international and some even global reach (Figure 12).

Name	Relevance (* = migl	URL	Description (short description or some keywords)	Country	Region	Type	Founded	Employees	Members	Association/Society	Foundation	Network	Other
European Society for Biomaterials	***	https://www.esbion	"virtual environment", scientists, clinicians, industri	FR	Europe	non-profit	1976			x			
International Union of Societies for Biomateria	***	http://www.iusbse.(	body that brings together national and multi-nation	CN	Asia		1980						x
Society for Biohydrogels	***	https://rmes.univ-n	The Society for Biohydrogels, created in March 2015	FR	Europe	non-profit	2015			x			
Swiss Society for Biomaterials + Regenerative r	***	https://ssbrm.ch/	The SSB+RM is the assembly of people in Switzerlar	CH	Europe	non-profit	1995			x			
MedTech Europe	***	https://www.medte	MedTech Europe is the European trade association f	BE	Europe		2012			x			
AO CMF	**	https://www.aofour	The goal of AOCMF has always been to foster a mult	CH	global	nonprofit					x	x	
AO Trauma	**	https://www.aofour	AOTrauma is an organization that creates a dynamic	CH	global	nonprofit	2008	201-500			x	x	
Netherlands Society For Biomaterials and Tissu	***	https://nbte.nl/	The society aims to promote the interests of biomat	NL	Europe	nonprofit				x			
BIOMAT: Association pour le développement d	***	https://biomat.fr/	BIOMAT Association: Association for the developme	FR	Europe		1984			x			
International Team for Implantology (ITI)	**	https://www.iti.org/	The ITI is a global association of professionals in imp	CH	global	non-governn	1980			x			
Tissue Engineering Network	*	https://www.tissue-	This page comprehensively explains everything abo	DE	DACH								x
European Orthopaedic Research Society (EORS	***	https://www.eors.in	To promote research and development in orthopaed	DE	Europe					x			
European Federation of National Associations	***	efort.org	The European Federation of National Associations o	CH	Europe	nonprofit	1991			x			
Österr. Gesellschaft f. Orthopädie (ÖGO)	**	https://www.orthoc	Die Österreichische Gesellschaft für Orthopädie sieh	AT	Europe	nonprofit				x			
Società Italiana Biomateriali	***	https://www.bioma	The SIB aims to encourage, support, promote resear	IT	Europe	non-profit	2003			x			
Consorzio Interuniversitario Nazionale per la S	***	https://www.instm.(	INSTM brings together 50 Italian universities, basica	IT	Europe	non-profit	1992	1,001-5,000		x			
Gruppo Nazionale di Bioingegneria (GNB)	***	https://www.gruppi	The GNB aims to promote and coordinate research i	IT	Europe	non-profit				x			
Confindustria Dispositivi Medici	**	https://www.confin	Confindustria Medical Devices is the Federation that	IT	Europe	non-profit	2019	11-50		x			
IngegneriaBiomedica.org	*	https://www.ingegn	A community of students and professionals of Biom	IT	Europe	non-profit	2008	11-50					x
EMBS Technical Committee on BioNanotechno	**	https://www.embs.(	The BNM is a Technical Committee of the Engineerir	US	global	non-profit	1963			x			
Society for Biomaterials	***	https://biomaterials	The Society For Biomaterials is a multidisciplinary sc	US	global	non-profit	1969			x			
Biomat.net	**	https://biomat.net/	Biomat.net is an organized and meaningful Biomate	PT	Europe	non-profit	1998					x	
Democenter	***	https://www.democ	Fondazione Democenter promotes change in the mi	IT	Europe	non-profit	1991	11-50			x		
Fondazione Tes	***	https://www.fondaz	Tes (Tissue Engineering and Signaling), Foundation f	IT	Europe	non-profit	2006				x		

Figure 12. Enablers collection sheet

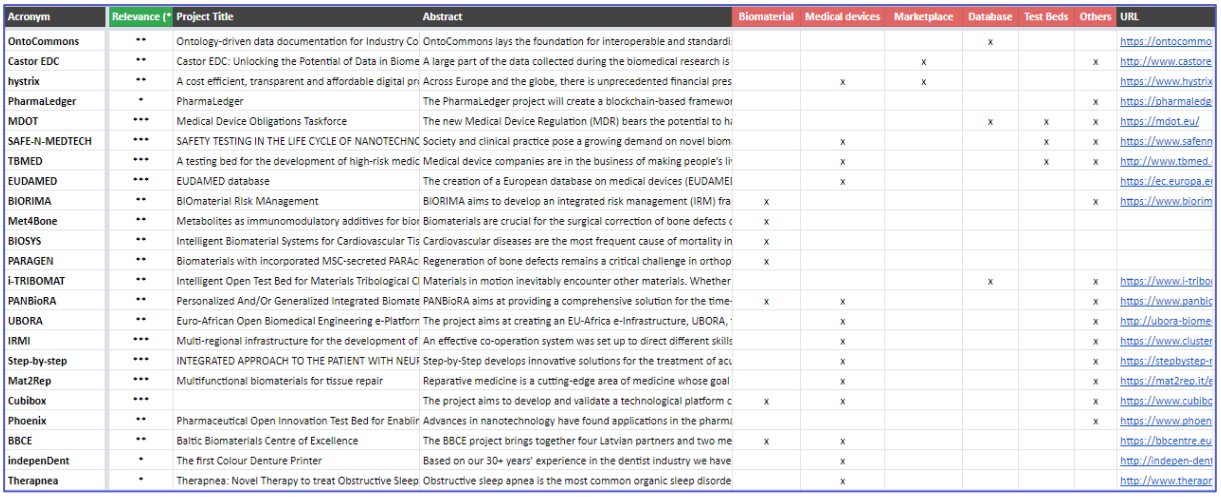
The **Events collection sheet** (Figure 13) serves for the collection of relevant events such as conferences, expositions, fairs or similar in the medical devices or biomaterials field. On the one hand, this collection is useful to find opportunities to promote the BIOMATDB project, on the other hand, the BIOMATDB consortium wants to publish this comprehensive collection of events on the BIOMATDB website to become a useful source of information for our stakeholders who may be interested in participating in such events. Currently, 64 events are included in the Events collection sheet (Figure 2).



Name	Relevance	URL	Country	City	Location	Host / Initiator	Geographical Focus	Start	End	Participants	Conference	Exposition	Other
2022 International Conference on Biotechnology and B	***	https://www.icbb.apaset.edu.pl/	Webinar		(Webinar)	Asia-Pacific Association of Science, En	International	27/09/2022	30/09/2022		x		
BIOMEDevice	***	https://www.biomedboston.com/	US	Boston	Boston (US)	Informa PLC	New England	28/9/2022	29/9/2022				
IDS Internationale Dental-Schau	***	https://www.ids-cologne.de/die-r	DE	Köln	Köln (DE)	GFDI Gesellschaft zur Förderung der D	International	14/3/2023	18/3/2023	2000 exhibitors, 65 c		x	
32nd Annual Conference of the European Society of Bic	***	https://www.esbbordeaux2022.o	FR	Bordeaux	Bordeaux (FR)	European Society of Biomaterials & B	Europe	4/9/2022	8/9/2022	1200	x		
12th World Biomaterials Congress (WBC)	***	https://www.wbc2024.com	KR	Daegu	Daegu (KR)	The Korean Society for Biomaterials	Worldwide	26/5/2024	31/5/2024		x		
European Advanced Materials Congress	***	https://www.advancedmaterialsc	IT	Genoa	Genoa (IT)	International Association of Advancec	Europe	25/6/2022	2/7/2022		x		
International Conference Bioceramics32	***	https://bioceramics32.org/	IT	Venice	Venice (IT)	International Society for Ceramics in I	International	20/9/2022	23/9/2022		x		
World Orthopaedic Research Congress, ICORS 2022	**	https://www.2022icors.org/	UK	Edinburgh	Edinburgh (UK)	British Orthopaedic Research Society	International	7/9/2022	9/9/2022		x		
2022 International Conference on Advances in Nanotec	*	https://icanm2022.iaemm.com/C	CA	Victoria BC	Victoria BC (CA)	ICANM2022 Organizing & Scientific Cc	International	08/08/2022	10/08/2022		x	x	
27th International conference on Biotechnology and Bi	***	https://biotechnology.euroscicon.	DE	Berlin	Berlin (DE)	EuroSciCon Ltd	International	23/08/2022	24/08/2022		x		
Medtech World	**	https://www.medtechchina.com/e	CN	Shanghai	Shanghai (CN)	Informa PLC	Global	31/8/2022	2/9/2022	> 800 exhibitors; > 40	x	x	
14th Symposium on Biodegradable Metals Conference	**	https://www.biodegradablemetal	ES	Alicante	Alicante (ES)	Biometal	international	24/8/2022	29/8/2022		x		
European Society of Craniofacial Surgery (ESCFS) Bienni	**	https://escfs2022.com/	UK	Oxford	Oxford (UK)	ESCFS	Europe	23/9/2022	24/8/2022		x	x	
Biofabrication 2022 Pisa	*	https://www.biofabrication2022.c	IT	Montecatini Terme	Montecatini Terme (IT	Valeria Chiono, Chiara Vitale-Brovaror	international	25/9/2022	28/8/2022		x		
BIOMAH 2022 - BIOMATERIALS AND NOVEL TECHNOLO	***	https://biomah.ism.cnr.it/	IT	Roma	Roma (IT)	CNR	International	18/10/22	21/10/2022		x		
OMTEC - The Orthopaedic Manufacturing & Technology	*	https://www.omtecexpo.com/	US	Chicago	Chicago (US)	ORTHOWORLD Inc.	International	13/06/2023	15/06/2023		x	x	
2023 TERMIS-EU - Broadening the Targets and Approac	***	https://eu2023.termis.org/	UK	Manchester	Manchester (UK)	Tissue Engineering and Regenerative	International	27/03/2023	30/03/2023	Over 1.200	x		
2023 TERMIS-AM - Tissue Engineering Strategies for Hu	**	https://am2023.termis.org/	US	Boston	Boston (US)	Tissue Engineering and Regenerative	International	11/04/2023	14/04/2023		x		
2022 TERMIS-AP - New Chapter of Future Regenerative	**	https://ap2022.termis.org/	KR	Jeju Island	Jeju Island (KR)	Tissue Engineering and Regenerative	International	05/10/2022	10/10/2022		x		
KMM-VIN Industrial Workshop (IW9): "Design and moc	**	https://www.kmm-vin.eu/worksh	AT	Vienna	Vienna (AT)	KMM-VIN, the Vienna Center for Engi	Europe	22/09/2022	23/09/2022				
Micro and Nanotechnology in Medicine (MNM) confere	***	https://mnm.embs.org/2022/	US	Hawaii	Hawaii (US)	IEEE Engineering in Medicine and Biol	International	05/12/2022	09/12/2022		x		
SFB 2023 Annual Meeting	***	https://biomaterials.org/2023-SFE	US	San Diego	San Diego (US)	The Society For Biomaterials	International	19/04/2023	22/04/2023		x		

Figure 13. Events collection sheet

The **Projects collection sheet** (Figure 14) collects projects that may provide relevant assets or collaboration opportunities for the BIOMATDB project. Some of the projects collected in the Projects collection sheet, have been identified as possible assets or collaboration partners for BIOMATDB and are described in more detail in section Additional project and technology assets of this deliverable. As of now, 52 entries have been collected (Figure 2).



Acronym	Relevance (*	Project Title	Abstract	Biomaterial	Medical devices	Marketplace	Database	Test Beds	Others	URL
OntoCommons	**	Ontology-driven data documentation for Industry Co	OntoCommons lays the foundation for interoperable and standardi				x			https://ontocommo
Castor EDC	**	Castor EDC: Unlocking the Potential of Data in Biome	A large part of the data collected during the biomedical research is			x			x	http://www.castore
hystrix	**	A cost efficient, transparent and affordable digital pr	Across Europe and the globe, there is unprecedented financial pres		x	x				https://www.hystrix
PharmaLedger	*	PharmaLedger	The PharmaLedger project will create a blockchain-based framewor						x	https://pharmaledg
MDOT	***	Medical Device Obligations Taskforce	The new Medical Device Regulation (MDR) bears the potential to hi				x	x	x	https://mdot.eu/
SAFE-N-MEDTECH	***	SAFETY TESTING IN THE LIFE CYCLE OF NANOTECHNC	Society and clinical practice pose a growing demand on novel biom		x			x	x	https://www.safenn
TBMED	***	A testing bed for the development of high-risk medic	Medical device companies are in the business of making people's li		x			x	x	http://www.tbmed.
EUDAMED	***	EUDAMED database	The creation of a European database on medical devices (EUDAMEI		x					https://ec.europa.e
BIORIMA	**	BIOmaterial RIsk MAnagement	BIORIMA aims to develop an integrated risk management (IRM) fra	x					x	https://www.biorim
Met4Bone	**	Metabolites as immunomodulatory additives for bior	Biomaterials are crucial for the surgical correction of bone defects c	x						
BIOSYS	**	Intelligent Biomaterial Systems for Cardiovascular Tis	Cardiovascular diseases are the most frequent cause of mortality in	x						
PARAGEN	**	Biomaterials with incorporated MSC-secreted PARAc	Regeneration of bone defects remains a critical challenge in orthop	x						
i-TRIBOMAT	**	Intelligent Open Test Bed for Materials Tribological Cl	Materials in motion inevitably encounter other materials. Whether				x		x	https://www.i-tribo
PANBioRA	**	Personalized And/Or Generalized Integrated Biomate	PANBioRA aims at providing a comprehensive solution for the time-	x	x				x	https://www.panbic
UBORA	**	Euro-African Open Biomedical Engineering e-Platforn	The project aims at creating an EU-Africa e-Infrastructure, UBORA,		x				x	http://ubora-biome
IRMI	***	Multi-regional infrastructure for the development of	An effective co-operation system was set up to direct different skills		x				x	https://www.cluster
Step-by-step	***	INTEGRATED APPROACH TO THE PATIENT WITH NEUF	Step-by-Step develops innovative solutions for the treatment of acu		x				x	https://stepbystep-r
Mat2Rep	***	Multifunctional biomaterials for tissue repair	Reparative medicine is a cutting-edge area of medicine whose goal		x				x	https://mat2rep.it/e
Cubibox	***		The project aims to develop and validate a technological platform c	x	x				x	https://www.cubibo
Phoenix	**	Pharmaceutical Open Innovation Test Bed for Enablir	Advances in nanotechnology have found applications in the pharma						x	https://www.phoen
BBCE	**	Baltic Biomaterials Centre of Excellence	The BBCE project brings together four Latvian partners and two me	x	x					https://bbcentre.eu
indepenDent	*	The first Colour Denture Printer	Based on our 30+ years' experience in the dentist industry we have		x					http://indepen-dent
Therapnea	*	Therapnea: Novel Therapy to treat Obstructive Sleep	Obstructive sleep apnea is the most common organic sleep disorde		x					http://www.therapr

Figure 14. Projects collection sheet

The **Research community collection sheet** (Figure 15) is particularly relevant to identify potential users of the BIOMATDB solutions, and to find participants for the BIOMATDB surveys and interviews. Two distinct tabs were created within the Research community collection sheet: One tab to collect relevant research institutions (e.g., universities, departments, private research institutions) and the other to collect contacts of individual researchers in the field of biomaterials. All the contact details included in this list were found publicly available e.g., on institutional websites. At this point in time, the consortium has already collected 226 research institutions and 252 individual researchers (Figure 2).

Institution	Department	Research Group	URL	Description (short descriptio	Type	Founded	Employees	Country	Street	ZIP Code	City
Texas A&M University College of Engineering	Department of Biomedical		https://engineering.tamu.e	The Department of Biomedic	public	1972	501-1.000	US	125 Spence S	77843-3127	College Sta
Texas A&M University College of Engineering	Department of Biomedical	Translational and Innovati	https://nanomedicine.eng	The Translational and Innovat	public	2019	11	US	126 Spence S	77843-3128	College Sta
Texas A&M University College of Engineering	Department of Biomedical	Bio-instructive Materials La	https://sites.google.com/t	The Bio-instructive Materials	public		11	US	5045 Emergir	77843-3125	College Sta
IRCCS IRST Meldola	Laboratorio di Bioscienze		https://www.irst.emr.it/it/	The Bioscience Laboratory is	private	1997		IT	Via Piero Mar	47014	Meldola (F
IRCCS Istituto Ortopedico Rizzoli	Research, Innovation & Te		https://www.ior.it/en/ricer	The RIT - Research, Innovatio	public	1896	1001-5000	IT	Codivilla-Putt	40136	Bologna
Consiglio Nazionale delle Ricerche	Institute of science and tec		https://www.cnr.it/en/inst	ISTEC, belonging to the CNR I	public	1945		IT	Via Granarolo	48018	Faenza (RA
Fondazione IRET			https://iret-foundation.org	The IRET Foundation is a scie	non profit	2006		IT	Via Tolara di S	40064	Ozzano Em
Università di Bologna	Centro Interdipardimental		https://centri.unibo.it/aero	CIRI Aeronautica promote the	public			IT	via Baldassar	47121	Forlì
Università di Bologna	Centro Interdipartimentale		https://centri.unibo.it/mar	CIRI-MAM is the Interdepartr	public			IT	Viale Risorgir	40136	Bologna
Università di Bologna	Centro Interdipartimentale		https://centri.unibo.it/tecr	CIRI SDV - Centro Interdipartı	public			IT	Via Tolara di S	4140064	Ozzano de
Università degli Studi di Ferrara	TekneHub		https://teknehub.tecnopol	TekneHub is one of the indus	public			IT	Via Saragat, 1	44122	Ferrara (FE
Consiglio Nazionale delle Ricerche	Institute of Polymers, Com		http://www.ipcb.cnr.it/ind	The IPCB's mission is to devel	public	2014		IT	Via Campi Fle	80078	Pozzuoli (N
Politecnico di Milano	Department of Electronics		https://www.deib.polimi.it	DEIB aims at being a world-cl	public	2013		IT	Via Ponzio 34	20133	Milano
Politecnico di Milano	Department of Chemistry,		https://www.cmic.polimi.it	The Department's common v	public	2001		IT	Via Luigi Mar	20131	Milano
Consiglio Nazionale delle Ricerche	Institute for Biomedical Re		https://www.irib.cnr.it/en/	The goal is the search for new	public	2019		IT	Via Ugo La M	90146	Palermo
Università degli studi di Napoli Federico II	Department of Chemical E		https://www.ricerca.unina	The Department is one of the	public	2013		IT	Piazzale V. Te	80125	Napoli
Università Campus Bio-Medico di Roma	Tissue Engineering and Ch		http://www.unicampus.it/	Within the Faculty of Enginee	private	1993		IT	Via Alvaro de	00128	Roma
Università degli Studi di Perugia	Department of Civil and En		https://ing1.unipg.it/en/	The research activity in the fi	public	2014		IT	Via G. Durant	06125	Perugia
Università degli Studi di Ferrara	Department of Life Science		http://sveb.unife.it/it?set_	The researches performed in	public			IT	Via L.Borsari,	44121	Ferrara (FE
Politecnico di Torino	Interdepartmental Center		https://www.biomedlab.p	The Interdepartmental Cente	public			IT	Corso Castelf	10138	Torino
Politecnico di Torino	Department of Applied Sci		https://www.disat.polito.it	DISAT develops and promotes	public			IT	Corso Duca d	10129	Torino
Istituto Italiano di Tecnologia	Center for Advanced Biom		https://www.iit.it/cabhc-c	The Center for Advanced Bior	public			IT	Via Morego,	16163	Genova
Università degli studi di Napoli Federico II	Interdepartmental Centre		http://www.crib.unina.it/h	CRIB is one of the earliest inte	public	1992		IT	Piazzale Tecc	80125	Napoli
Università degli Studi di Pavia	Interdepartmental Researc		https://fisica.unipv.it/MAD	MADE is made up of research	public	2015		IT	Via Bassi 6	27100	Pavia

Researcher	Description (Researcher, s	Title (Rese	Role (Researcher)	Phone (Researcher)	E-Mail (Researcher)	Research areas	Institution	Department	Research Group
Isaac Adjei	Dr. Isaac Adjei's goals are t	PhD	Assistant Professor	979-458-2536	adjeii@tamu.edu	Biomaterials, micro/nanotechnology, tiss	Texas A&M University College	Department of Biomedical	Translational and Innovati
Daniel Alge	Dr. Daniel L. Alge's researcl	PhD	Associate Professor,	979-458-9248	dalge@tamu.edu	Biomaterials, tissue engineering, medical	Texas A&M University College	Department of Biomedical	Bio-instructive Materials L
Catherine Ambrose	Dr. Catherine Ambrose ser	PhD	Visiting Professor	979-845-5532	cambrose@tamu.edu	Biomaterials, bone health, orthopaedic i	Texas A&M University College	Department of Biomedical	
Brunella Grigolo	Dr. Brunella Grigolo has a l	PhD	Head	+39-051-6366803	brunella.grigolo@ior.it	Regenerative medicine in orthopedic fiel	IRCCS Istituto Ortopedico Rizzo	Research and Innovation T	RAMSES Laboratory
Carla Renata Arciola	Carla Renata Arciola is Full	MD, PhD	Head and Full Professo	+39 51-6366747	carlarenata.arciola@ior.it	Pathology of implant associated infection	IRCCS Istituto Ortopedico Rizzo	Orthopedic-Trauma Pathol	Laboratory on Implant Infe
Nicola Baldini	Nicola Baldini is Associate	MD	Head, Director and As	+39-051-6366566	nicola.baldini@ior.it	Musculoskeletal oncology; pathophysiolc	IRCCS Istituto Ortopedico Rizzo	Research and Innovation T	Biomedical Science and Te
Milena Fini	Milena Fini is the new Scie	MD	Scientific Director	+39-051-6366557	milena.fini@ior.it	Prevention, diagnosis and therapy of acu	IRCCS Istituto Ortopedico Rizzo	Research and Innovation T	
Maria Letizia Focarete	Maria Letizia Focarete is Fu	PhD	Full Professor	+39 051 20 9 9577	marialetizia.focarete@un	Functional polymeric materials, biomatei	Università di Bologna	Department of Chemistry	Polymer Science and Biom
Anna Tampieri	Anna Tampieri has 30 year	PhD	Research Executive - I	+390546699753	anna.tampieri@istec.cnr.	Drug delivery, Biologically inspired proce	Consiglio Nazionale delle Ricer	Institute of science and tec	
Simone Sprio	Simone Sprio is the Scienti	PhD	First researcher	+390546699759	simone.sprio@istec.cnr.it	Innovative nanomaterials and nanotechn	Consiglio Nazionale delle Ricer	Institute of science and tec	
Barbara Zavan	Prof Zavan's research seek	PhD	Associate Professor	+390532 455882	barbara.zavan@unife.it	Translational medicine: bench to bedside	Università degli Studi di Ferrara	Department of Translation	Tissue Engineering and Re
Claudio Nastruzzi	The research activity of Pr	PhD	Associate Professor	+390532 455348	claudio.nastruzzi@unife.i	Biomaterials, bioencapsulation, drug forr	Università degli Studi di Ferrara	Department of Life Science	Biomaterials
Gianluca Ciardelli	Gianluca Ciardelli is coordi	PhD	Full Professor	+39 0110906919	gianluca.ciardelli@polito	Soft tissue engineering, Synthesis of bion	Politecnico di Torino	Department of Mechanica	Materials in bionanotechn
Valeria Chiono	Valeria Chiono's research i	PhD	Full Professor	+39 0110906920	valeria.chiono@polito.it	Soft tissue engineering, Synthesis of bion	Politecnico di Torino	Department of Mechanica	Materials in bionanotechn
Chiara Vitale-Brovarone	Prof. Chiara Vitale-Brovaro	PhD	Full Professor	+39 0110904564	chiara.vitalebrovarone@p	3D bioprinting, Biomaterial processing, B	Politecnico di Torino	Department of Applied Sci	Biomaterials
Laura Montanaro	Prof. Laura Montanaros's r	PhD	Full Professor	+39 0110904680	laura.montanaro@polito	3D printing, Bioceramics, Ceramics, Cera	Politecnico di Torino	Department of Applied Sci	Ceramic Materials
Guido Maria Macaluso	Prof Guido Maria Macalusi	MD, DDS	Professor and Dean	+39 0521033659	guidomaria.macaluso@u	Bone regeneration, scaffold, 3D printing,	Università degli studi di Parma	Department of Medicine a	Biomaterials and Tissue En
Filippo Causa	Filippo Causa is an associat	PhD	Associate Professor	+39 0817682603	filippo.causa@unina.it	Biomedical equipment,biomedical mater	Università degli Studi di Napoli	Department of Chemical, I	
Paolo Antonio Netti	Paolo A. Netti is a full profe	PhD	Full Professor	+39 0817682408	paoloantonio.netti@unin	Design of novel biomaterials, Drug delive	Università degli Studi di Napoli	Department of Chemical, I	
Maurizio Ventre	Maurizio Ventre is a mater	PhD	Associate Professor	+39 0817685929	maurizio.ventre@unina.it	Biomaterials, Tissue engineering, Biophy	Università degli Studi di Napoli	Department of Chemical, I	
Laura Calzà	Prof. Laura Calzà is full pro	MD	Full Professor	+39 051 798776	laura.calza@unibo.it	animal models; neural stem cells; neurot	Università di Bologna	Department of Pharmacy a	
Livia Visai	Livia Visai is Associate Prof	PhD	Associate Professor	+39 0382 987725	livia.visai@unipv.it	Nanotechnology and Nanomedicine	Università degli Studi di Pavia	Department of Molecular	Laboratory of cell-biomate
Silvia Farè	Silvia Farè's main research	PhD	Full Professor	+39 02 2399 3389	silvia.fare@polimi.it	Additive Manufacturing, Artificial Organs	Politecnico di Milano	Department of Chemistry,	Biomaterials and Biofabric
Gabriele Candiani	Gabriele Candiani is Profes		Associate Professor	+39 02 2399 3181	gabriele.candiani@polim	Antibacterial Surfaces, Biocompatibility, I	Politecnico di Milano	Department of Chemistry,	Biocompatibility and Cell C

Figure 15. Research community collection sheet – Collection of institutions & researchers

Within the **Policy makers & Regulators collection sheet** (Figure 16) the consortium has collected public bodies, public administrations, governmental, regulation and standardisation bodies, certifiers, policy stakeholders, and policy makers involved in the regulation and certification of biomaterials or in the approval of medical devices. At the moment the collection contains 135 entries (Figure 2).

Name	URL	Company	Authority	Agency	Organisation	Others	Description (short description or some keywords)	Country	Type	Founded
Bundesamt für Sicherheit im Gesundheitswesen (BASG)	https://www.basg.gv.a		x				The BASG has been entrusted with a multitude of tasks in	AT	governmental	2006
European Medicines Agency (EMA)	https://www.ema.euro			x			The European Medicines Agency (EMA) is a decentralised	NL	networking organi	1995
Italian Medicines Agency	https://www.aifa.gov.it			x			The Italian Medicines Agency - AIFA is a public body opera	IT	governmental	2004
Direzione generale dei dispositivi medici e del servizio far	https://www.salute.go		x				The Directorate-General for Medical Devices and the Phar	IT	governmental	
Istituto Superiore di Sanità	https://www.iss.it/web				x		The Notified Body (ON ISS) operates at the Italian Nationa	IT	public body	
Certiquality	https://www.certiqual	x					Certiquality, acting as Notified Body (no. 0546) for the Reg	IT	private	1989
Eurofins Product Testing	http://tech.eurofins.it/	x					Today Eurofins Industrial & Product Services Italy with its t	IT	private	1970
Kiwa	https://www.kiwa.com	x					We are Kiwa, a world top 20 leader in Testing, Inspection a	IT	private	
ITALCERT	https://www.italcert.it	x					ITALCERT Srl is a Conformity Assessment Body, which has l	IT	private	1992
Istituto Italiano del Marchio di Qualità	https://www.imq.it/en	x					IMQ supports medical device manufacturers with product	IT	private	1999
ASTM International	https://www.astm.org				x		ASTM International is a globally recognized leader in the d	US	non-profit	1902
CEN	https://www.cencenel					x	CEN provides a platform for the development of European	BE	non-profit	
ISO	https://www.iso.org/h				x		ISO is an independent, non-governmental international or	CH	non-governmental	1946
ITA - Italian Trade Agency	https://www.ice.it/en/			x			ITA - Italian Trade Agency is the Governmental agency that	IT	governmental	1926

Figure 16. Policy makers & Regulators collection sheet

Currently, the **Investors collection sheet** (Figure 17) consists of a collection of 46 individuals, companies, or other entities who invest money in the biomaterials or medical device field (Figure 2).

Investor (Person/Entity)	URL	Description (short description or some keywords)	Legal Name	Type	Founded	Employees	Street	ZIP Code	City	Country
Innogest	http://www.innoge	Innogest is a Venture Capital firm focused on seed a	Innogest Sgr	private	2006	11-50	Via Locatelli Antonio, 2	1	Milano	IT
Italian Angels for Biotech (IAI	http://www.italians	IAB is an association made by a group of people wit	Italian Angels for Biot	non-profit	2015		Via Antonio Meucci 3	20091	Bresso (MI)	IT
Italian Angels for Biotech (IAI	http://www.panake	Panakes is a venture capital firm with the ultimate g	Panakes Partners SGR	private	2015	11-50	via Boscovich 31	20124	Milano	IT
3B Future Health Ventures	https://3bfuturehe	3B Future Health Fund supports US and European-b	3B FUTURE HEALTH V	private	2016		7-9 Av. de Grande Bretagne	98000	Monaco	MC
Angels for Impact	https://angels4imp	A group of Business Angels investing in startups wit	Angels for Impact	non-profit	2015	2-10	C/O Impact Hub Milano, Vi	20155	Milano	IT
DSW Ventures	https://dsw.vc/	DSW Ventures is a national firm of seed and early-st	DSW Angels LLP	private	2019	1-10	Department Bonded Warel	M3 4AP	Manchester	UK
DuPont Capital Management	https://dupontcapi	At DuPont Capital we apply value-based global inve	DuPont Capital Mana	Private	1993	80-100	974 Centre Road	19805	Wilmington, DE	US
NLC	https://nlc.health/	We find inventions, select the most promising ones,	NLC - The European H	private	2014	51-200	Amsterdam Health and Tec	1105	BP Amsterdam	NL
Sofinnova Partners	https://sofinnovap	Sofinnova Partners is a leading European venture ca		private	1972	11-50	7-11, Boulevard Haussman	75009	Paris	FR
Business Finland	https://www.busin	government organization for innovation funding and trade, travel and inve		non-profit			Porkkalankatu 1		Helsinki	FI
CDP Venture Capital	https://www.cdpve	CDP Venture Capital – Fondo Nazionale Innovazione	CDP Venture Capital S	private		51-200	Via Alessandria 220	00198	Roma	IT
Club degli Investitori	https://www.clubd	Club degli Investitori is one of the main business an	Club degli Investitori	non-profit	2008	2-10	c/o Talent Garden Fondazic	10125	Torino	IT
EUREKA! Venture	https://www.eurek	We are the first independent Italian venture capital	EUREKA! Venture SGF	private	2019	2-10	Via Vincenzo Monti 8	20123	Milano	IT
Fondo Italiano d'Investiment	https://www.fondo	We promote the competitiveness of Italy's industria	Fondo Italiano d'Inve	private	2010	51-200	Via San Marco 21A	20121	Milano	IT
Health Technology Holding	https://www.hthvc.	HTH is a full fledge investment and advisory compa	Health Technology Hc	private	2020		Corso Italia 15	20122	Milano	IT
Italian Business Angels Netw	https://www.iban.it	IBAN is the Italian National Association focused on t	Associazione Italiana	non-profit	1999	2-10	C/O Impact Hub Milano, Vi	20155	Milano	IT
Indaco Venture Partners	https://www.indac	Indaco Venture Partners today is the largest indepe	Indaco Venture Partn		2016		Galleria San Babila 4/B	20122	Milano	IT
Invitalia	https://www.invital	Invitalia is the National Agency for Inward Investme	Agenzia nazionale per		2007	1,001-5,000	Via Calabria, 46	00187	Roma	IT
Italian Angels for Growth	https://www.italian	The largest network of business angels in Italy, inve	Italian Angels for Gro	non-profit	2007	2-10	Via Manfredo Camperio, 4	20123	Milano	IT
LIFTT	https://www.liftt.c	We invest in newly conceived projects by providing	LIFFT	private	2019	11-50	Via Pier Carlo Boggio, 61	10138	Torino	IT
Mercia Asset Management	https://www.merci	Mercia Asset Management providing equity and de	Mercia Asset Manage	Private	2014	<25	17 High St	B95 5AA	Henley-in-Arden	UK
META	https://www.meta-	META Group is an international advisory and investi	META Group	private	1993	11-50	Avenue des Arts, 12		Brussels	BE
Northwater Capital Managen	https://www.north	Northwater Capital Management Inc. operates as a	Northwater Capital M	Private	1989	10-20	Brookfield Place, 161 Bay S	M5J 2S1	Toronto	CA
Pangea Ventures	https://www.panga	We believe advanced materials have the ability to s	Pangea Ventures, Ltd.	Private	2000	2-10	1500 W Georgia St, Ste 152	V6G 2Z6	Vancouver	CA

Figure 17. Investors collection sheet

The **Marketplaces and Online Platforms collection sheet** (Figure 18) includes marketplaces, such as platforms that sell biomaterials products or services from multiple suppliers or mediate contacts between suppliers and demanders in order to sell biomaterials products or services (B2B), or other online platforms, where information about biomaterials can be found. Online biomaterials databases were added to this list as well. 41 entries can be assigned to this individual collection sheet (Figure 2).

Name	Relevance	URL	Description	Biomaterials products	Services	Information	Database
Medical Device + Diagnostic Industry (MD+DI)	*	https://directory.qmed.com/form-supplied-code006122.htm	Medical Device + Diagnostic Industry (MD+DI) is a resource e			x	
Medical EXPO	***	https://www.medicalexpo.com/medical-manufacturer/elbow	The marketplace for medical devices and supplies	x			
Omnia Health	***	https://www.omnia-health.com/	B2B medical marketplace	x			
The Biomaterial Store	***	https://www.thebiomaterialstore.co.uk/	The Biomaterials store has been set up to supply all the need	x			
GUDID	**	https://accessgudid.nlm.nih.gov	The Global Unique Device Identification Database (GUDID) co				x
Science Exchange	*	https://ww2.scienceexchange.com/s/	With our enterprise SaaS-enabled marketplace, R&D teams c		x		
ZPP Dentalmedizintechnik GmbH	***	https://www.dental-markt.com	The company ZPP is a family business with over 20 years of e	x			
Wound Reference	**	https://woundreference.com/about	We are a self-funded startup building a decision support platf			x	
scientist.com	*	https://scientist.com	Use our award-winning marketplace to quickly find the tools		x		
Medwish	***	https://www.medwish.com/	B2B marketplace for medical supply and devices	x			
Euro Biotechnologies	***	https://www.eurobiotechnologies.com.au	Euro Biotechnologies is a leading Medical and Dental Supplie	x			
Prospector	**	https://www.ulprospector.com	Search thousands of materials from global suppliers by keywo	x			
Total Materia	**	https://www.totalmateria.com/	Allow to find mechanical and physical properties of diverse m	x		x	
ChemSpider	**	https://www.chemspider.com/	ChemSpider is a free chemical structure database providing f	x		x	x
Material Properties Database	**	https://www.makeitfrom.com/	Curated database of engineering material properties that em	x		x	x
MATDAT	**	https://www.matdat.com/	Constituted by a Database of Materials Properties, a DIRECTC	x	x	x	x
Matmach	**	https://matmatch.com/	Find the optimal material based on your required performanc	x		x	
BoneZone	***	https://bonezonepub.com/	Comprehensive database of orthopedic-focused suppliers. La	x			x
Bioz	***	https://www.bioz.com/	Bioz supports researchers in their product-selection and purc	x		x	x
Oisto	**	https://oisto.com/	A site that sells products online. Allows users to create a purc	x			
MediBid	**	https://www.medibid.com/	MediBid offers cash paying patients seeking care the ability to	x			
Chamfr	**	https://chamfr.com/	Accelerate your medical device development Start ordering t	x			
ICIJ Medical Devices Database	***	https://medicaldevices.icij.org/	This database contains information on more than 120,000 Re	x		x	x
Materials Marketplace	**	https://go.materialsmarketplace.org/	The Materials Marketplace connects businesses and organiza	x			

Figure 18. Marketplaces + Online Platforms collection sheet

Within the **Publications collection sheet** (Figure 19) the consortium collected 640 biomaterials journals, books, and other publications (e.g., presentations, …) relevant to the BIOMATDB project (Figure 2).

Name	Relevance	Journal	Book	Other	Contents/Description	ISSN/ISBN	Country	Region	Publisher	Author/Editor	Year	URL
Regenerative Biomaterials	***	x			Regenerative Biomaterials is a fully open access,	20563418, 20563426	UK	Western Europe	Oxford University Press	las Peppas; Xingdong		https://academic.oup.com/rb
Biomaterials and Engineering for Implantology : In	***		x		Biomaterials are composed of metallic materials,	978-3-11-074013-4	DE	Western Europe	De Gruyter	i, Oshida; Takashi, Mi	2022	https://www.degruyter.com/document/
Biopolymers and Biomaterials	***		x		Biopolymers are attracting immense attention of	1-315-16198-2	CA	Northern America	Apple Academic Press	Padinjakkara et. al	2018	https://www.routledge.com/Biopolymer
Nature Reviews Materials	***	x			Biomaterials; Electronic, Optical and Magnetic M	20588437	UK	Western Europe	Nature Publishing Group	Giulia Pacchioni		https://www.nature.com/natrevmats/
Advanced Functional Materials	***	x			materials science, nanotechnology, liquid crystals	1616301X	DE	Western Europe	Wiley-VCH Verlag	Jörn Ritterbusch		https://onlinelibrary.wiley.com/journal/
Advanced healthcare materials	***	x			Biomaterials; Biomedical Engineering; Pharmace	21922640, 21922659	UK	Western Europe	John Wiley and Sons Ltd	Uta Goebel		https://onlinelibrary.wiley.com/journal/
Acta Biomaterialia	***	x			Hypothesis-driven design of biomaterials, Biomat	17427061	NL	Western Europe	BioMed Central Ltd.	William R. Wagner		https://www.journals.elsevier.com/acta-
Biomaterials Research	***	x			Biomaterials; Biomedical Engineering; Ceramics a	20557124	UK	Western Europe	Springer Nature	Byeongmoon Jeong		https://biomaterialsres.biomedcentral.c
Biocomposites and Hybrid Biomaterials of Calcium	***		x		Mimicking the structure of calcified tissues and a	0-429-43937-7	US	Northern America	CRC Press	Sergey V., Dorozhkin	2018	https://www.routledge.com/Biocompos
Biomaterials science and technology : fundamental	***		x		Biomaterials Science and Technology: Fundamen	0-429-87835-4	US	Northern America	CRC Press	Yaser, Dahman	2019	https://www.routledge.com/Biomateria
Biomaterials and immune response : complications	***		x		The interactions of the biomaterials with the hos	1-351-37756-6	US	Northern America	CRC Press	Nihal Engin, Vrana	2018	https://www.routledge.com/Biomateria
Peptide-based biomaterials	**		x		Covering the fundamental concepts of self-assem	978-1-83916-114-8	UK	Western Europe	Royal Society of Chemistry	Mustafa Ö., Güler	2021	
European Cells and Materials	***	x			eCM Journal (Eur Cell Mater) provides an interdis	14732262	CH	Western Europe	AO Research Institute			https://www.ecmjournal.org/index.html
Transactions of the Annual Meeting of the Society f	*			x	Biochemistry; Biomaterials; Biophysics; Biotechn	15267547	US	Northern America				
Definitions of Biomaterials for the Twenty-First Cen	***		x		Definitions of Biomaterials for the Twenty-First C	978-0128182918	NL, UK, US	International	Elsevier	long Zhang, David Wil	2019	https://www.elsevier.com/books/definit
The Biomedical Engineering Handbook: Four Volum	***		x		The definitive "bible" for the field of biomedical e	978-1439825334	US	Northern America	CRC Press	, Bronzino, Donald R.	2018	https://www.routledge.com/The-Biome
Advanced Dental Biomaterials	**		x		Advanced Dental Biomaterials is an invaluable ref	476-8, 9780081024775			Elsevier	Najeeb, Muhammad S	2019	https://www.elsevier.com/books/advan
Additive Manufacturing Processes in Biomedical En	*		x		This book covers innovative breakthroughs in adc	9781003217961	US	Northern America	CRC Press	kit Sharma, Vivek Jain	2023	https://www.routledge.com/Additive-M
Tissue Engineering Applications and Advancement	**		x		This new volume on applications and advances in	9781003180531	CA	Northern America	Apple Academic Press	wani, Raj K. Keservan	2022	https://www.taylorfrancis.com/chapters
Biomaterials Science: An Introduction to Materials	***		x		The revised edition of the renowned and bestsell	978-0128161371	UK, US		Academic Press	Shelly E. Sakiyama-Elk	2020	https://www.elsevier.com/books/bioma
Bio Engineering Database. Part 1: Introduction to B	***			x			UK	Western Europe	ANSYS	shby, Ana G. Pereira-I	2008	https://www.ansys.com/content/dam/a
White Paper on the Biologization of Materials Rese	*			x	The recommendations of the panel of experts on				Preprints	Bastmeyer, Stefan Brä	2018	https://www.preprints.org/manuscript/
Fundamentals in Biomaterials	***		x		Integrates materials and biological properties to	978-1493988549	CH	Western Europe	Springer	sif Hasirci, Nesrin Hasi	2018	http://link.springer.com/book/10.1007/
Engineering of Biomaterials	***		x		Presents case studies on different applications of	978-3-319-58607-6	CH	Western Europe	Springer	mary Nichele Brandal	2017	http://link.springer.com/book/10.1007/

Figure 19. Publications collection sheet

Another Google spreadsheet was provided for the collection of websites and sources containing an abundance of information about stakeholders, entities, or materials that might be relevant for the other collection sheets (Figure 20). For example, this could be websites where lists of suppliers, demanders, products, enablers, publications, and so forth are presented or where a large number of suppliers, demanders, products, enablers, publications, etc. can be identified.

Name	URL	Description	Conferences	Demanders	Enablers	Suppliers	Products	Books/Jounals	Marketplaces
Euroscicon	https://euroscicon.com	Euroscicon is the longest running independent life science ev	x						
conferenceseries	https://biomaterials.insightconferences.com	Conferenceseries LLC Ltd and its subsidiaries including iMedP	x		x	x			
VentureRadar	https://www.ventureradar.com/similar/Science%20Exchange	VentureRadar discovers and ranks companies, making them v							x
Medtec China	https://www.medtecchina.com/en-us/OnlineDirectory	exhibitor list, international suppliers, emphasis on China		x		x			
MedtecLive	https://www.medteclive.com/en/exhibitors-products	exhibitor list, international suppliers, emphasis on DACH regi		x		x			
BioSpace	https://www.biospace.com/about-us/	company information and news, not specialized on medical d		x		x			
Medical EXPO	https://www.medicalexpo.com/medical-manufacturer/elbov	find suppliers of medical devices and products		x		x			
Medical Device + Diagnostic Industry	https://directory.qmed.com/form-supplied-code006122.htm	Medical Device + Diagnostic Industry (MD+DI) is a resource e				x	x		
Newsweek	https://www.newsweek.com/worlds-best-specialized-hospit	hospital rankings		x					
MedTech Europe	https://www.medtecheurope.org/market-data/	list of partners (companies, associations, institutions)			x	x			
Medical Tenders	https://www.medicaltenders.com/index.php	Welcome to Medical Tenders, an exclusive portal where you c		x					
EHPPA	https://www.ehppa.com/Members/3/5/1013	The EHPPA association was created in 2012 by Resah (Fr) & N		x					
Biomat	https://biomat.net/site/events/	Biomaterial Information Platform; Biomat.net is an organized	x					x	
Scimago Journal & Country Rank	https://www.scimagojr.com/journalrank.php?category=2502	The SCImago Journal & Country Rank is a publicly available pc						x	
Science Exchange	https://ww2.scienceexchange.com/s/	With our enterprise SaaS-enabled marketplace, R&D teams c				x			
scientist.com	https://scientist.com	Use our award-winning marketplace to quickly find the tools				x			
ZPP Dentalmedizintechnik GmbH	https://www.dental-markt.com	The company ZPP is a family business with over 20 years of e				x	x		
Wound Reference	https://woundreference.com/about	We are a self-funded startup building a decision support platf				x	x		
Medwish	https://www.medwish.com/	B2B marketplace for medical supply and devices					x		
Medtec FZE	http://medtecme.com/en	Established in the year 2004, Medtec FZE is a leading distribu				x	x		
eSutures.com	eSutures.com	eSutures.com is a wholesale liquidator of surgical disposables				x	x		
Euro Biotechnologies	https://www.eurobiotechnologies.com.au	Euro Biotechnologies is a leading Medical and Dental Supplie				x	x		
European Federation of National Asso	https://www.efort.org/membership/membership-and-netwo	The European Federation of National Associations of Orthopa			x				
DEBBIE Database	http://debbie.bsc.es/search/	DEBBIE is the first automaticall curated database of biomater						x	

Figure 20. Collection sheet for meta lists and sites

The current status of the structured knowledge and material collection - how many entries have been collected per segment so far - is shown graphically in Figure 21. It should be noted that this collection does not aim at completeness, but only at generating a broad and large collection of information, materials and relevant stakeholders that can serve as a resource for the BIOMATDB project. Relevant new sources, entities, or information can be added to the collection at any time until the data collection is eventually submitted in the course of D2.5.

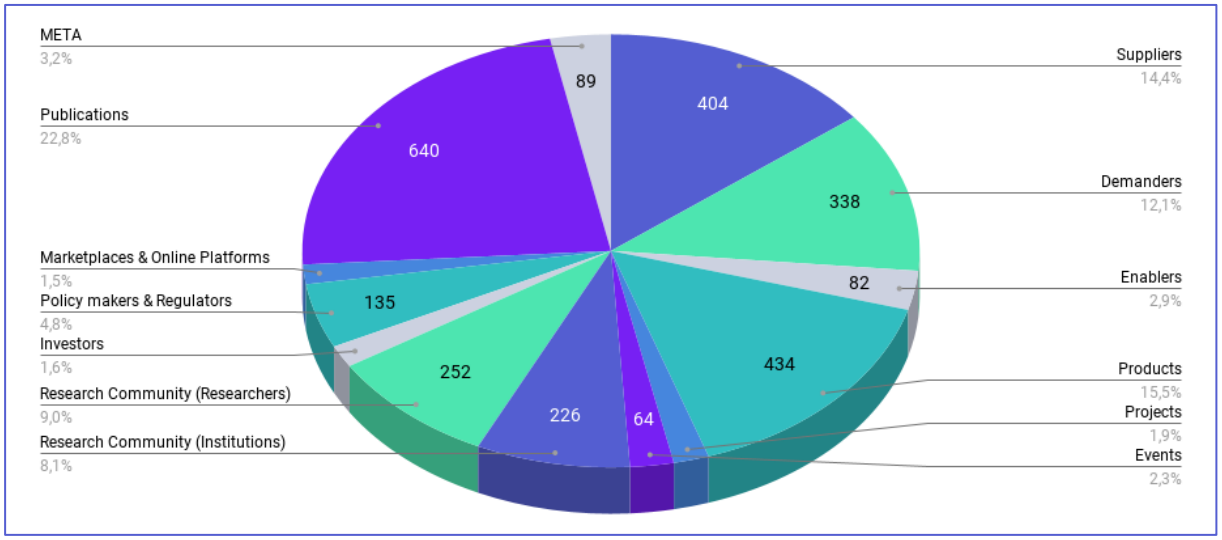


Figure 21. Current status of the structured knowledge and material collection

2.4 Literature and Publication collection

In order to store and document relevant files and documents from the internet research and to have access to the largest possible pool of information, we created an internal "Library" folder that can be accessed by all consortium members (Figure 22). Files and documents stored in this folder consist on the one hand of publications, white papers, brochures, journal articles, books, market analysis reports and other similar items relevant to the knowledge collection for BIOMATDB, or on the other hand of product catalogues for biomaterials or medical devices.

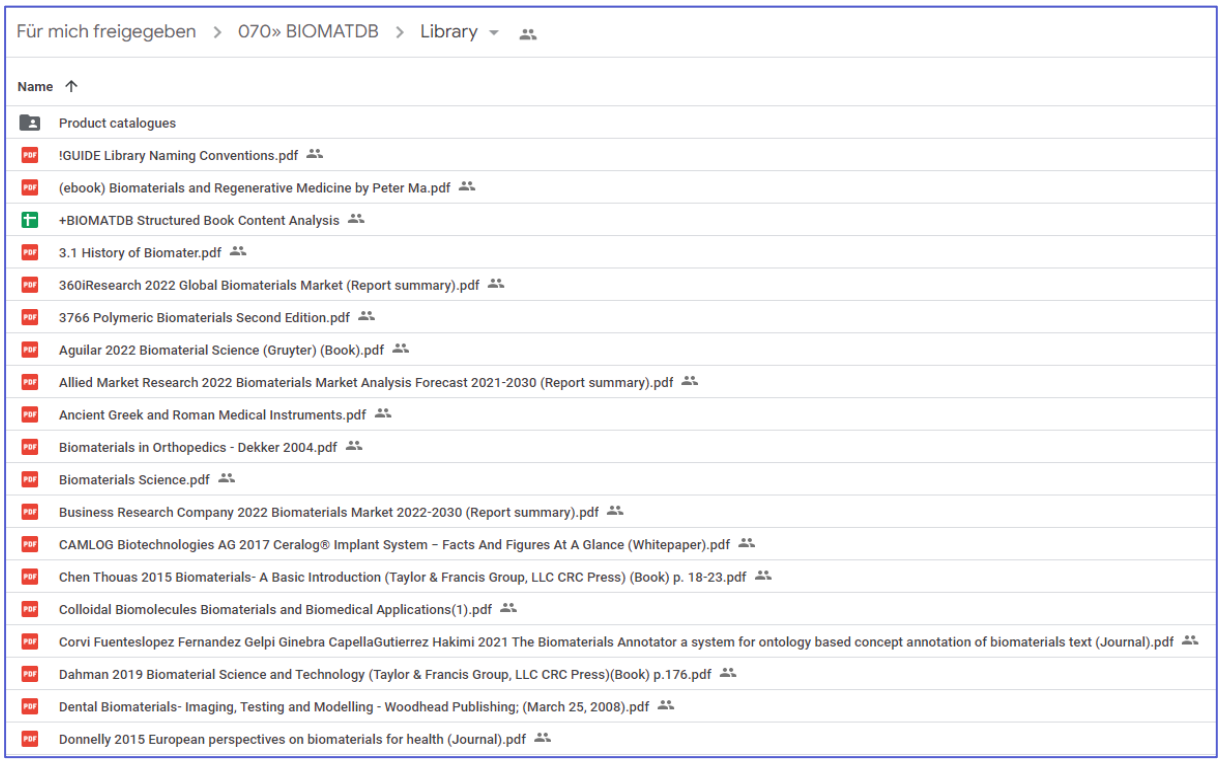


Figure 22. Library folder

On the one hand, to organise our references for the deliverables and, on the other hand, to share our knowledge resources with the public, the consortium created a knowledge library on the openly accessible repository tool **Zotero** (see Figure 23). To share the collected sources with the public, a link to the Zotero library will be posted on the BIOMATDB project website. Once they have created a Zotero account, interested parties can access the repository through any browser or by downloading the free software. If the files are open access, the PDF is provided along with the reference whenever possible. Otherwise, the reference includes a link to the original source.

So far, based on the research and analysis activities within D2.1 175 knowledge resources have been collected and were included in the Zotero repository. This number is expected to grow in the upcoming months as a result of the planned knowledge exchange with the key players in the field.

Figure 23. Zotero library

3 Biomaterials definitions, classifications and landscape

Biomaterials are known as materials that have been engineered to direct the course of a therapeutic or diagnostic procedure by interacting with components of a living system [1]. The biomaterials field has gained much interest, because of their wide range of applications in medicine. In this way, they are key components in medical devices and advanced therapies that benefit patients and society, by improving healthcare outcomes, increasing longevity, and improving quality of life.

Biomaterials have been employed from the beginning of human development, to act as structural supports, to aid healing processes or as prosthetics to restore body functions.

Materials and human bodies have come across each other, due to accidents or war traumas. In the Iliad (book 11) [2] a description on how a spear point was removed from a thigh is described. The "Kennewick man", found in southern Washington State, USA, had a spear point in his hip, apparently a healing process occurred without foreign body reaction, at about 7000 B.C. [3]. A finding in Slovenia suggests that 6500 years ago beeswax was used as dental filling, while in Italy, a more sophisticated case has been reported: dental fillings composed of bitumen, plant fibres, and hair (with possible antiseptic properties) are dated 13.000 years ago. As for sutures, all kinds of available materials have been utilised from linen (Egypt), catgut, gold wire, even insect claws [4].

In southern Iran, at Shahr-i-Sokhta, archaeologists discovered an artificial eyeball, made of gold, dated to 2900 B.C. More amazingly, in a mummy's knee, dated at between 1600-1100 B.C., an iron orthopaedic screw was found, with the pin held together with an organic resin, similar to the orthopaedic cement of today. Many artefacts have also shown the use of wood for orthopaedic applications [4]. One may summarise that in ancient times, worldwide, the pertinent available materials, with probably no or very little modification have been the following: wood, ivory, linen, catgut, beeswax, hair, leather, quartz, seashells, carbon, bitumen paste, silver, gold, copper, iron.

While ancient references are abundant on early use of materials to restore body functions, it was only in the last 50 years that the word "biomaterials" became common in scientific literature. Before the 1950s, the interactions between the body and materials employed for medical applications were poorly understood and implants presented a relatively low probability of success. The functional deficit from these devices has driven over the past several decades significant efforts into understanding the interaction between living systems and biomaterials, which has contributed to the development of this field as a multidisciplinary science, which encompasses engineering, medicine, and basic science like physics, chemistry and biology [5].

In medical applications, biomaterials are rarely used as isolated materials, but are more commonly integrated into medical devices, implants or ATMPs. Further, complex devices may use multiple biomaterials [6], [7]. As an example, titanium can be called a biomaterial, but shaped titanium in conjunction with ultrahigh molecular weight polyethylene becomes the device, a hip prosthesis. Biomaterials are commonly used as prostheses in cardiovascular, orthopaedic, dental, ophthalmological, and reconstructive surgery, and in other interventions such as surgical sutures, bio-adhesives, and controlled drug release systems or diagnostic devices. The translation of biomaterials science to clinically approved medical devices or ATMPs is dependent on **(1)** engineering design, **(2)** testing *in vitro*, in animals and in humans, **(3)** clinical realities, and **(4)** the involvement of industry permitting product development and commercialization [7].

As a constantly growing field, research in biomaterials that can be potentially employed as part of medical devices or ATMPs is exponentially increasing. In the *PubMed* database, the number of results by year for the search term "biomaterial" has increased 10 times in 20 years. Some investigational materials are patented, tested, and ultimately become part of a clinically usable product. In addition, the growth of the field is ensured with the ageing population, the increasing standard of living in developing countries, and the growing ability to address previously untreatable medical conditions [7].

3.1 Definition

To correctly identify which data is related with the biomaterials field, an updated concise and unambiguous definition of *biomaterial* is required. This is difficult to achieve, as the elements to be considered are manifold. Over the years, different definitions of biomaterial have been given and these have changed and adapted along with the development and expansion of the field. Figure 24, created by BIOMATDB, shows a timeline of the evolution of the definition of biomaterials since the first formal proposal in 1986 until now.

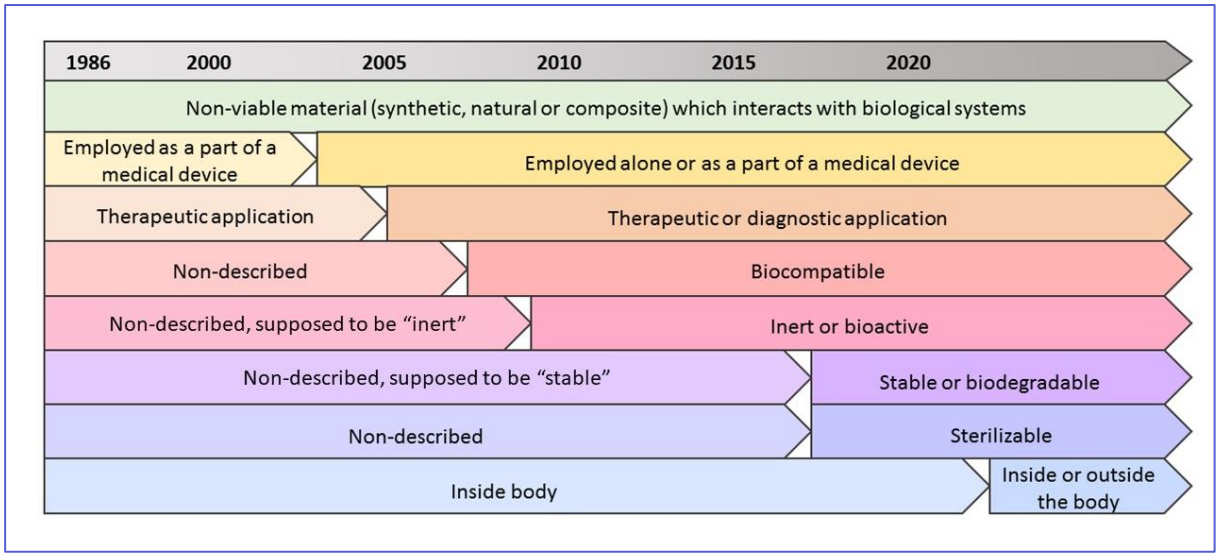


Figure 24. Timeline - Evolution of the definition of biomaterials

From the very beginning of the development of biomaterials science, in the 60s, they were defined as "materials employed as constituents of implants", which highlights the concept of implanting a material in the body [8]. However, the first formal definition of biomaterials was coined in the 1st Biomaterials Consensus Conference in 1986, where biomaterial was defined as "a non-viable material used in a medical device, intended to interact with biological systems" [1, p. 257]. This definition introduced two key concepts: that it has to be a "non-viable material", which means that it does not contain any living entity, and that the material interacts somehow with a biological system.

In the early 2000s, some specifications were included. Biomaterials were suggested to be of natural or synthetic origin (or combination of that in the case of composites) and specifications about the therapeutic functions that they can accomplish (replacing a tissue, part of an organ, enlarging them, replacing their function, etc.) [9]. It was in 2005 at the European Society of Biomaterials (ESB) conference where biomaterial was defined as "material intended to interface with biological systems as an integral part of a process designed to evaluate, monitor, or treat tissues of the body, to replace

or augment tissues, or to facilitate the regeneration of tissues", highlighting the new applications of biomaterials also for diagnostics [9].

As previously mentioned, biomaterials have been employed as structural supports for healing or replacement of body functions but presenting a high risk of failure. The evolution in the field in the direction of evaluating the biological repercussions of biomaterials are also noticed in the evolution of the definition. For example, Williams defined in 2008 that a biomaterial needs to have the ability to "exist in contact with tissues of the human body without causing an unacceptable degree of harm" [10, p. 2941]. In 2009, he also stated for the first time that biomaterials can be used by themselves for their purpose, without the requirement of being part of a medical device [11]. Another important concept introduced in this year by Mooney was that biomaterials do not just act as structural support, but also can incorporate biologically active components to enhance their function and biocompatibility (natural proteins, synthetic peptides, antibiotics, etc.) [12].

The second definition coined by Williams remained unaltered for almost 10 years, when the most recent advances in biomaterials required a change in the definition. For example, the development of dynamic biomaterials with the ability to degrade after their purpose was fulfilled involved the requirement of considering this concept in new definitions [13], [14]. In addition, the economic development of the biomaterials market also involved the incorporation of concepts like a biomaterial need to be processable, sterilisable without difficulty, economical and available [14]. The high development of the research in the interactions between biomaterial and a living system and how these interactions drive the success of its medical purpose is highlighted in the last definition of Williams in 2019, stating that a biomaterial is "a material designed to take a form which can direct, through interactions with living systems, the course of any therapeutic or diagnostic procedure" [1, p. 22]. One last consideration is found in a recent book, in 2022, which considered that biomaterials can be inside or outside the body; for example, tubing and filtering systems that are exposed during prolonged times to body fluids [15].

A compilation of the collected definitions is presented in Table 4.

Table 4. A rough matrix of the evolution of the definition of biomaterials

Year	Author	Type	Definition (as cited in Ref.)	Ref.
1967	Cohen, J.	Article	All materials, excepting drugs and sutures, which are used as implants. These fall conveniently into the following groups: (1) metals; (2) bone and derivatives of bone used as grafts; (3) plastics; (4) ceramics and composites.	[8]
1986	Williams, D.	Consensus Conference	A non-viable material used in a medical device, intended to interact with biological systems.	[1]
2003	Miller B. & Keane C.	Encyclopaedia & Dictionary	Any substance (other than a drug), synthetic or natural, that can be used as a system or part of a system that treats, augments, or replaces any tissue, organ, or function of the body.	[9]
2005	European Society of Biomaterials	Consensus Conference	A material intended to interface with biological systems as an integral part of a process designed to evaluate, monitor, or treat tissues of the body, to	[9]

			replace or augment tissues, or to facilitate the regeneration of tissues.	
2007	Park J. & Lakes R.	Book	Any material used to make devices to replace a part or a function of a living system in intimate contact with it in a safe, reliable, economic, and physiologically acceptable manner.	[16]
2008	Williams, D.	Article	Material that has the ability to exist in contact with tissues of the human body without causing an unacceptable degree of harm to that body.	[10]
2009	Williams, D.	Article	A biomaterial is a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine.	[11]
2009	Huebsch N. & Mooney D.	Article	Biomaterials made today are routinely information rich and incorporate biologically active components derived from nature.	[12]
2012	Ratner, B.	Book	Synthetic and natural materials that are used in a wide variety of implants, devices and process equipment that are in physical and chemical interactions between complex biological systems.	[17]
2016	Phillips P. L. et al.	Book chapter	A biomaterial is currently defined as a material that has been designed to be used in any therapeutic or diagnostic procedure to regulate the interactions of single or multiple components of living systems when applied alone or as part of a complex device.	[18]
2016	Mahyudin F.& Hermawan H..	Book	Any inert or active substance, other than a drug, synthetic or natural in origin, which can be used for any period of time, which augments or replaces any tissue, organ, or function of the body or support the healing process of an injured tissue, in order to maintain or improve the quality of life of an individual.	[19]
2017	dos Santos V. et al.	Book	Every material (except drugs) that have the ability to be in contact with human body tissues without causing damages of unacceptable magnitude. Usually, for an undetermined period of time these materials are employed as the whole or an integral portion of a system for treatment, enlargement, or replacement of any tissues, organs, or body functions. The biomaterial must be biocompatible, biofunctional, inert and sterilisable.	[13]
2018	Hasirci V. & Hasirci N.	Book	[S]ubstances implanted within or used in conjunction with the body, designed to have properties closely matching that of the biological system, be stable enough for the aimed use, have appropriate levels of bioactivity and are designed to partially or completely	[14]

			fulfil the functions of the diseased, damaged or malfunctioning tissues and organs. According to Hasirci & Hasirci (2018) biomaterials should be biocompatible, have physicochemical and mechanical properties comparable to those of the tissue it replaces or is implanted in, be processable and sterilizable without difficulty and they should be economical and available.	
2019	Dahman, Y.	Book	(1) Any natural or synthetic material which can be used in a biological system. (2) Material implemented in medical devices with the primary objective of interacting with biological systems.	[20]
2019	Williams, D.	Consensus Conference	A material designed to take a form which can direct, through interactions with living systems, the course of any therapeutic or diagnostic procedure.	[1]
2020	Wagner, W.	Book	Synthetic and natural materials that are used in a wide variety of implants, devices, and process equipment that contact biological systems.	[7]
2022	Aguilar, L.	Book	Materials that are used inside or outside the body to augment or facilitate normal physiological functions are called biomaterials. It is an umbrella term used to classify materials having properties that are useful for the human body. A biomaterial must be compatible with the human body by allowing the body to tolerate its presence without the material causing any harm to the cells or the surrounding tissue.	[15]

Summarising the above considerations, we suggest that a strict definition for “biomaterials” is an evolving concept, depending on new applications, on new compositions, and hybrid systems involving pristine biomaterials, functionalized surfaces, and biomolecules/cells. These are intended for use inside the body (artificial internal organs), on the surface of the body, can be lifelong stable, or biodegraded in a prescribed time span. However, emerging applications, such as diagnostics (e.g., functionalized biomaterials with specific ligands to select/sort specific peptides/cells), 3D cell cultures and organoid disease models, promote the use of biomaterials. The need and search therefore of synthetic adhesives, “smart” multifunctional nanoparticles, and biological actuators may be based on specialised biomaterials as well.

After reviewing the available materials in literature related with the definition of biomaterial, we elaborate an updated definition, based on the timeline evolution of shared concepts considered in the collected definition and consensus of the project experts in the field:

Material employed to interact with biological systems for medical applications. A biomaterial can be of natural or synthetic origin or can be a combination of them and are employed alone or as a part of a more complex medical product, mainly medical devices, or ATMPs. A biomaterial requires to be biocompatible and present appropriate properties for their final function.

3.2 Classifications

Biomaterials can be classified following a wide range of criteria. Nevertheless, having an overview of the main systems of classification employed in the field could help to organise, filter, and facilitate the access to biomaterials data and may help to construct the functionalities of the database conceived in the BIOMATDB project.

Traditional classification of biomaterials in books and review articles establish a classification of biomaterials mainly based on their composition. This classification is also represented in raw material marketplaces. In these literature sources, four primary types of biomaterials are always described: (1) metals, (2) ceramics, (3) polymers, and (4) composites. Metals are mainly classified in noble metals, like gold or silver, or in alloys that constitute a wide diverse group that could be easily classified by their elemental composition (i.e., titanium alloys, magnesium alloys, zinc alloys, etc.). While metals are always of synthetic origin, ceramics and polymers could be of natural or synthetic origin. In the case of ceramics, their origin only determines the source from where the elements are taken to then produce the ceramic products, so the classification mainly relies, as well as for metals, on the elemental composition (i.e., calcium phosphates, calcium sulphates, zirconia, etc.). On the other side, natural polymers (mainly polysaccharides and polypeptides) and synthetic polymers (like PEG, PCL, PMMA, etc.) present marked differences both in their chemical characteristics and in obtaining them. Finally, these materials can be combined forming composite materials, commonly of two of them but even more complex ones [15].

Along with the classification by composition, books and mainly the market segmentation also identify a classification based on the final application of the biomaterial, with the main areas being neurology, cardiology, orthopaedics, ophthalmology, wound care, dental, plastic surgery, and other applications [21]. Both kinds of classification are also represented by categorization in ontologies and in the International Patent Classification, where raw materials are classified based on their chemistry, while the final complex objects are classified based on their application. As most biomaterials are employed composing these complex products, this kind of classification is also valuable in the biomaterials field.

Biomaterials need to fulfil complex and specific requirements instructed by their final use (i.e., physical properties, chemical properties, biological properties, etc.). As dynamically annotated in the term context evolution *per se*, these properties are crucial to define a biomaterial. This in turn makes biomaterial properties highly relevant for the classification and filtering of biomaterials, as also reflected in books [14], [16] and in relevant ontologies in the field (DEB, others).

Biomaterials are rarely used in their primary form (as raw material) and mostly employed once they are shaped (for example, as fibres, coatings, implants, etc.), modified (for example, by crosslinking, functionalization, chemical modification, etc.), or as a part of a complex object like medical devices or ATMPs. Under that prism, the shape and manufacturing/processing of biomaterials is also a key determinant of their final application [9]. The stage of development of a biomaterial until it is part of an approved medical product is also a key aspect for people working in biomaterials.

Taking all these into account, notwithstanding that other parameters may be determined in upcoming tasks of the project, we will focus on 5 different relevant aspects to classify biomaterials, i.e., *(1) composition, (2) application, (3) properties, (4) form/methods, and (5) stage of development.*

In the following sections, we collected different biomaterials resources which present biomaterials classification to organise the biomaterials knowledge. These classifications can be observed in the Screenshots of the databases and marketplaces collected in the Annex.

3.3 Terminology commonly encountered

Biomaterials science is an area of advanced technology where a large number of new terms are being introduced or invented. Some of them are words that had been derived from within an established area but are now being used in the context of biomaterials with a different meaning. In other situations, there is a clear need for a new word to describe a phenomenon or object, since there is no acceptable existing word. Part of the problem lies within the multi- and interdisciplinary nature of the subject. Table 5 aims to bring an overview of the most common and relevant terminology in the biomaterials' field, based on the definitions established in *Definitions of Biomaterials for the 21st Century, X. Zhang & D. Williams:*

Table 5. Overview of the most common and relevant terminology in the biomaterials field

Term	Definitions
Absorption	The process of taking some agent into a substance by chemical or physical action.
Artificial Organ	A medical device that replaces, in part or in whole, the function of one of the organs of the body.
Bioactive Material	A material which has been designed to induce specific biological activity.
Bioadhesion	The adhesion of cells and/or tissues to the surface of a material.
Bioattachment	The fastening of cells and/or tissue to the surface of a material, including mechanical interlocking.
Biocompatibility	The ability of a material to perform with an appropriate host response in a specific application.
Biodegradation	The gradual breakdown of a material mediated by specific biological activity.
Bioprosthesis	An implantable prosthesis that consists totally or substantially, of nonviable, treated, donor tissue.
Bioresorption	The process of removal by cellular activity and/or dissolution of a material in a biological environment.
Degradation	Deleterious change in the chemical structure, physical properties, or appearance of a material or an irreversible process leading to a change of the structure of a material, characterised by a loss of properties and/or fragmentation.
Device	Something contrived for a specific purpose or something made or adapted for a particular purpose.
Drug	Any substance, natural or synthetic, which has a physiological action on a living body, either when used for the treatment of disease, or the alleviation of pain,

	or for self-indulgence or recreation or a substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease.
Graft	A piece of viable tissue or collection of viable cells transferred from a donor site to a recipient site for the purpose of reconstruction of the recipient site.
Host Response	The reaction of a living system to the presence of a material.
Hybrid Artificial Organ	An artificial organ that is a combination of viable cells and one or more biomaterials.
Immunity	The capacity of a body to recognize the intrusion of foreign material and to mobilise cells and cell products to effectively remove that material.
Implant	A medical device made from one or more biomaterials that is intentionally placed within the body, either totally or partially buried beneath an epithelial surface.
Material	A substance useful for making objects.
Medical Device	An instrument, apparatus, implement, machine, contrivance, *in vitro* reagent, or other similar or related article, including any component, part or accessory, which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in humans.
Mesh	An open fabric made of intertwined fibres.
Nanoscale	Having one or more dimensions of the order of 100 nm or less.
Organ	Part of a body adapted and specialised for the performance of a particular function.
Percutaneous Device	A medical device that passes through the skin, remaining in that position for a significant length of time.
Permucosal Device	A medical device that passes through a mucosal surface, remaining in that position for a significant length of time.
Prosthesis	A device that replaces a limb, organ or tissue of the body.
Resorption	The breakdown of a structure and consequent assimilation of resulting components into their environment.
Thrombogenicity	The property of a material which induces and/or promotes the formation of a thrombus.
Tissue	A level of organisation in multicellular organisms consisting of a group of structurally and functionally similar cells and their intercellular material.
Transplant	A complete structure, such as an organ, that is transferred from a site in a donor to a site in a recipient for the purpose of reconstruction of the recipient site.
Vector	A carrier that transfers a biological substance, especially an infective agent, from one site to another.

3.4 Market overview

Based on the summary reports from market research providers, which are available online (see Table 6), the size of the global biomaterials market in 2021 was estimated to be $115.02 billion (as median from values available for that year). The biomaterials industry is foreseen to expand substantially in the upcoming years, with a global market size projected to reach $212.41 billion by 2030 and an expected compound annual growth rate of 12.74%.

Table 6. Global biomaterials market data derived from online market analysis providers

Market analysis provider	2021 global biomaterials market size (in billion USD)	2030 global biomaterials market size (in billion USD)	Compound Annual Growth Rate (%) to 2030
360iResearch	125.44	N/A	N/A
Allied Market Research	N/A	212.4052	12.7
Grand View Research	135.4	N/A	15.4
Inkwood Research	115.02	269.55	12.78
Market Research Future	N/A	212.40	7.80
Research and Markets	N/A	212.4052	12.7
The Business Research Company	91.08	N/A	N/A
Verified Market Research	112.74	361.45	14.80
Median	**115.02 billion USD**	**212.41 billion USD**	**12.74%**

The unprecedented global need for COVID-19 vaccines demonstrated the critical importance to upscale both the biomaterial/nanomaterial manufacturing capacity and supply chains, globally and timely. Moreover, it underlined the need to map, articulate, and employ the raw material producers and suppliers in all regions, to enable equity in production and distribution. Along with the need for raw materials for vaccine development, issues of ancillary material production (e.g., needles and glassware for vaccination) emerged. In addition, the COVID-19 pandemic has disrupted healthcare services globally. Indeed, many hospitals and clinics had to prioritise emergency procedures while focussing their resources to care for COVID-related patients [22]. The COVIDSurg Collaborative, a global research network, focussed on the impact of COVID-19 on surgical care, studied the impact of the pandemic on elective surgeries. In June 2020 it estimated that, based on a 12-week period of peak disruption to hospital services due to COVID-19, over 28 million elective surgeries worldwide would be cancelled or postponed in 2020. They projected orthopaedic procedures to be those cancelled most

frequently, with more than 6 million orthopaedic surgeries cancelled worldwide over a 12-week period [23]. Therefore, the COVID-19 pandemic negatively affected the global demand for biomaterials. It also adversely influenced the supply of biomaterials, as manufacturers and sellers were forced to shut down temporarily during times of imposed nationwide lockdowns. These combined consequences resulted in a negative impact on the biomaterials market.

However, a few elements are expected to positively drive the growth of the biomaterials market in the future:

- **Ageing population:** Across the world, people are living longer than ever before. According to the United Nations, the proportion of the global population aged 65 years or over is expected to increase from 10 per cent in 2022 to around 16 per cent in 2050, so that one in six people in the world will be aged 65 years or over [24]. This rising prevalence of the geriatric population is anticipated to trigger an increase in the demand for implantable devices to deal with common conditions associated with older age such as osteoarthritis, osteoporosis, and other musculoskeletal disorders.
- **Increasing prevalence of chronic diseases:** The rising incidence of chronic conditions such as obesity, diabetes, and cardiovascular disease is driving demand for medical devices and treatments that use biomaterials. For example, the increasing prevalence of obesity is driving the demand for weight loss surgery, which often involves the use of biomaterials. Similarly, the rising incidence of diabetes is leading to an increase in the demand for insulin pumps and other devices that use biomaterials [25]–[27]. Data from the World Health Organisation indicate a majority of deaths worldwide are caused by cardiovascular diseases. In 2019, 17.9 million people died from cardiovascular diseases, representing 32% of all deaths globally. Heart attacks and strokes accounted for 85% of these deaths [28]. This high burden of cardiovascular diseases constitutes a great potential to boost the market with demand for biomaterials including stents, heart valves, cardiopulmonary bypass system, and vascular grafts.
- **Funding and regulatory support:** Along with the rising demand for medical implants, a number of government organisations and universities have increasingly provided investments, funds and grants or regulatory support to promote research and innovation activities in the field of biomaterials. This is creating new scope for growth in the biomaterials market. On the other hand, the supported research activities will likely encourage discoveries and technological advancements in areas in expansion such as tissue engineering and regenerative medicine [25]–[27].
- **Growing awareness of the benefits of biomaterials:** As more people become aware of the benefits of biomaterials, such as their biocompatibility and ability to improve patient outcomes, there is increasing demand for products made from these materials. For example, the use of biomaterials in drug delivery systems is growing as more people become aware of their ability to control the release of medications and improve treatment outcomes. Similarly, the use of biomaterials in tissue engineering and regenerative medicine is growing as more people become aware of their ability to promote tissue growth and repair markets [25], [26], [29]–[31].

Biomaterials are poised to revolutionise the medical and healthcare industries with their cutting-edge, game-changing technologies. These advancements will significantly shape the future of these industries for years to come. One of the most significant trends is the increasing use of 3D printing technology [32]–[36] to produce customised medical devices and implants. Additionally, biodegradable and bioresorbable biomaterials that can be absorbed by the body over time are being developed for various applications, like drug delivery systems, tissue engineering, and medical devices [29], [32], [35], [37]. Bioactive materials, which can interact with living tissue to promote healing, are also being explored in the biomaterials industry [26], [29], [30]. Natural materials, such as collagen and chitosan, are being used to replace synthetic materials due to their biocompatibility [30], [33]. Lastly, smart materials are being developed, which can change their properties in response to stimuli such as temperature or pH, allowing for more adaptive and controlled delivery of drugs [35]. All of these trends point to amazing potential for the biomaterials industry.

Despite the many opportunities for growth and innovation in the biomaterials industry, there are also a number of challenges that need to be addressed. Some of these challenges include [25], [30]–[32], [38]:

- **Regulatory hurdles:** The process of getting regulatory approval for medical devices that use biomaterials can be lengthy and costly. This can create barriers to entry for new companies and slow the pace of innovation in the industry [25], [30]–[32], [38].
- **High cost of research and development:** Developing new biomaterials and medical devices that use them is a complex, expensive and even risky process as there is always the potential for biocompatibility issues. This can limit the number of companies that are able to enter the market and can also make it difficult for smaller companies to compete with larger, established players [26], [29], [39].
- **Limited availability of raw materials:** Some biomaterials are made from rare or hard-to-obtain raw materials, which can limit the production of these materials and create supply chain challenges [25], [30].
- **Ethical concerns:** There are also ethical concerns surrounding the use of biomaterials, particularly when it comes to the use of materials of animal or human origin. This can create challenges for companies that are developing products using these materials [40], [41].

As explained in section 3.2 above, the biomaterial market can be segmented by composition (metals, ceramics, polymers and natural materials) or by application (orthopaedics, cardiovascular, dental, plastic surgery, etc.). With regard to composition, the majority of market research providers listed in Table 6 agree that the metallic biomaterials segment accounted for the largest share of the global market in the past few years (2019 to 2021) and the segment is expected to retain its dominance over the forecast period. This is attributed to their good mechanical properties including high strength, stiffness and resistance to fatigue degradation that make them suitable for the manufacturing of medical devices that are extensively used for orthopaedic, cardiac and dental procedures. Polymeric materials are also predicted to witness a strong increase in revenue generation owing to their wide range of applications and in particular their broad usage in the field of tissue engineering. Based on application, the cardiovascular and orthopaedic segments were leading the biomaterials market in the past few years (2019 to 2021). The increasing prevalence of cardiovascular diseases and the rising adoption of biomaterials in advanced cardiovascular devices have contributed to the growth of the former segment. A major factor behind the growth of the latter segment is the rising use of metallic

biomaterials in orthopaedic applications due to their high load-bearing capacities. Continuous developments for the introduction of advanced orthopaedic implants by market players as well as the growing prevalence of orthopaedic replacements are expected to boost the market share of the orthopaedic segment in the forecast period. In addition, the plastic surgery industry is experiencing a tremendous transition. Plastic surgery demand is expected to increase in the forecast period thanks to a positive perception of cosmetic procedures and technological advancements.

In terms of regions, North America dominated the global biomaterials market in the past few years (2019 to 2021). This was attributed to a number of factors including the rising prevalence of cardiovascular diseases and orthopaedic replacements, a growing incidence of cancer, high government funding in research and development, favourable government policies and a growing number of products launched by key market players. In the forecast period, Asia-Pacific has been identified as the most promising market for the growth of biomaterials, owing to a rise in the geriatric population along with the increasing incidences of chronic illnesses such as cardiovascular diseases, diabetes and arthritis, and a growing, improved healthcare industry in the area.

Around 25% of the world's gross national income is generated by the BRICS countries - Brazil, the Russian Federation, India, China and South Africa - while more than 40% of the world's population lives in these countries and about 40% of the global disease burden is borne by them [42]. Recent projections foresee a trend in all BRICS countries toward increasing their per capita health spending in terms of purchasing power parity by 2030 [43]. There is therefore scope for biomaterials market players to take advantage of future growth opportunities in these emerging economies, as there is expected to be a rise in the demand for novel medical devices as well as advanced healthcare services in the respective healthcare systems of those countries in the coming years.

The biomaterials market is moderately competitive. Some of the best-known companies in this market are Koninklijke DSM NV (Royal DSM), Corbion NV, Zimmer Biomet, Noble Biomaterials Inc. and Bayer AG. Currently, with the increasing focus of all companies in emerging economies, some of the small and medium-sized companies are also penetrating the market and competing for market share. The polymeric biomaterials market is also moderately competitive. It consists of several major players. In terms of market share, a small number of major players currently dominate the market. However, with technological advances and product innovations, small and medium-sized companies are increasing their presence in the market. Companies such as BASF SE, Bezwada Biomedical LLC, Corbion NV, Zimmer Biomet and Royal DSM have a substantial share of the market.

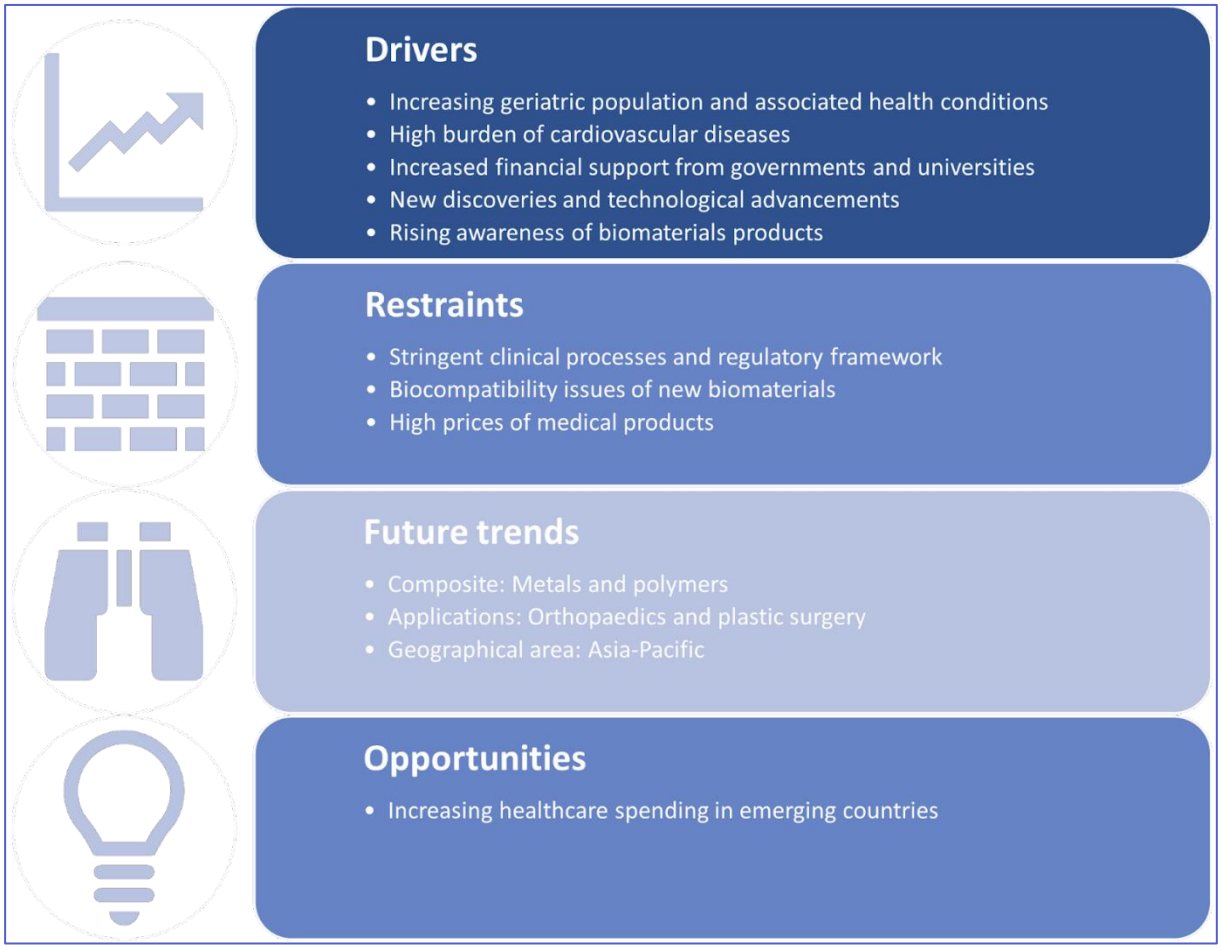


Figure 25. Overview of the dynamics that govern the global biomaterials market.

Overall, the biomaterials industry is poised for significant growth in the coming years, with many exciting developments on the horizon. The increasing prevalence of chronic diseases, the ageing population, and technological advances are all driving the demand for biomaterial-based products. In addition, the increasing use of 3D printing technology and the development of biodegradable and bioresorbable materials are expected to open up new markets for biomaterials. The future of the biomaterials industry looks bright, with many opportunities for growth and innovation.

3.5 Landscape and Community

After this comprehensive overview of the most important developments, terms, definitions, and distinctions in the field of biomaterials, the next sections are intended to provide an overview of the key players in the extended field of biomaterials.

3.5.1 Industrial landscape

In the last few decades, the biomaterials industry has not only grown in the number of products available and under development, but also has advanced economically in a significant way. The market related to the biomaterials area is significant both from the point of view of the number of units sold annually and the financial turnover observed and can be conveniently segmented based on two main criteria [25]–[27], [29], [30], [32], [33]. The first refers to the types of compounds from which biomaterials are made, such as metals, ceramics, polymers, and materials of natural origin. The second

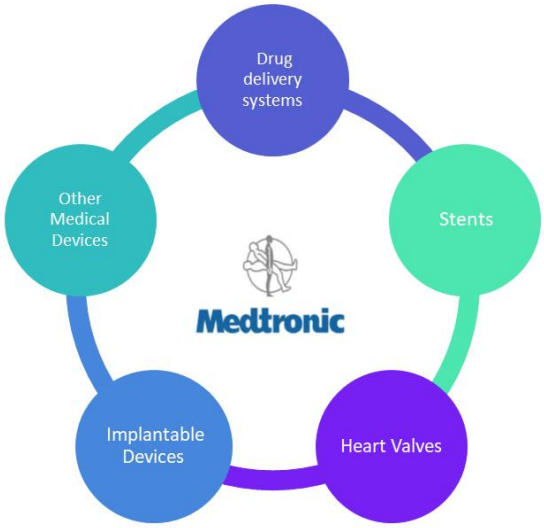
criteria is based on the application, such as orthopaedic, cardiovascular, dental, ophthalmologic, plastic surgery, tissue engineering, injury treatment, neurological, and central nervous system disorders, as well as devices for central nervous system disorders, and also includes devices for other applications, such as gastrointestinal and urinary, as drug delivery systems, or for bariatric surgery. However, there are some additional ways to segment the biomaterial market [40], [44], [45] that are the following:

- **By end user:** The biomaterial market can be segmented based on the type of organisation that is using the biomaterials, such as hospitals, research institutions, or pharmaceutical companies [31], [33];
- **By geography:** The market for biomaterials can vary significantly by region, and it can be useful to segment the market based on geographic location [26], [27], [29], [31];
- **By technological advancement:** Biomaterials can be classified based on the level of technological advancement of the material, such as traditional biomaterials or advanced biomaterials [25], [33];
- **By phase of product life cycle:** Biomaterials can be classified based on whether they are in the research and development phase, the commercialization phase, or the mature phase of their product life cycle [33];
- **By price point:** Biomaterials can be segmented based on their price or cost, such as high-priced or low-priced biomaterials [33], [46];
- **By regulatory approval status:** Biomaterials can be classified based on whether they have received regulatory approval for use in medical and healthcare applications, such as FDA-approved biomaterials [31], [47], [48];
- **By manufacturing process:** Biomaterials can be segmented based on how they are produced, such as through traditional manufacturing processes or through advanced manufacturing techniques like 3D printing [33];
- **By target patient population:** Biomaterials can be classified based on the type of patient population that they are intended to serve, such as paediatric biomaterials or geriatric biomaterials [33].

This is a market with some competitiveness, since, although it is possible to list some major players, we cannot speak of a concentrated domain. Among the companies active in the biomaterials business in the world, both in obtaining raw materials and in manufacturing of products for use in the healthcare area, the following can be cited as the key players [25]–[27], [29]–[33]:

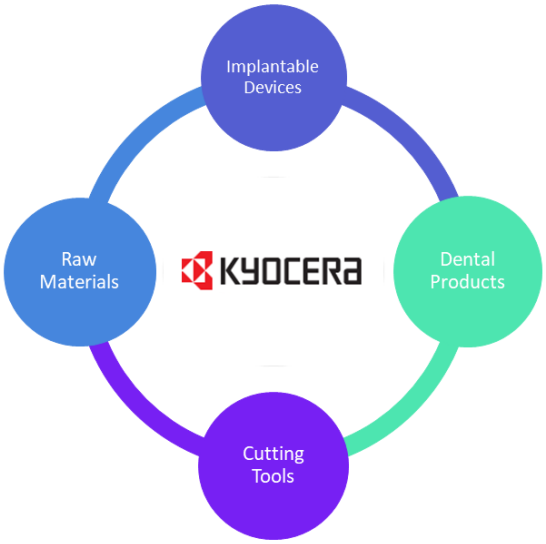
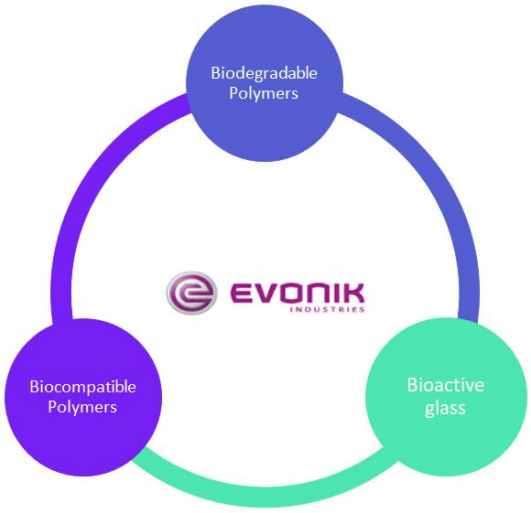
Table 7. Industrial landscape

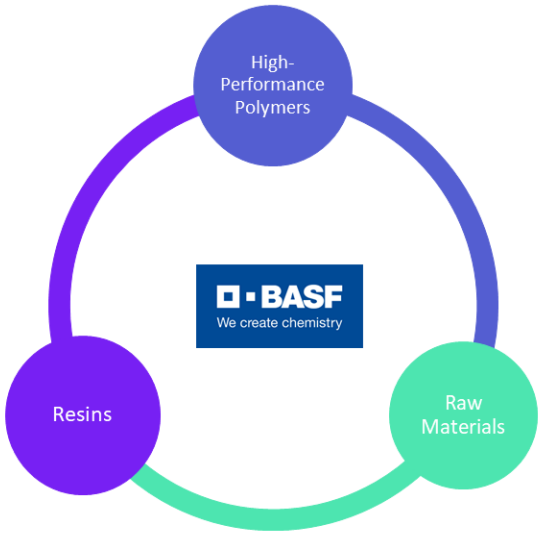
Product Portfolio	Company Description
	DSM is a global consumer health and wellness company that develops, markets and distributes branded products that support health and wellness. DSM produces a wide range of biomaterials, including polymers, resins, and other materials used in medical devices and other healthcare products. DSM is currently expanding internationally. DSM has a strong presence in countries such as the United States, Canada, China, Australia, Brazil, and India, and holds a significant market share in the health and wellness industry. DSM's main customers are health and wellness retailers, distributors, and consumers [49]–[53].
	Bayer AG is a global company that engages in the development, manufacture, and distribution of products in the healthcare, nutrition, and high-tech materials industries. The company operates through several segments, including Pharmaceuticals, Consumer Health, Crop Science, Animal Health, and Covestro. The Pharmaceuticals segment focuses on the development and marketing of prescription products in various areas, including women's healthcare, oncology, and ophthalmology. The Consumer Health segment manufactures and sells a range of products, including dietary supplements, cold and allergy medications, and sun protection products. The Crop Science segment provides seeds, plant traits, and crop protection products. The Animal Health segment offers prescription and non-prescription veterinary products. The Covestro segment produces raw materials for polyurethane and polycarbonate products, as well as by-products of polyether production and chlorine production and use. Bayer AG is headquartered in Leverkusen, Germany [54]–[56].

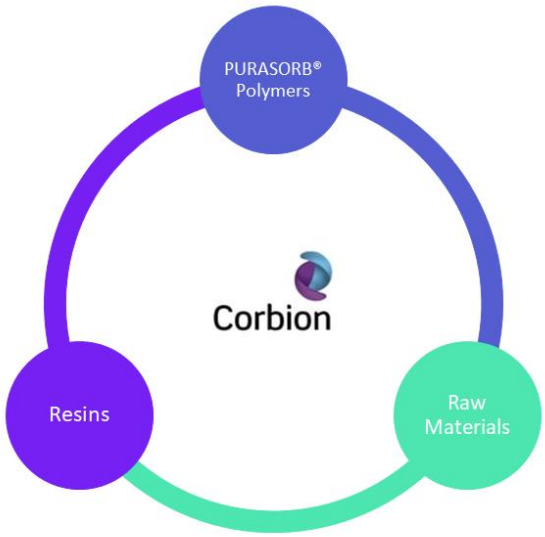
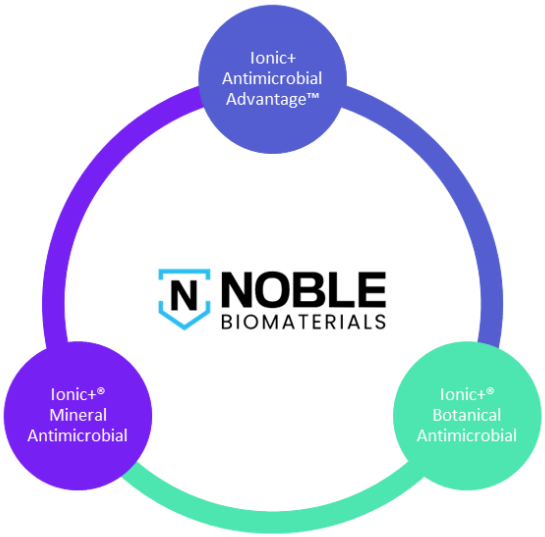
	Johnson & Johnson (J&J) is an American multinational corporation that is a global player in the healthcare industry. Founded in 1886, the company produces medical devices, pharmaceuticals, and consumer packaged goods and serves customers in more than 175 countries through operations in more than 60 countries. J&J has a strong presence in key markets such as the United States, Canada, China, India, and Brazil and holds a significant market share in the healthcare industry. J&J's main customers are healthcare providers, distributors, and consumers. The company's business is divided into three segments: Consumer, Pharmaceutical, and Medical Devices. The Consumer segment produces products for baby care, oral care, beauty, over-the-counter pharmaceuticals, women's health, and wound care markets. The Pharmaceutical segment focuses on therapeutic areas such as immunology, infectious diseases and vaccines, neuroscience, oncology, cardiovascular and metabolism, and pulmonary hypertension. The Medical Devices segment offers products used in the orthopaedic, surgery, cardiovascular, diabetes care, and eye health fields [57]–[59].
	Medtronic is a medical technology company that is a global leader in the development, manufacture, distribution, and sale of device-based medical therapies and services. Founded in 1949, the company has operations in more than 140 countries and serves customers in more than 160 countries, making it a truly global player. Medtronic has a strong presence in key markets such as the United States, Canada, China, India, and Brazil and holds a significant market share in the healthcare industry. Medtronic's main customers are healthcare providers, distributors, and consumers. The company's business is divided into four segments: Cardiac and Vascular Group, Minimally Invasive Technologies Group, Restorative Therapies Group, and Diabetes Group. The Cardiac and Vascular Group segment includes the Cardiac Rhythm and Heart Failure, Coronary and Structural Heart, and Aortic and Peripheral Vascular divisions. The Minimally Invasive Technologies Group segment comprises the Surgical Innovations and Respiratory, Gastrointestinal, and Renal

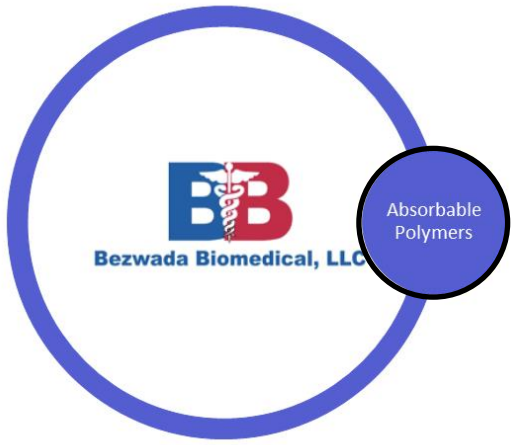
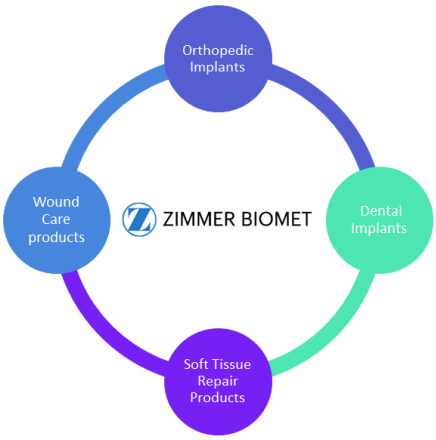
	divisions. The Restorative Therapies Group contains the Spine, Brain, Specialty Therapies, and Pain Therapies divisions. The Diabetes Group segment focuses on the development, manufacturing, and marketing of products and services for the management of Type I and Type II diabetes. Medtronic is headquartered in Dublin, Ireland [60]–[62].
	Stryker is a diversified medical technology company that is a global player in the development, manufacture, and marketing of innovative medical devices, instruments, and implants. Founded in 1941, the company has operations in more than 100 countries and serves customers in more than 130 countries. Stryker has a strong presence in key markets such as the United States, Canada, China, Australia, Brazil, and India and holds a significant market share in the medical technology industry. Stryker's main customers are healthcare providers, distributors, and consumers. The company's business is divided into three segments: Orthopaedics, MedSurg and Neurotechnology, and Spine. The Orthopaedics segment provides reconstructive and trauma implant systems. The MedSurg segment deals with surgical equipment and navigation systems, endoscopy, patient handling, and reprocessed medical devices. The Neurotechnology and Spine segment pertains to spinal implants and neurovascular products. Stryker is headquartered in Kalamazoo, MI [63]–[65].

	3M is an innovative technology company that is a global player in the manufacture of industrial, safety, and consumer products. Founded in 1902, the company has operations in more than 70 countries and serves customers in more than 200 countries. 3M has a strong presence in key markets such as the United States, Canada, China, India, and Brazil and holds a significant market share in the healthcare, communications, and office business industries. 3M's main customers are healthcare providers, distributors, and consumers. The company's business is divided into four segments: Safety and Industrial, Transportation and Electronics, Health Care, and Consumer. The Health Care segment includes medical and surgical supplies, skin health and infection prevention products, oral care solutions, separation and purification sciences, health information systems, inhalation and transdermal drug delivery systems, and food safety products. The Consumer segment products includes office supply products, stationery products, home improvement products, home care products, protective material products, certain consumer retail personal safety products, and consumer health care products [66]–[68].
	Victrex plc is a British-based supplier of high-performance polymers. The company's headquarters and manufacturing operations are located in the United Kingdom, and it has sales and distribution offices in more than 40 countries worldwide. With around 40 years' experience, Victrex develops world leading solutions in PEEK based polymers, semi-finished and finished parts which shape future performance for its customers and its markets, bring environmental and societal benefits and drive value for its shareholders. Victrex has a strong presence in countries such as the United States, Canada, China, Australia, Brazil, and India, and holds a significant market share in the health and wellness industry. Victrex's main customers are health and wellness retailers, distributors, and consumers [69], [70].

	Kyocera is a leading global supplier of printing solutions, electronics, and components. The company is also a leading supplier of biomaterials, using its advanced ceramics and metal technologies to provide innovative solutions in the healthcare industry. Kyocera has developed a wide range of biomaterials for use in medical devices, such as implants, prosthetics, and drug delivery systems. These materials have been used in a variety of medical applications, including joint replacements, dental implants, and orthopaedic surgery. Kyocera has also developed a range of biocompatible materials for use in the development of drug delivery systems, such as micro needles and other drug delivery devices. Kyocera has operations in over 160 countries and serves customers in over 180 countries, making it a truly global player. Kyocera has a strong presence in key markets such as the United States, Canada, China, Australia, Brazil, and India and holds a significant market share in the printing, electronics, and components industries. Kyocera's main customers are distributors, retailers, and consumers. The company's business is divided into six segments: Fine Ceramics, Semiconductor Components, Applied Ceramic Products, Electronic Devices, Telecommunications Equipment, and Information Equipment. Kyocera is headquartered in Kyoto, Japan [71]–[75].
	Evonik Industries is a leading specialty chemicals company that produces a wide range of industrial and consumer products. The company has a strong presence in key markets such as the United States, China, India, Brazil, and the United Kingdom, and holds a significant market share in the specialty chemicals industry. Evonik's main customers are industrial and consumer product manufacturers, distributors, and retailers. Evonik's business is divided into five segments: Nutrition and Care, Resource Efficiency, Performance Materials, Services, and Other Operations. The Nutrition and Care segment produces specialty chemicals, mainly for use in consumer goods for daily needs and in animal nutrition and healthcare products. The Resource Efficiency segment supplies materials and specialty additives for environment-friendly and energy-efficient

	system solutions for the automotive, paints, coatings, adhesives, construction industries, and other sectors. The Performance Materials segment manufactures polymer materials and intermediates, mainly for the rubber, plastics, and agriculture industries. The Services segment comprises site management, utilities, waste management, technical, process technology, engineering, and logistics services for the chemical segments and external customers. Evonik Industries is headquartered in Essen, Germany [76]–[78].
	Celanese is a global technology and specialty materials company that operates in three main segments: Engineered Materials, Acetate Tow, and Acetyl Chain. The Engineered Materials segment includes businesses that produce materials for diverse industries, such as food, automotive, and construction. The Acetate Tow segment produces acetate tow and acetate flake, which are used primarily in filter products. The Acetyl Chain segment consists of intermediate chemistry, emulsion polymers, and ethylene vinyl acetate (EVA) polymers businesses. Celanese is headquartered in Irving, Texas and has a strong presence in countries around the world, including the United States, China, India, Brazil, and the United Kingdom. The company serves a variety of customers, including manufacturers, distributors, and retailers in the healthcare, medical device, and other industries [79]–[82].
	BASF is a multinational chemical company with a strong presence in countries such as the United States, China, India, Brazil, and the United Kingdom. The company operates in several segments, including Chemicals, Materials, Industrial Solutions, Surface Technologies, Nutrition and Care, Agricultural Solutions, and Other. BASF is a leader in the biomaterials industry, offering a wide range of innovative materials for the healthcare and medical device markets. The company serves medical device and healthcare manufacturers, distributors, and retailers as its main customers [83]–[86].

	Corbion is a global company that specialises in the development and production of biomaterials for use in the healthcare and medical device industries. The company has a strong presence in countries such as the United States, China, India, Brazil, and the United Kingdom, and holds a significant market share in the biomaterials industry. Corbion's main customers are medical device and healthcare manufacturers, distributors, and retailers. In addition to biomaterials, Corbion also produces a variety of other materials including polymers and resins [87]–[89].
	Noble Biomaterials is a leading company in the biomaterials industry, specialising in the development, manufacture, and marketing of advanced antimicrobial technologies. These technologies are designed to provide bacterial management, wound management, and odour elimination solutions through the use of X-STATIC, a silver fibre with anti-microbial, anti-static, heat transfer, and therapeutic properties. Noble Biomaterials was founded in 1997 and has a manufacturing facility in Pennsylvania. The company serves customers in various countries around the world, including the United States, China, India, Brazil, and the United Kingdom, and holds a significant market share in the biomaterials industry. Its main customers are medical device and healthcare manufacturers, distributors, and retailers [90]–[93].

	Bezwada Biomedical is a privately-held biomaterials company with a global presence in the healthcare and medical device markets. The company specialises in biomedical absorbable polymers and develops, manufactures, and markets absorbable monomers and polymers for various biomedical applications and medical devices. Bezwada Biomedical has a strong presence in countries such as the United States, China, India, Brazil, and the United Kingdom, and holds a significant market share in the biomaterials industry. The company's biomaterials are used in drug delivery systems, wound dressings, and implants for repair or replacement of tissues and organs [94]–[97]
	Zimmer Biomet is a global medical device company that specialises in musculoskeletal healthcare. The company designs, manufactures, and markets a wide range of products, including orthopaedic reconstructive products, sports medicine, biologics, extremities and trauma products, office-based technologies, spine, craniomaxillofacial and thoracic products, dental implants, and related surgical products. Zimmer Biomet is known for its focus on innovation and high-quality products and has a strong presence in countries such as the United States, China, India, Brazil, and the United Kingdom. Zimmer Biomet's main customers are healthcare providers, distributors, and consumers. The company is headquartered in Warsaw, Indiana [98]–[101].

Most companies have equity as one of the main sources of investment, followed by research and development projects, and finally loans, but mainly these companies have more than one source of investment [31].

3.5.2 Research landscape

To get a better sense of the major players in the field of biomaterials research, the built-in analysis tools on the *WoS* [102] and *Scopus* [103] databases were used. In *Scopus,* the search terms "biomaterial OR biomaterials" were used in the category "Title, Abstract, Keywords". The publication years were limited to 2022, 2021, and 2020, the document type was limited to articles in the final stage and the subject areas "Environmental Science", "Energy", "Economics, Econometrics and Finance", "Business, Management, and Accounting", "Earth and Planetary Sciences" were excluded from the search to limit the number of results. The search conducted in the middle of December, 2022 yielded in 17,808 results. In *WoS*, the search query "medical AND biomaterials" in the "topic" category was used to find relevant publications in the field of medical biomaterials from the last 10 years. The search conducted on December 13, 2022 resulted in 3,777 results from the *Web of Science* Core Collection.

These results were further analysed in terms of the institutions that the authors of the publications are affiliated with. In *Web of Science*, the institutions that were most frequently mentioned included the “Chinese Academy of Sciences”, the “University of California System”, “Centre National de la Recherche Scientifique (CNRS)”, and the “Harvard University” (Figure 26). Meanwhile, in Scopus the “Ministry of Education China”, the “Chinese Academy of Sciences”, the “Sichuan University” and again the “Centre National de la Recherche Scientifique (CNRS)”, and the “Harvard Medical School” were most frequently mentioned (Figure 27).

Figure 26. Documents by affiliation according to *WoS*

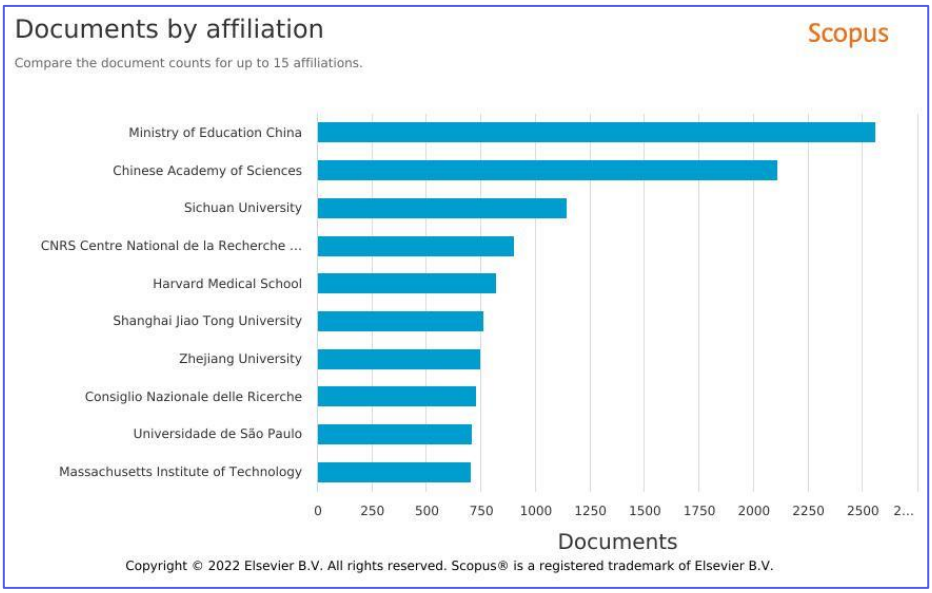


Figure 27. Documents by affiliation according to *Scopus*

3.5.3 Publications

In this section, the main journals, books and developments related to publications in the field of biomaterials are presented.

First, to gain a picture of the journal landscape in the field of biomaterials, the portal SCImago Journal & Country Rank was used. The SCImago Journal Rank (SJR) ranks journals based on scientific indicators calculated from the statistics and information contained in the Scopus® database (Elsevier B.V.) [103],

[104]. The SCImago Journal Rank allows one to set a specific subject category (according to Scopus® Classifications), then displays all journals matching this topic category, and ranks them according to their scientific prestige. More specifically, the SJR indicator "expresses the average number of weighted citations received in the selected year by the documents published in the selected journal in the three previous years, --i.e., weighted citations received in year X to documents published in the journal in years X-1, X-2 and X-3" [105]. In addition, SJR divides the journals of a certain subject category into quartiles, where quartile 1 represents the top 25% of the journals [105].

In order to get an idea of the most important journals in the field of biomaterials, the subject category "Biomaterials" was selected to get the most recent journal ranking (of the year 2021) from all regions/countries. In total, SJR listed 112 journals relevant to the field of biomaterials. The top 25% most prestigious journals are displayed in Table 21. Annex including the country of the journal, the H-index (quantifies journal scientific productivity and scientific impact [105]) and the subject categories fitting the journal. The table was supplemented by the Journal Impact Factor (JIF) from the Clarivate *Journal Citation Reports* (JCR) [106]. The JIF "provides a functional approximation of the mean citation rate per citable item" [107].

In addition, the most frequently represented journals in the *Scopus* database [103] were identified. For this purpose, the publications resulting from the search for "biomaterial OR biomaterials" in the *Scopus* database within the category "Title, Abstract, Keywords" were analysed. Publications from the last 10 years were selected, while the subject areas "Environmental Science", "Energy", "Economics, Econometrics and Finance", "Business, Management, and Accounting", "Earth and Planetary Sciences" were excluded. Based on the results of this search, the most frequently published-in journals were:

- "Materials Science And Engineering C",
- "Acta Biomaterialia",
- "Biomaterials",
- "ACS Applied Materials And Interfaces",
- the "Journal Of Biomedical Materials Research Part A"
- and the "Journal Of Applied Polymer Science".

The number of documents published in each of these journals per year is displayed in Figure 28.

Further, to identify trends in the field, the Google search trend for the keyword "biomaterials" was also analysed. As can be seen in Figure 29, the search for the term "biomaterials" has been, except for a few outliers, consistently popular over the last five years and the tendency to search for the word is increasing. The term was searched for particularly frequently in China, South Korea and Singapore.

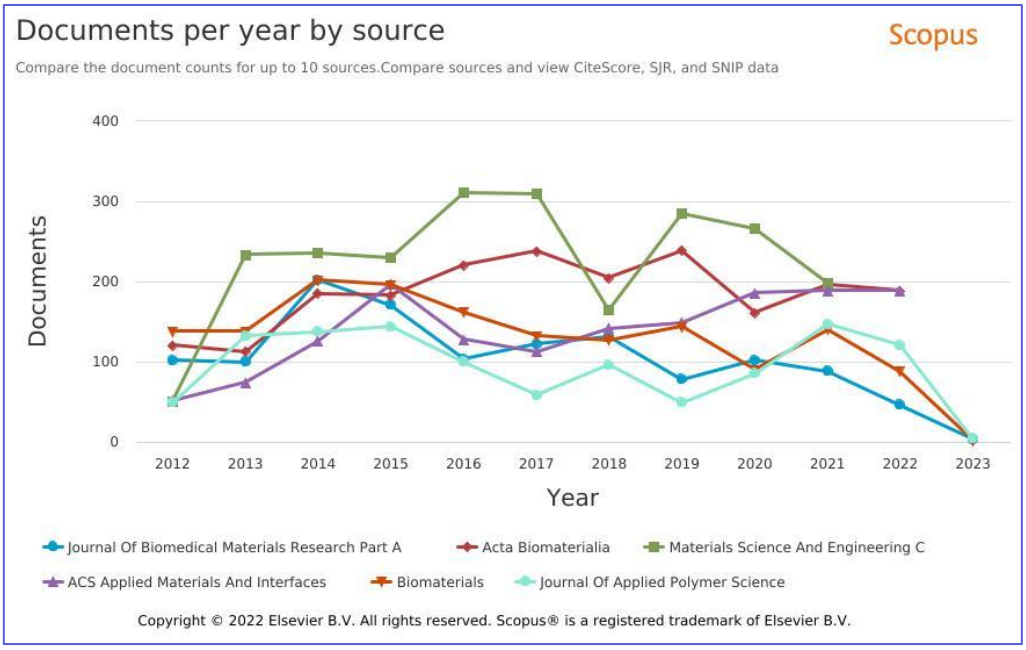


Figure 28. Number of documents published per year in the most prominently used journals

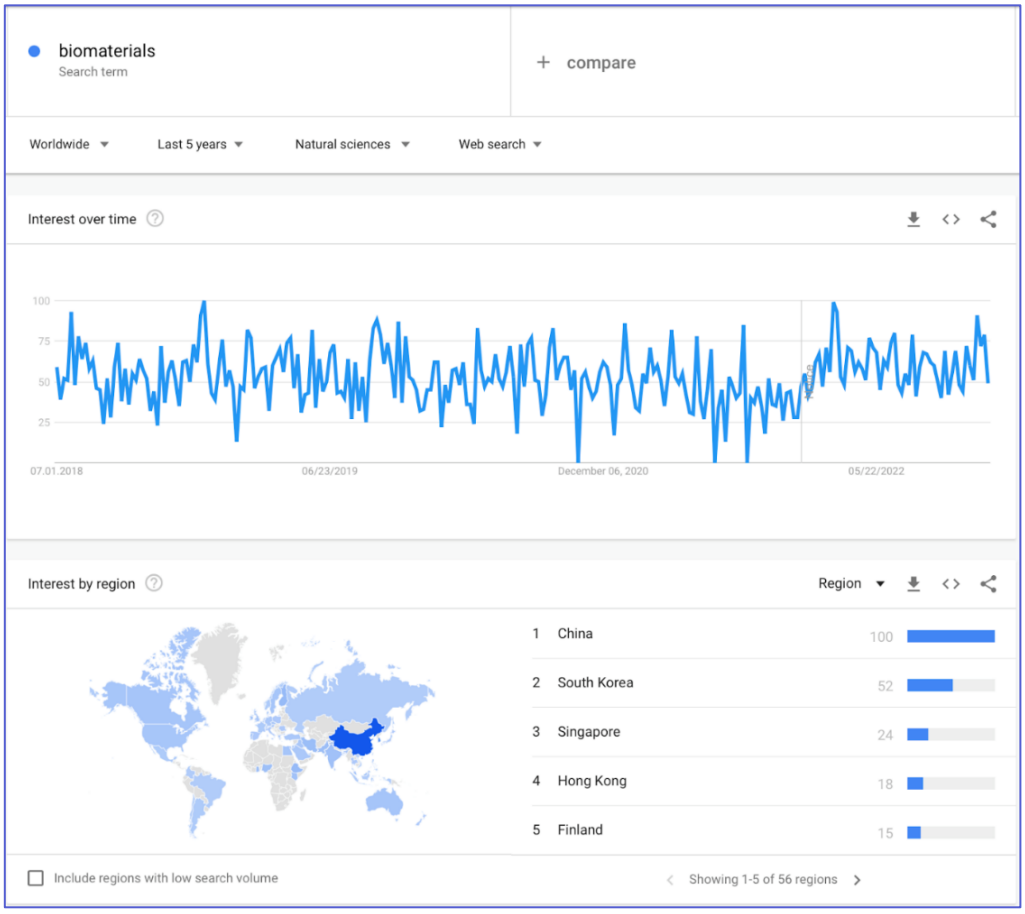


Figure 29. Google Trend analysis for the term “biomaterials” search conducted on 04.01.2023

In order to get a better impression of the most researched topics and topic clusters in the field of biomaterials, keyword co-occurrence networks were created with the software *VOSviewer* [108], based on the search results from the *Web of Science* (*WoS*), *Scopus* and *PubMed* databases.

First, in the *WoS* database [102], the search query "medical AND biomaterials" in the "topic" category was used to find relevant publications in the field of medical biomaterials from the last 10 years. The search conducted on December 13, 2022 resulted in 3,777 results from the *Web of Science* Core Collection. The full reports for all of the results were downloaded manually, concatenated, and uploaded to *VOSviewer*. After the upload, the 8092 author keywords from the collected publications were selected. The minimum number of occurrences of a keyword was set to 10. In total, 170 keywords met this threshold and for each of the 170 keywords the total strength of the co-occurrence links with other keywords was calculated. Below, the resulting keyword co-occurrence network can be seen (Figure 30) and is intended to give an impression of which topics have been of particular relevance in publications on biomaterials over the past 10 years and which thematic clusters (displayed in different colours) exist in this field.

Additionally, in the Scopus database [103], the query "biomaterial OR biomaterials" was searched in the category "Title, Abstract, Keywords". The publication years were limited to 2022, 2021, and 2020, the document type was limited to articles in the final stage and the subject areas "Environmental Science", "Energy", "Economics, Econometrics and Finance", "Business, Management, and Accounting", "Earth and Planetary Sciences" were excluded from the search to limit the number of results. The results were subsequently sorted by the latest date. Unfortunately, Scopus only allows the download of the first 2000 results. Hence, the first 2000 newest articles from the 17,808 results (all from the year 2022) were downloaded as csv file and uploaded to *VOSviewer* [108] to create the co-occurrence network of the author keywords. Again, the minimum number of occurrences of a keyword was set to 10 and 76 keywords met the threshold in this case. The co-occurrence network for these author keywords as well as the topic-clusters (in colour) can be seen in Figure 31.

Next, in the *PubMed* [109] database the search query "biomaterial OR biomaterials" was used in the MeSH Terms category to find relevant publications in the field of biomaterials. The search was focused on the period from 2017-2023 to keep the number of results below 10,000. The search resulted in 8,657 publications. The publication information of all results was saved and uploaded to *VOSviewer* [108]. After the upload, the 4648 MeSH terms from the collected publications were selected. The minimum number of occurrences of a keyword was set to 10. In total, 962 keywords met this threshold and for each of the 962 keywords the total strength of the co-occurrence links with other keywords was calculated. Below the resulting keyword co-occurrence network can be seen (Figure 32) and should illustrate which topics have been of particular relevance in publications on biomaterials over the past 5 years and which thematic clusters (displayed in different colours) exist in this field.

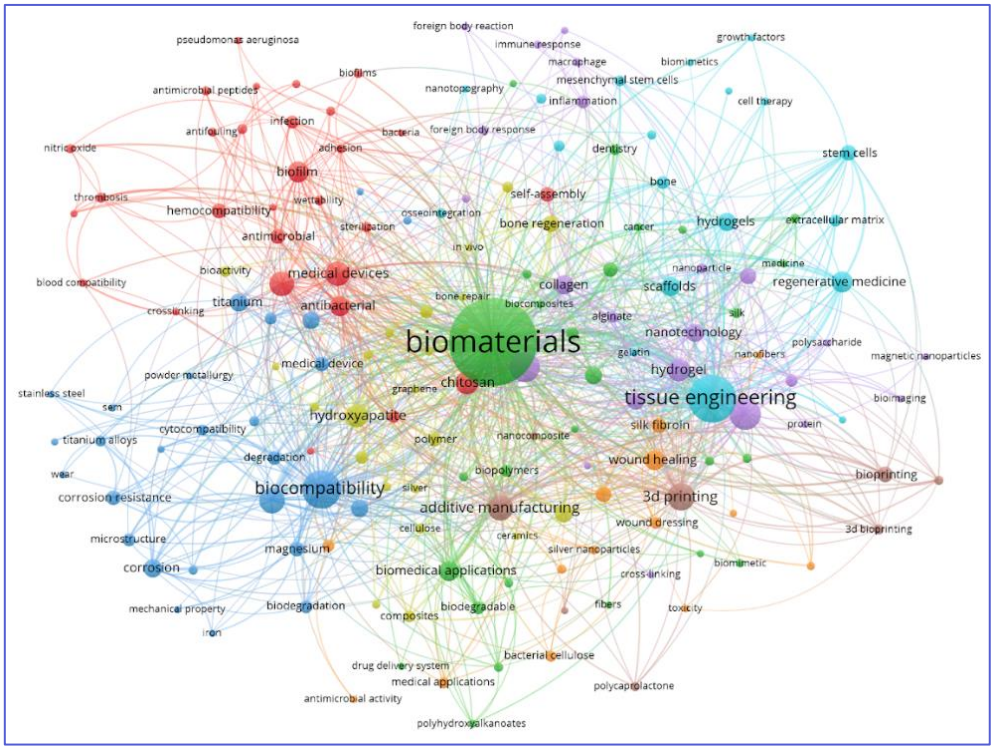


Figure 30. Keyword co-occurrence network based on the author keywords from *WoS*

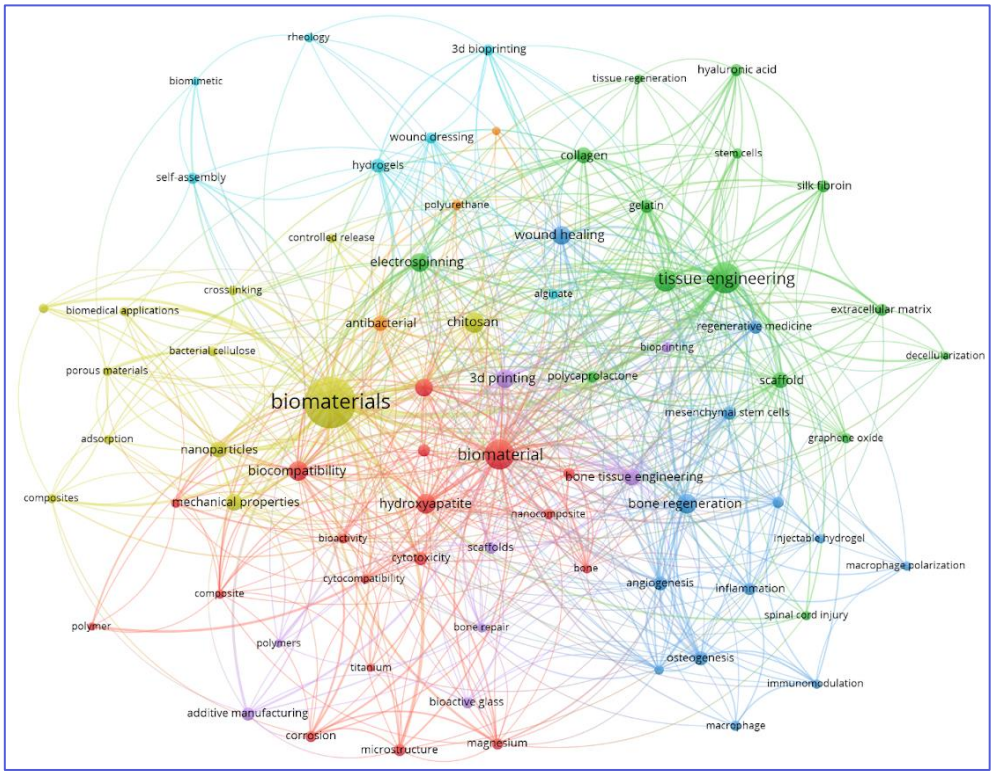


Figure 31. Keyword co-occurrence network based on the author keywords from *Scopus*

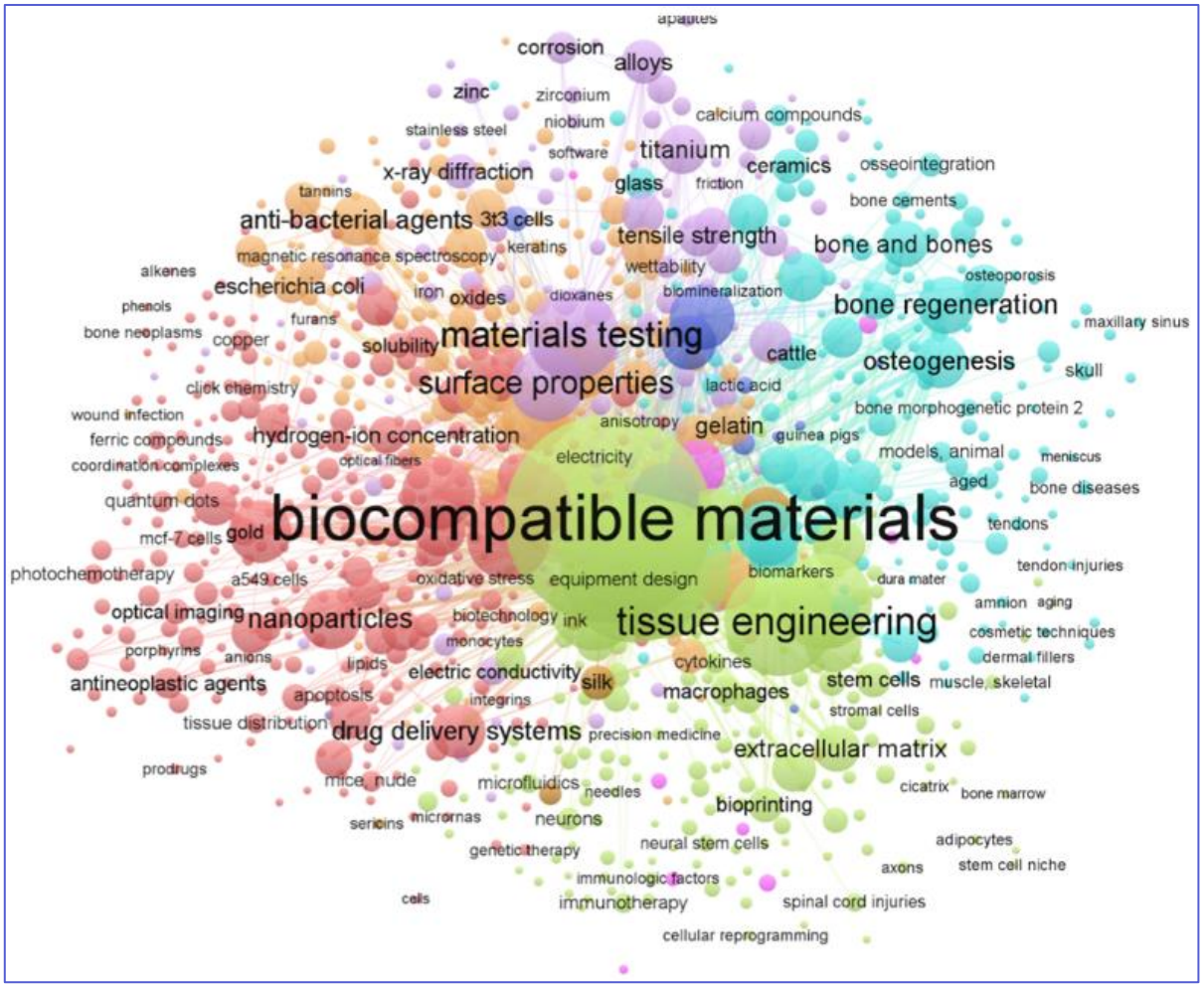


Figure 32. Keyword co-occurrence network based on the MeSH terms from *PubMed*

Additionally, the results from *PubMed* [109], (settings as described above, only the period was set to 2012-2023), *Web of Science* [102] (settings as described above), and 85,649 results from *Scopus* [103] (settings as described above, but the document type was not limited and publications from 2012-2023 were included) were further analysed with the different analysis and visualisation tools that these databases offer.

The three following graphs (Figure 33, Figure 34, Figure 35) will illustrate how the **number of publications published per year** in the field of biomaterials increased over the last 10 years on all three publication databases. Keep in mind that in all three graphs it may seem like the number of publications decreases in the years 2022 and 2023. This is due to a time lag between the time an article is accepted by a journal until it is actually published. The delay results from the review processes involved in publishing articles in peer reviewed journals. All the graphs were retrieved in the middle of December 2022.

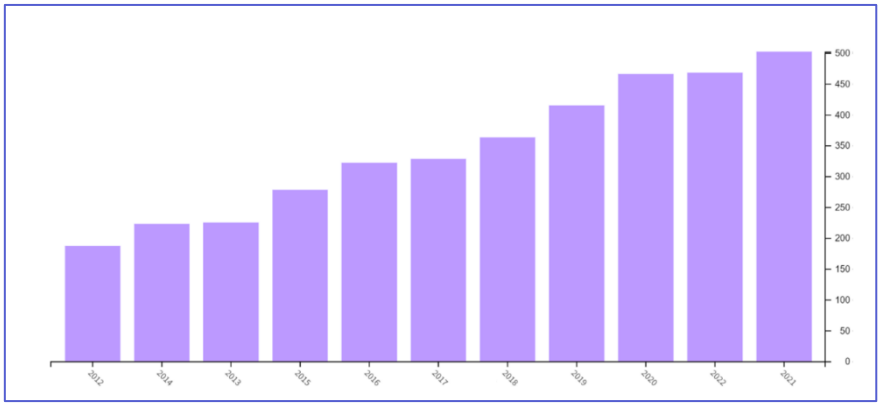


Figure 33. Number of publications per year according to *WoS*

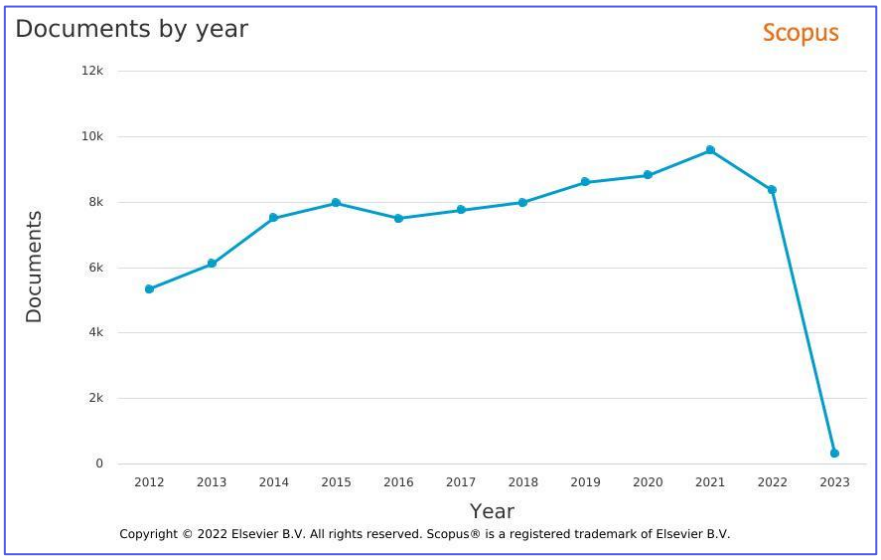


Figure 34. Number of publications per year according to *Scopus*

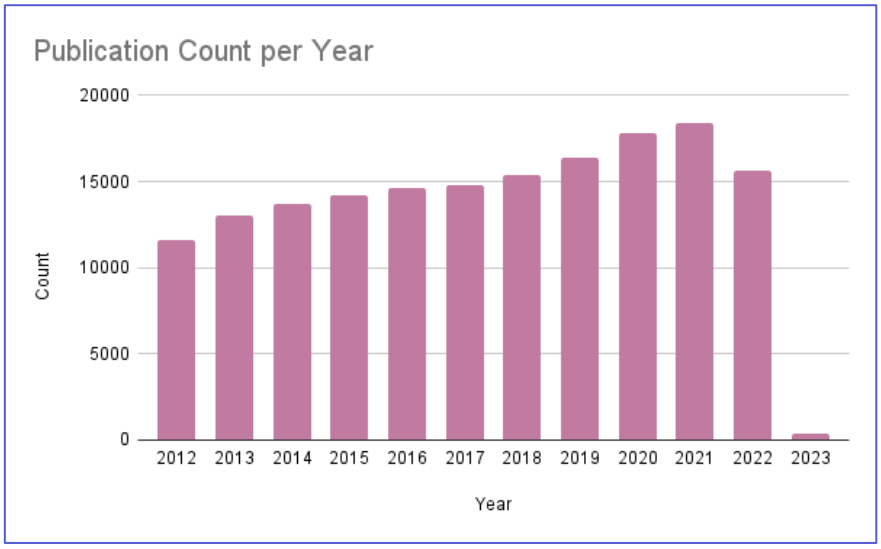


Figure 35. Number of publications per year according to *PubMed*

Finally, to control for the overall increase in publications, the 'europepmc' R package was used to access the *EuropePMC* database [110] RESTful Application Programming Interface (API) in order to assess the publication trend in biomaterials relative to overall number of documents in the database (script available on GitHub [111]). The search query was similar to above, searching for the terms: 'biomaterial', 'biomaterials', or 'biocompatibility' in the fields: Title, Abstract, or Keywords. The range of results was limited to the past 10 years (2012–2022). Importantly, the results (the number of query hits) were normalised to the total number of documents in the database. Thus, the results reflect the *fraction* of indexed publications in the field of biomaterials, relative to the indexed biomedical literature. The results are presented below in Figure 36. Hence, Figure 36 shows the fraction of publications per year for the query "biomaterial OR biomaterials or biocompatibility" in the Title, Abstract, and Keyword fields of EuropePMC. The blue line represents the local regression (LOESS) to guide the eye. As can be clearly noted, the fraction is increasing. This indicates that the field of biomaterials is more active in terms of publications than the overall biomedical community: it is outpacing the overall growth in publications.

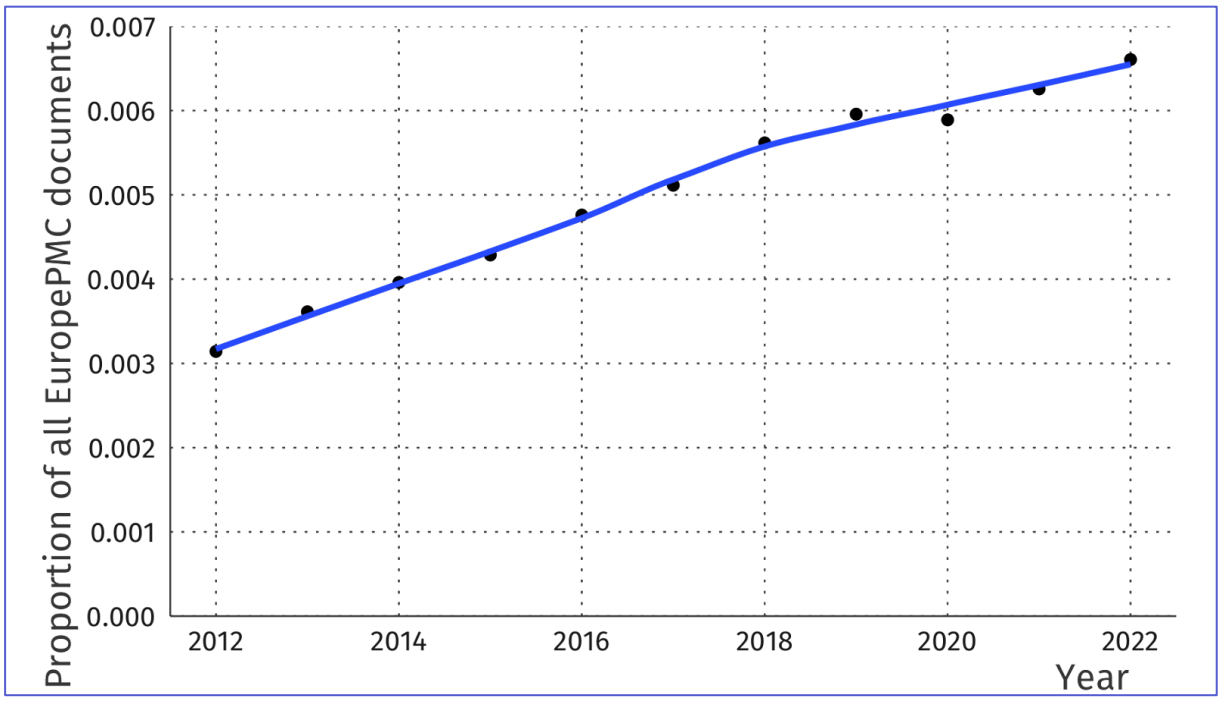


Figure 36. Fraction of publications per year based on results from *EuropePMC*

Next, the **subject areas** in the field of biomaterials were analysed. The subject areas that were most frequently represented in the results of *WoS* [102] and *Scopus* [103] are presented in the Figure 37 and Figure 38. In the publications from *WoS*, the subject areas "Nanofibres, Scaffolds and Fabrication", "Polymers and Macromolecules" and "Metallurgical Engineering" were featured most frequently. Meanwhile, in the *Scopus* database, the publications were most frequently assigned to the research areas "Materials Science", "Engineering", as well as "Biochemistry, Genetics and Molecular Biology".

Finally, it was important to the BIOMATDB consortium to provide an overview of relevant books in the field of biomaterials. For this purpose, the analysis functions in *Web of Science* were used to identify relevant book series in the field of biomaterials. As Figure 39 shows, the "Woodhead Publishing Series in Biomaterials" and "Advanced Structured Materials" are comprehensive book series.

Figure 37. Subject areas included the publications of *WoS*

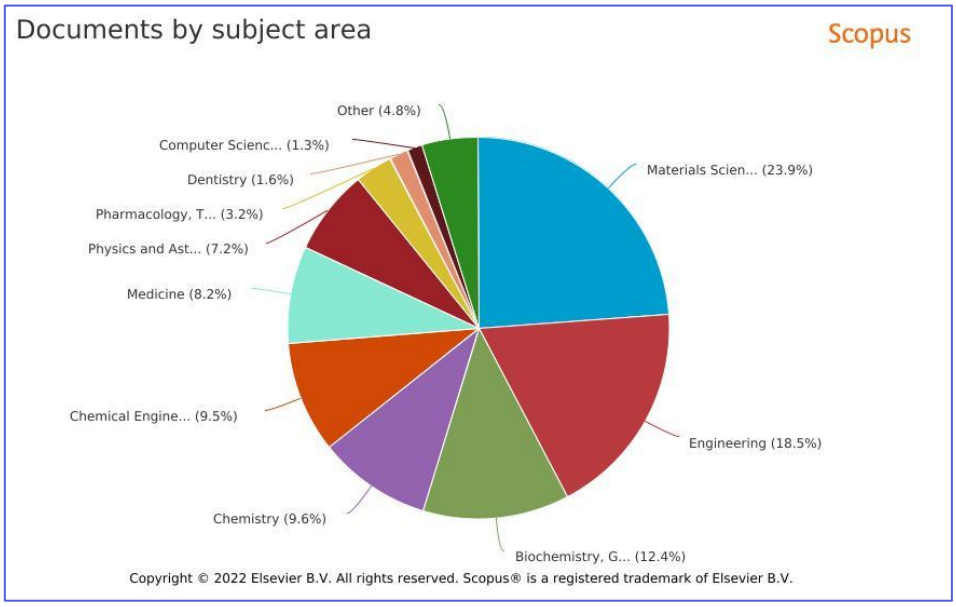


Figure 38. Subject areas included in the publications on *Scopus*

Figure 39. Relevant book series in the field of biomaterials based on the results from *WoS*

Additionally, based on an online search and on recommendations of the consortium, a subjective selection of books was made that can give a good overview of the whole field of biomaterials or that give insights into special applications of biomaterials, such as Translational Medicine, Organ and Tissue Regeneration or Smart Biomaterials. The selected books are displayed in Table 22. Annex.

3.5.4 Societies and networks

Societies and networks play an important role in supporting and sustaining the ecosystem of their particular scientific field. Their objectives include the representation of the interests of their members but also the promotion of research; the dissemination of scientific knowledge; the creation of opportunities for communication among peers across career stages, institutions, and countries; the financial support of students and early career scientists to attend conferences; and the provision of latest research developments and policy advice to funders and governmental organisations. These are achieved through activities and services such as specialised scientific journals, scientific meetings and conferences, guidelines and white papers, and awards that recognise the scientific background or accomplishments in a particular area.

The main biomaterials societies are organised according to geographic location. The oldest one, the Canadian Biomaterials Society (CBS) was created in 1973 and promotes the development of biomaterials research, technology, and education at Canadian universities, industry, and government [112]. The Society For Biomaterials (USA) was founded in 1974 and strives to advance excellence in all aspects of biomaterial science, engineering, and technology for promoting health and wellness through its interactive global community [113]. Established in 1976, the European Society for Biomaterials (ESB) consists of members from more than 20 countries that are dedicated to addressing unmet clinical needs with advanced materials for medical devices and regenerative medicine [114]. Since its conception in 1978, the goal of the Japanese Society for Biomaterials (JSB) is to improve science and technology related to materials used in the body [115]. The Society for Biomaterials & Artificial Organs India (SBAOI) was created in 1986 and cultivates an environment nationwide conducive to the development of research in Biomaterials and Artificial Organs that is both basic and technologically oriented [116], [117]. Biological materials, tissue engineering and medical devices are the main focuses of the Australasian Society for Biomaterials and Tissue Engineering (ASBTE), which since 1989 is bringing together professionals with an interest in research, education, development and regulation [118]. Originated in 1996, the Korean Society for Biomaterials (KSBM) seeks to further the applications of biomaterials through the exchange of the latest information between academic, clinical and industrial researchers [119]. The Chinese Taipei Society for Biomaterials and Controlled Release, founded in 1997, promotes the participation of its members in activities for the advancement of biomaterials and drug delivery science and technology [120]. Established in 1998, the Latin American Society of Biomaterials and Artificial Organs (SLABO) brings together a critical mass of professionals from research, development, testing and clinical application of biomaterials and artificial organs [121]. The Chinese Society for Biomaterials (CSBM) was created in 2007 to drive the development of biomaterials in China [122].

All these societies are gathered within the International Union of Societies for Biomaterials Science and Engineering (IUSBSE) that, since its establishment in 1980, organises the World Biomaterials Congress every four years in order to promote biomaterials science and engineering [123].

3.6 Regulatory overview

Biomaterials are the raw materials and components of final medical products, devices, and advanced therapeutics. As a result, they both indirectly and directly affect safety and performance. In order to become final medical products, biomaterials need to be specifically engineered and designed for the final product specifications and application requirements, to eliminate unacceptable risks and achieve desirable benefits demonstrated in benchtop, biocompatibility, biosafety, pre-clinical, clinical performance, and post-market surveillance.

Designation of biomaterials-based medical products as medical devices, pharmaceuticals/ biological products, or combination products, as well as classification of biomaterials-based medical devices (Class I, II or III) are very important for their regulatory approval pathways. The classification of biomaterials-based medical devices depends on the assessment of risks and control procedures and both designation and classification follow regulations that can be country/area-dependent. However, typically these classifications are performed by the manufacturer of the medical product/device. Depending on the Class of the medical device, the regulatory requirements will differ, because of the different risks involved.

An additional important regulatory aspect of biomaterials is related to their manufacturing. Materials used in medical environments, specifically those that are in direct contact with the body of a patient, should be of "medical grade." However, there are no definitive standards in place for what exactly "medical grade" means; usually medical grade is related with Good Manufacturing Practice (GMP) of the raw material. Further, patient-contacting materials must be biocompatible, meaning that they perform without causing an adverse effect. This is assessed following the International Organisation for Standardisation (ISO) standard (ISO-10993 series and others), ASTM International, and the International Medical Device Regulators Forum (IMDRF). Different tests are indicated depending on the duration and type of contact (Figure 54. Annex). Achieving ISO 10993 certification helps with getting approval from the corresponding regional regulatory agencies [47].

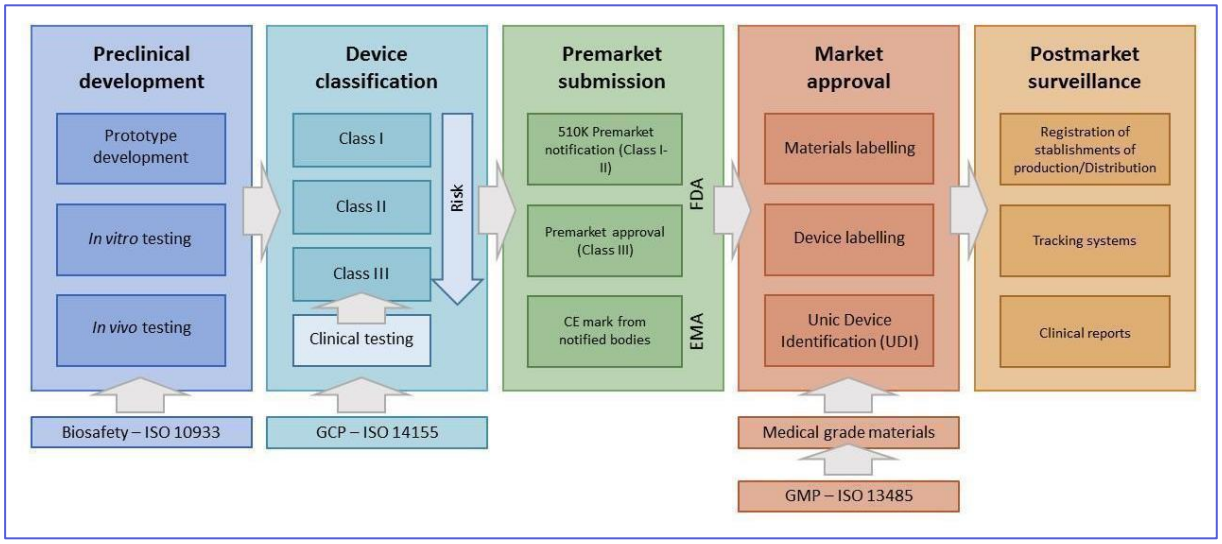


Figure 40. Generalised overview of the regulatory pathway of medical devices.

3.6.1 Medical Device Regulation in Europe

Product markings are a specialised form of product certification that often applies to geographic regions. There are many differences between Europe and the United States, as well as between other countries, in reviewing and approving new medical devices. In particular, in the United States, the Food and Drug Administration (FDA) takes a centralised approach, while in Europe the process is more decentralised via the European Medicines Agency (EMA). New medical devices are often first approved in the EMA through a specialised certification marking, before undertaking the separate U.S. FDA approval process.

The project is financed by the European Commission and so our main focus is of course on EU regulations. Since the US and China represent big markets and are of potential interest for European SMEs, the project will seek to also cover them. Any other markets, which can potentially be identified during the knowledge collection and exchange activities in a later phase of the project, will be reported in the upcoming deliverables.

The European Medical Device Regulation (MDR)

As of May 26, 2021, the new European Medical Device Regulation (EU)2017/7458 MDR) [124], [125] also applies to implants. In the following the main regulatory requirements according to MDR for medical implants in Europe as well as the connected procedure are outlined.

CE-Certification

The CE mark is a prerequisite for launching a new implant in the EU. Before marketing, a manufacturer must first and foremost prove that the implant is safe and efficient and has a positive benefit-risk ratio. A notified body tests and certifies this proof. Only then may the manufacturer label the product with the CE mark and place the implant on the market. With regards to the requirements under medical device law, the following essential steps can be differentiated on the way to placing a product on the market and the downstream market phase: 1. qualification of the implant as a medical device; 2. risk classification of the implant; 3. manufacturer's obligations; 4. product requirements; 5. declaration of conformity; 6. CE marking; 7. registration and 8. monitoring [126].

Qualification of the implant as a medical product

The manufacturer must first determine whether their implant is a medical product as defined in Art. 2 (1) MDR on the basis of its intended purpose. Other characteristics of a medical device are that it is intended for use in humans, its principal action takes place in or on the body, and that this is not achieved by pharmacological or immunological means or metabolically. If the implant in question is a medical device, both the device and the manufacturer are subject to the provisions of the MDR. It should be noted that the scope of the MDR now also includes products without a medical purpose, such as coloured contact lenses or implants and substances for aesthetic purposes [126].

Risk classification of the implant

Manufacturers must classify their medical devices into classes I, IIa, IIb and III, taking into account the intended purpose and the associated risks (Art. 51 MDR). The risk class is the basis for the further steps up to CE marking, in particular for the choice of the conformity assessment procedure and for the scope of the clinical evaluation. Under the previous European regulatory framework, implants were classified according to Annex IX of Directive 93/42/EEC supplemented by Directive 2007/47/EC. In the

body periphery, implants were generally assigned to Class IIb and, for the cardiac, central circulatory and nervous system site of application, to Class III [127]. Directives 2003/12/EC and 2005/50/EC specified Class III classification for breast and joint implants. An exception were denture implants, which were assigned to Class IIa. Guidance for the classification of medical devices according to MDR is provided by the MDCG Medical Device Coordination Group Guideline 2021-24 [128].

Manufacturer's obligations

Regardless of the risk class and type of medical products, all manufacturers are subject to the obligations set forth in Art. 10 MDR. Some of these include fulfilment of essential safety and performance requirements; establishment, documentation, application, maintenance of a risk management system; performance of clinical evaluation including clinical follow-up; preparation and continuous updating of technical documentation; performance of a conformity assessment procedure (including product classification) and preparation of an EU declaration of conformity; establishment of a unique device identification (UDI) system and all necessary registrations of devices and the manufacturer, etc. [126].

Product requirements

The product range of implants is very wide. It includes passive and active implants with application in different body regions for a different duration. In addition, active implants may require control software and programming devices. Therefore, only some of the basic safety and performance requirements for implants are explained below as examples, which may not be applicable to every product in individual cases.

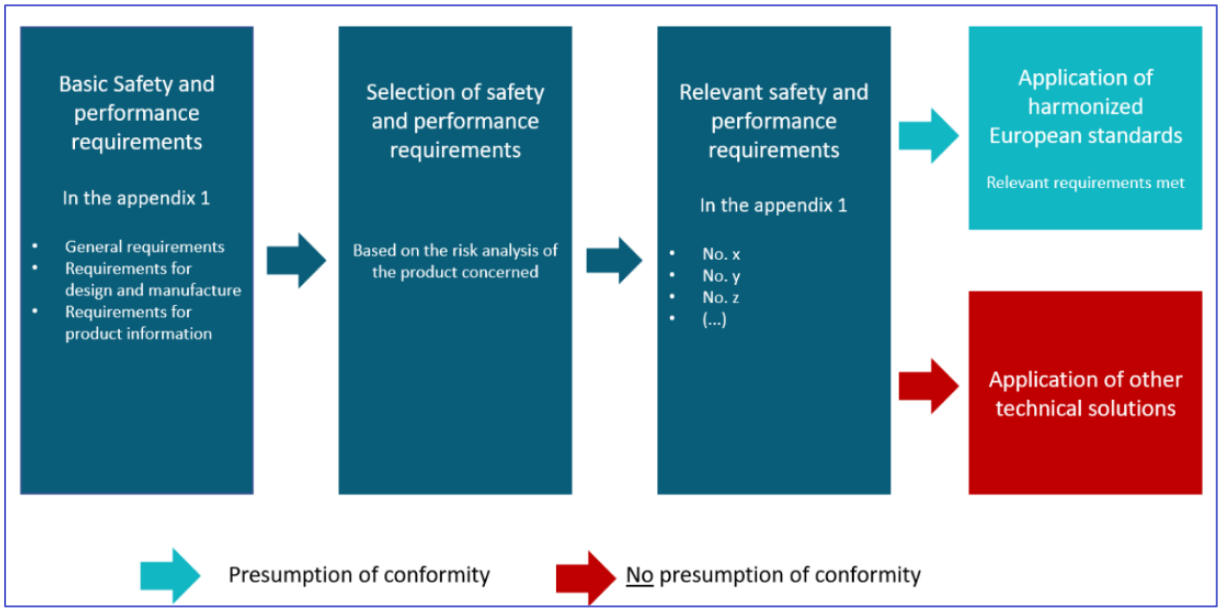


Figure 41. Role of harmonised standards, modified according to **[129]**

Based on the essential safety and performance requirements (GRUSULA) in Annex I, MDR, the manufacturer makes a selection based on a risk assessment, i.e., an identification of the applicable requirements for the respective product (Figure 41). Compared to the essential requirements in Directive 90/385/EEC, the MDR now also applies many requirements to implants that were previously

limited to other medical devices. Other requirements have been retained, such as the specific requirements for active implantable devices in Section 19, MDR.

Custom-made devices, such as those from the dental and dental technology fields, are subject to special requirements. The procedure for custom-made devices is described in Annex XIII, MDR. For example, custom-made devices do not bear a CE mark (Art. 20 (1), MDR) and are subject to a simplified conformity assessment and reduced documentation requirements (Art. 10 (5), MDR).

Information security is also increasingly coming into focus for programmable medical devices or medical products in the form of software, which also applies for some implants. Sections 17.2. and 17.4. in Annex I, MDR require the manufacturer to define risk management including information security as well as minimum requirements for IT security measures. Standards contain detailed descriptions of requirements regarding the technical specifications of medical devices and the relevant processes [130].

Declaration of Conformity

Through the EU declaration of conformity, the manufacturer assumes product responsibility. This is continuously updated and contains specific information according to Annex IV, MDR. In the case of implants that basically belong to risk class IIa or higher, the manufacturer who carries out the conformity assessment procedure, receives a corresponding EU certificate from the notified body and declares conformity [126].

CE conformity mark

The CE conformity mark indicates that the relevant requirements of the MDR have been met. The manufacturer affixes the CE mark with the number of the notified body involved (not for risk class I) on the product, packaging, instructions for use and promotional material. Annex V MDR regulates the appearance of the CE marking [126].

Registration

Before placing the medical device on the market, manufacturers, authorised representatives, and importers must register in the European database on medical devices (EUDAMED) (Art. 31, MDR). In case of a conformity assessment with the involvement of a notified body, the information (Annex VI Part A Section 1) is transmitted to EUDAMED before the application is submitted to the notified body. The manufacturer must register their devices with the information from Annex VI Part A in EUDAMED (Art. 29, MDR).

Monitoring

MDR medical device surveillance is divided into three measures:

- post-market surveillance by the manufacturer (Arts. 83-86),
- vigilance by the manufacturer (Arts. 87-91), and
- regulatory market surveillance (Arts. 93-100).

The manufacturer must integrate a *post-market surveillance system* (PMS) into its Quality Management System (Art. 84 (1), MDR). The related PMS plan and report (Art. 84 and 85, MDR) are components of the technical documentation (3.3.5).

Vigilance of the manufacturer includes reporting of serious incidents and safety corrective actions in the field (Art. 87, MDR). Serious incidents such as death or unforeseen serious deterioration of health must be reported immediately via EUDAMED, no later than ten days after becoming aware of them (Art. 87 (5), MDR). All other serious incidents must also be reported immediately, at the latest within 15 days (Art. 87 (3), MDR).

Although *regulatory market surveillance* remains a task of the individual member states, it is to be coordinated across the EU. Art. 93 (1), MDR requires competent authorities to inspect the conformity characteristics and performance of medical devices through appropriate reviews of documentation, and through physical checks or laboratory testing of samples. The competent authorities report the results of their monitoring activities (Art. 93 (4), MDR) and file monitoring reports via EUDAMED (Art. 93 (7), MDR) [126].

Medical Device Sterilisation Requirements and Regulations

A key aspect that cannot be overlooked in the context of biomaterials development and medical devices is sterilisation. Note that in the EU, the MDR states the requirements for sterile devices, but does not define the term “sterile”. Depending on the classification of the device, particularly if it is “critical” or in contact with the blood stream or internal tissues, cleaning and sterilisation procedures may vary. However, sterile devices are those that are free of viable microorganisms and spores. The requirements for such a designation are in the EN 556 series of standards. In Part 1, EN 556 defines the requirements for terminally sterilised devices, while in Part 2 the requirements of aseptically produced devices are presented. In the age of multidrug-resistant bacteria (MDR) these requirements play an even more important role [131].

The choice of sterilisation method will also depend on the physical and chemical resistance of the medical device and the biomaterials it is composed of. In fact, the properties of the material(s) used can be altered by the sterilisation process. In some cases, this can be an advantage, but frequently it is a limitation. Further, sterilisation methods are also regulated. For example, in the US, sterilisation methods used in device manufacturing are subject to FDA Quality System (QS) regulations per 21 CFR Part 820. In this context, sterilisation methods for medical devices are divided into two categories: established methods and novel methods.

Established sterilisation methods are then further divided into two more categories: A and B. Category A methods are those that have a long track record of use and have well-known effectiveness. Examples include dry heat, ethylene oxide gas (EtO), radiation (gamma, electron beam) and steam. Meanwhile, Category B methods have published FDA-recognized information regarding development, validation, and controls along with validated data from sterilisers, which are evaluated by the FDA but there are no FDA-recognized consensus standards. Examples of Category B methods include hydrogen peroxide (H_2O_2), ozone (O_3), or flexible bag systems (e.g., EtO in a flexible bag system, diffusion method, injection method). Finally, novel methods are those that have not been reviewed and determined to effectively sterilise devices for their intended use. This category includes any novel chemical substance or process that has not been reviewed, cleared, or approved by the FDA. Some examples include vaporised peracetic acid, high-intensity light or pulsed light, microwave radiation, sound waves, ultraviolet-light-mediated methods, or supercritical CO_2 [131].

International Harmonisation of Medical Device Approval and Compliance Standards

Importantly, there is a mechanism in place for the EU to recognize Good Laboratory Practice (GLP) and GMP surveillance inspections, as well as medical device conformity assessment results (e.g., testing or certification). So-called Mutual Recognition Agreements (MRA) are bilateral treaties between the EU and third countries aimed at promoting trade and facilitating market access. For example, for medical devices, such agreements are in place with Australia, New Zealand, Switzerland, and the United States. These agreements outline the conditions under which each party will accept that a medical device meets all applicable requirements to enable it to be sold, as well as inspection bodies and conformity assessment bodies (CAB) that can show compliance with each parties' requirements [132].

3.6.2 Medical Device Regulation outside of Europe

As our research in the Industrial landscape and Market overview chapters revealed, North America dominated the global biomaterials market in recent years, while the Asia-Pacific region, and especially China, has been identified as the most promising market for the growth of biomaterials, both in relation to industry and research. Therefore, in the following paragraphs, we will also give a brief overview of the Medical Device Regulation in the USA and China.

U.S. Medical Device Regulation

In the United States, medical devices are regulated by the Food and Drug Administration (FDA). Recently, in 2019, the FDA issued "Statement on continued efforts to evaluate materials in medical devices to address potential safety questions." This document presented a roadmap of efforts regarding the evaluation of materials used in medical devices, in order to address potential safety concerns [133].

An important aspect of the FDA's evaluation of the safety and effectiveness of a medical device involves the premarket review of information about the materials used in the device. The FDA considers the specific properties of the material, the intended use of the device, and the function of the device when evaluating the safety of the device materials. As part of premarket submissions, medical device manufacturers submit information such as an evaluation of biocompatibility to the FDA to demonstrate that the materials they plan to use in their device can be safely used in or on the human body. The FDA has published guidance, which describes how a risk-based approach is utilised to determine what types of biocompatibility information are typically needed to demonstrate the safety of a material:

Premarket submission - 4 steps:

1. Classify Your Device and Understand Applicable Controls:

Medical devices are categorised into one of three classes (I, II, or III), based on the degree of risk they present. As device class increases from class I to class II to class III, the regulatory controls also increase, with class I devices subject to the least regulatory control, and class III devices subject to the most stringent regulatory control. The classes of devices, regulatory controls, and submission types are summarised:

Class I: Lowest, present minimal potential for harm - General 510(k)

Class II: Moderate, higher risk than class I devices - General 510(k)

Class III: Highest, sustain or support life, are implanted, or present potential unreasonable risk of illness or injury – Premarket approval (PMA).

2. Select and Prepare the Correct Premarket Submission:

The most common types of premarket submissions include:

510(k) (Premarket Notification): Some class I and most class II devices require a 510(k). In a 510(k), the sponsor must demonstrate that the new device is "substantially equivalent" to a predicate device in terms of intended use, technological characteristics, and performance testing, as needed.

PMA (Premarket Approval): Class III devices require a PMA. A PMA is the most stringent type of premarket submission. Before the FDA approves a PMA, the sponsor must provide valid scientific evidence demonstrating reasonable assurances of safety and effectiveness for the device's intended use.

De Novo Classification Request: The De Novo process provides a pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device.

HDE (Humanitarian Device Exemption): HDE provides a regulatory pathway for class III devices that are intended to benefit patients with rare diseases or conditions. In order for a device to be eligible for an HDE, a sponsor must first obtain designation as a Humanitarian Use Device (HUD), which is granted through an application to FDA's Office of Orphan Products Development (OOPD).

The FDA encourages the use of FDA-recognized consensus standards [134] in premarket submissions and encourages **clinical evidence of the safety of the product.** Prior to initiating a clinical study, the study sponsor may need to obtain approval of an Investigational Device Exemption (IDE) by the FDA. Clinical studies must comply with all applicable IDE regulations and Good Clinical Practices (GCPs). In this sense, materials employed in the intended devices must accomplish proper GxPs.

The **labelling** for a device must be written according to the established labelling regulations (Title 21 of the Code of Federal Regulations (CFR), Sections 801.1–801.437) and included also in the premarket submission of the medical device [135]. Labelling includes both the actual labels on the device, as well as all printed materials including the device packaging, product insert, etc. For example, General Labelling Provisions require that the labelling must ensure that the name of manufacturer and place of manufacturing are conspicuous, that all the "intended use" conditions/purposes are stated, and that required information and symbols are correct and sufficiently prominent. For investigational devices or those that fall in other special categories, such as containing natural rubber, there are additional, special labelling requirements.

FDA has also established a unique device identification (UDI) system to identify approved medical devices throughout their time of distribution and use. The UDI regulations became final in September 2013 and have been phased in over the past several years, based primarily on device classification [136]. When fully implemented, the UDI System will offer a range of benefits to industry, FDA, consumers, health care providers and health care systems including improved

patient safety and post market surveillance. This UDI is required to be present on the label of every medical device.

3. Prepare the Appropriate Information for the Premarket Submission:

Once the appropriate premarket submission for a device is prepared, the submission to the FDA must be sent, and the interaction with FDA staff should be maintained during its review.

4. Comply with Applicable Regulatory Controls, Including Establishment Registration and Device Listing:

(1) register the establishments and list the medical devices they market with FDA;

(2) manufacture the devices in accordance with Good Manufacturing Practices;

(3) label the devices in accordance with labelling regulations; and

(4) prevent adulteration or misbranding. A device facility must register its establishment and list its devices with the FDA.

Medical device manufacturers as well as other firms involved in the distribution of devices must also follow specific requirements and regulations once devices are on the market. These include such things as tracking systems, reporting of device malfunctions, serious injuries or deaths, and registering the establishments where devices are produced or distributed. Postmarket requirements also include postmarket surveillance studies required under section 522 of the act as well as post-approval studies required at the time of approval of a premarket approval (PMA), humanitarian device exemption (HDE), or product development protocol (PDP) application.

Importantly, for the case of medical devices, frequently materials, subcomponents, processes etc. are from a third party, such as a supplier or are used in multiple device-related submissions. In these cases, there is a process, the so-called Master File (MAF), that enables the FDA to review data and information related to the material/subcomponent, manufacturing process, etc. without the device manufacturer having direct access to proprietary information. For example, the MAF can cover aspects of manufacturing and quality control needed to fulfil GMP requirements. However, there are no specific requirements for the content, just that it be “substantive” and contain confidential information. Note that the MAF is submitted by organisations/entities that are not the ones directly participating in a device-related submission, but those involved in material synthesis, manufacturing, sterilisation, packaging, etc. MAF holders then can provide an authorization letter to the entity pursuing a device-related submission, approving the inclusion of the MAF in their submission. Finally, it is also important to note that the presence of a MAF does not imply that a material or process has FDA approval—only devices are subject to approval and MAFs simply contain third party confidential information needed for the approval process [137].

Medical Device Regulation in China

Medical devices in China are regulated by the National Medical Product Administration (NMPA; http://english.nmpa.gov.cn/), formerly known as the China Food and Drug Administration or CFDA.

Manufacturers must first register their devices with the NMPA before they can sell or distribute them in China. All device applications are reviewed by NMPA, which has its own strict requirements for the submission documentation, testing, and clinical data. These requirements are largely the same for

domestic and foreign applicants. In March 2020, the NMPA issued the annual report for the registration of medical devices. This shows that the NMPA approved a total of 8,471 applications in 2019, which was a 53.2% increase over 2018. In 2017 and 2018, there have been bottlenecks, on the one hand, because the testing of electromagnetic compatibility (EMC) has become increasingly necessary. On the other hand, applications were delayed due to strict clinical requirements. The figures in the Annual Report 2020 show that these difficulties have now been resolved [138, p. 20].

The medical device classification determines the documentation required for the submission to NMPA submission. The Classification is based on the Chinese NMPA Decree No.15 and the NMPA classification database. The device classification requirements are described below in brief:

- Class I : registration dossier / no testing reports
- Class II: full registration dossier & technical review
- Class III : full registration dossier & technical review

Thus, manufacturers must submit a technical dossier that includes detailed technical information, clinical data, and quality documentation. Of note, China usually requires in-country testing for all Class II and III devices, although the Chinese NMPA may opt to accept the manufacturers' previous and existing testing reports. Testing requirements vary depending on the device type.

Additionally, foreign manufacturers are required to show proof of home country approval with a Certificate of Free Sale or Certificate to Foreign Government. Moreover, if they do not have an office in China, they should be aware that they need to appoint two in-country representatives, i.e., an agent and an after sales service provider.

Agent: manages registration and leads communications with the NMPA both before and after registration, and during vigilance reporting.

After Sales Service Provider: who is responsible for the device after NMPA approval; it is common that manufacturers appoint a distributor. The appointment of such a role, however, brings its own risks: since distributors tend to gain a disproportionate amount of power by keeping the original certificates, including the appendix - the PTRs. This can be fatal to the flexibility of the company. Alternatively, an independent service provider can act as an NMPA legal agent, which has the advantage that the foreign manufacturer protects its intellectual property and maintains its independence and flexibility [138, p. 21].

Since December 2019, the Chinese regulatory framework is also drawing increasing attention from global partners, due to its possible future paramount role in the collection of Real-World Evidence (RWE) and Real-World Data (RWD) for other policy related and other regulatory decision making. In November 2020 NMPA published draft technical guidelines for the use of RWD for the clinical evaluation of medical devices. In it, RWD are defined as follows: Hospital data, regional health data, health insurance data, personal health data, public surveillance data, self-reported patient data, and data generated by mobile devices. In addition, RWD may be generated during the production, distribution, transportation, storage, installation, use, maintenance, delisting, and disposal of medical devices.

It is expected that RWD will become increasingly important in China as the above data can be collected on Chinese patients. This is often a NMPA requirement for the approval of higher-risk class devices and may usefully support a subsequent clinical evaluation for NMPA registration in the Chinese market.

Currently, RWD can only be used as a supplement to CERs. Drafts suggest that in the future, large clinical trials may be avoidable with the help of RWDs [138, p. 22].

In contrast to the strict regulatory requirements in mainland China, in Hong Kong an approval for imported med-tech products is voluntary and, in any case, less burdensome, provided that the manufacturer already has certification from its home country. One reason is that the procurement system in Hong Kong is strongly influenced by the Hospital Authority, which gives priority to the Medical Device Administrative Control System (MDACS) approved products. In the future, mandatory registration is expected for Hong Kong, with existing certifications to be honoured.

Finally, a policy initiative is expected to allow foreign med-tech companies to market their products without prior NMPA registration as long as there is a local participation in the business activities [138, p. 22].

3.6.3 ISO Standards

When we think about internationally recognized protocols, the most important entity is the International Organisation for Standardisation (ISO)**.** ISO standards are a set of internationally recognized parameters and protocols, created to assist companies establish levels of homogeneity in relation to the management, provision of services, and product development in the industry. Different ISOs are related with biomaterials and biomaterials-related products. In this section we tried to summarise the most relevant ones, concerning analysis of biomaterial features once they are part of a medical device, according to Schuh & Funk (2019) [47]. They were also summarised by Schuh & Funk (2019) as can be seen in Figure 54. Annex, Figure 55. Annex, Figure 56. Annex.

ISO 10933 Biological and Clinical Evaluation of Medical Devices

Medical devices require varying degrees of biological safety testing, according to their classification and use. The main source of guidance on the essential requirements for biological safety is *ISO 10993 - Biological evaluation of medical devices.* This standard defines devices in terms of their category, type of contact, and the duration of patient contact. It subsequently serves as a framework to develop a biological evaluation plan for a medical device, with the aim of determining the relevant biological responses to the device. In this context, based on the medical device classification, it provides endpoints for the biological risk assessment.

ISO/TC 150 Implants for surgery

Standardisation in the field of implants for surgery - i.e., objects or devices which are surgically implanted in the body either temporarily or permanently for diagnostic or therapeutic purposes - and their required instrumentation, covering terminology, specifications, and methods of tests for all types of implants, and for the materials both basic and composite used in their manufacture and application.

ISO/TC 172/SC 7 Ophthalmic Optics and Instruments

Standardisation of terminology, requirements, interfaces, and test methods in the field of Ophthalmic Optics and Instruments.

ISO/TC 106 Dentistry

Standardisation in oral health care including terms and definitions; performance, safety, and specification requirements of dental products; and clinically relevant laboratory test methods.

4 Biomaterials data, repositories and databases

As it is described in the previous section, the field of biomaterials has seen rapid advances up to now. Implants and devices such as artificial joints, cochlear implants, and stents have been expanded over the years. Tissue engineering, a strongly related field, has equally been making progress, with increased sophistication in design and manufacture of scaffolds, as well as the use of cells and bioactive molecules within the materials.

Biomaterials-related product processes are rather similar between academia and industry and between different sectors [139]. As it can be seen in Figure 40 (regulatory overview), they start with the prototype development and preclinical evaluation, followed by the clinical evaluation, regulatory approval and commercialization of the product. All these processes lead to a large volume of data generated during a product's lifecycle, which appear in different data sources under different formats, like research publications, patent applications, clinical studies, regulatory information and product catalogues, among others. This section intends to describe and summarise the different sources of available information in the biomaterials field.

4.1 General resources

By general resources we mean the different tools where we can find all the biomaterials-related data but which are not specialised tools in this field (they also contain data from other not-related fields). This section will provide a summary of the following main four types of biomaterials data: journal repositories, clinical trial repositories, raw data collections, and patent databases.

4.1.1 Journal repositories

The most common and vast source of biomaterial information are publications in scientific journals. A summary of Q1 journals according to the SJR journal ranking can be seen in Table 21. Annex.

As a highly multidisciplinary science, biomaterials science may be also published in journals from diverse domains, such as materials science, engineering, medicine, or biology. For this reason, the most correct way to access a large number of articles containing biomaterials data is through search engines. The most commonly used and preferred for searching disciplines related to medicine is PubMed [109]. **PubMed** is a free search engine accessing primarily the MEDLINE database [140] of references and abstracts on life sciences and biomedical topics. It constitutes an open source which provides unlimited abstract retrieval and user-friendly software. Then, other search engines with more general fields (not only medical) are Scopus and Web of Science, which are paid-access platforms. **Scopus** [103] is Elsevier's abstract and citation database launched in 2004 and covers three types of sources: book series, journals, and trade journals. **Web of Science** [102] provides access to multiple databases that provide reference and citation data from academic journals, conference proceedings, and other documents in various academic disciplines. It is currently owned by Clarivate [102]. A summary of the dominating resources can be found in Table 8. The number of results was recorded by searching for the terms "biomaterial", "medical material" and "tissue engineering".

Table 8. List of journal repositories

	PubMed	Scopus	Web of Science
Records	773K	470K	107K
Metadata download	Up to 10,000 records	Up to 20,000 records	Up to 1000 records
Access	Open access	Require registration	Require registration
Sponsor	NIH	Elsevier	Clarivate

4.1.2 Clinical trial repositories

The final goal in the development of a biomaterial is to demonstrate both its efficiency for its specific purpose and its long-term security in the clinical situation. For that, clinical trials are a highly valuable source of information in medicine and more concretely for the biomaterials field. Clinical trial repositories allow access to detailed information about protocols and clinical reports. Some of them filtrate some common data, for example the study status, allocation type, phase, recruitment status, etc. Clinicaltrials.gov provides a first filtering by treated disease and country and a tabular view of the results. TrialSearch allows to filter by phase and specifications about rare diseases/orphan drugs and genome editing. All the clinical trial repositories registered and free of access and resumed in Table 9.

Table 9. List of free clinical trial repositories

Name	Description	Size	Open
EU Clinical Trials Register	The European Union (EU) Clinical Trials Register enables protocol and result exploration of interventional clinical trials conducted in the EU and the European Economic Area (EEA) and clinical trials conducted outside the EU / EEA linked to European paediatric-medicine development.	43K	Yes
ECRIN	The Clinical Research Metadata Repository, an online tool to help researchers explore data linked to clinical research study, and obtain information on the accessibility of those results. ECRIN made the Clinical Research Metadata Repository freely available to all scientific researchers and is updated regularly through global data collection.	>10K	Yes
Clinicaltrials.gov	ClinicalTrials.gov is a database of global, privately and publicly funded clinical studies.	424K	Yes
TrialSearch	The Clinical Trials Search Portal provides access to a central database and links to the full original records.	-	Yes
OpenTrials	Collaboration between Open Knowledge International and Dr Goldacre (University of Oxford DataLab), aiming to locate, match, and share all publicly accessible data/documents, on all trials conducted, on all medicines/ treatments, globally.	-	Yes

4.1.3 Raw data collections

Also known as primary data, raw data are simply the data as it is when collected from a source, like unprocessed images, or numerical data for each tested sample prior to pooling or statistical analysis. Examples could include numerical data from materials' characterization or mechanical testing techniques, or measured gene expression on a specific scaffold. The sharing of raw data remains sadly low in many scientific domains. Authors hesitate to share their raw experimental data for multiple reasons, ranging from intellectual property issues to technical reasons. Nevertheless, in areas such as protein biochemistry or genetics, raw data sharing in open repositories is now common practice. In the biomaterials domain, recent years saw publishers encouraging or even requiring authors to share the raw datasets supporting their manuscript. Thus, there are at least a few options for gathering raw biomaterials data for analysis from general raw data collections (Mendeley Data, Zenodo and Figshare). It is also possible to find biomaterials data, as mentioned before, about RNAseq that is most commonly shared (in GEO profiles). A summary of the search is found here:

- Mendeley Data (1,22M records, Dataset: 513K, Publications: 321K, Images 36K)
- Zenodo (350K records, Publications: 296K, Dataset: 21K, Images: 10K)
- Figshare (1,1M records, Publications: 280k, Dataset: 240k, Images: 214k)
- GEO profiles (RNAseq data, Dataset 100K)

4.1.4 Patent databases

An effective way to protect findings in science is to resort to patents. A huge amount of information about biomaterials can be found in these sources, and similarly to research articles they are archived in different services. Espacenet and U.S. Patent and Trademark Office (USPTO) are the European and American patent offices providing datasets. PATENTSCOPE, belonging to the World Intellectual Property Organization (WIPO), provides patent documents but does not allow batch download. Google Patents has a wider, more global coverage of patents from many regional and country offices. Lens serves patent records from over 95 different jurisdictions. Its patent search capabilities offer advanced Boolean functions, structured search, biological search, classification search, filtering and sorting options to find the most relevant and important patents. Finally, Scopus also includes information from patents. Patent sources are summarised in Table 10. The number of results was recorded by searching for the terms "biomaterial", "medical material" and "tissue engineering".

Table 10. List of open patent databases

	Google Patents	ESPACENET	PATENTSCOPE	LENS	USPTO	SCOPUS PATENTS
Records	128K	1,9M	114K	1,78M	30K	2,1M
Metadata download	ca. 25K records	ca. 500 records	ca. 10K records (with account)	ca. 1000 records	No	No
Sponsor	Google	EPO	WIPO	Cambia	USPTO	Elsevier
API	No	Yes	No	No	Yes	No

4.2 Ontologies

In practice, knowledge representation often takes the shape of one or several ontologies. An ontology is an explicit description of concepts in a specific domain, which enables common understanding of the structure of information and its re-use. Ontologies provide a common terminology that can be shared by researchers and are represented in a machine-readable language. They also provide logical structure for performing knowledge-based searches using informatics tools and software, speeding up retrieval and analysis of data and facilitate semantic sharing and integration of data stored in disparate resources by providing the logical relationships between different pieces of information [141].

The knowledge in an ontology is represented as a set of classes, concepts relevant to the domain, their properties, describing various features and attributes of the concept, and the relationships between the classes. By recognizing hierarchy, rules and relations between concepts, ontologies can set the ground for reasoning. The last decade saw a large increase in the number of publicly available ontologies, many of which are in the biomedical domain. The easiest way to find ontologies is by using a keyword search in one of the following ontology repositories:

1. **NCBO-Bioportal** is a web portal enabling search, download, review, and integration of disparate ontological resources in all aspects of biomedical investigation.
2. **Ontology Lookup Service** (OLS) is a repository for biomedical ontologies providing access to the latest ontology versions. The ontologies can be browsed through the website as well as programmatically via the OLS API.
3. **Ontobee** is developed by a group from the University of Michigan Medical School, being a web-based linked data server and browser specifically designed for ontology terms. Ontobee supports ontology visualisation, query and development.

Table 11 shows a list of ontologies where the term “biomaterial” or synonyms are registered, described and divided in subcategories. This list was the result of the keyword search conducted by the BIOMATDB consortium.

Table 11. List of relevant ontologies, described and divided in subcategories

Name	Description	Last update	Classes	Relevant categories	Notes
Devices, Experimental scaffolds and Biomaterials Ontology (DEB)	An ontology developed to facilitate information curation in the area of medical devices, experimental scaffolds and biomaterials. The ontology was designed to complement existing medical vocabularies, with emphasis on material processing, structures and features associated with biomaterials and experimental scaffolds.	2021	601	BIOMATERIAL: A non-drug raw material or substance suitable for inclusion in systems which augment or replace the function of bodily tissues or organs. Subcat: alginate, hydroxyapatite, gelatine, etc. BIOMATERIAL TYPE: Classification or nature of biomaterials. Subcat: Alloy, ceramic, composite, metal, etc. BIOLOGICALLY ACTIVE SUBSTANCE: Substance, often a peptide or protein included in a manufactured object in order to impart a biological	Subcategories by raw materials, biomaterial types are classified by Composition of materials, no hierarchy between the rest of classes (properties of the materials) Definition of biologically active substance could help to distinguish this with biomaterials.

				activity. Subcat: antibiotics, BMP, heparin, etc.	
Bone and Cartilage Tissue Engineering Ontology (BCTEO)	Ontology that describes the field of Tissue Engineering for what concerns bone and cartilage tissues	2014	253	BIOMATERIAL: A non-drug substance suitable for inclusion in systems which augment or replace the function of bodily tissues or organs. Subcat: Ceramic, composite, metal, polymer, etc. BIOMATERIAL BEHAVIOR: The set of behaviors that characterize a material on its chemical-physical nature. Subcat: Bioerosion, bioabsorption, etc. SCAFFOLD PROPERTIES: Property that is typical of a specific scaffold, depending not only on the material but even on the shape, the size, the structure etc. Subcat: Mechanical properties, morphological properties, etc.	Subcategories of biomaterials by composition, separate classes for properties and behaviour
NanoParticle Ontology (NPO)	An ontology that represents the basic knowledge of physical, chemical and functional characteristics of nanotechnology as used in cancer diagnosis and therapy.	2012	1904	CHEMICAL COMPOSITION A quality inhering in an object by virtue of the type, quantities or relative ratios of chemical components of the inhering entity. Subcat: mineral, metallic, etc. PROCESS A processual entity that is a maximally connected spatiotemporal whole and has *bona fide* beginnings and endings corresponding to real discontinuities Subcat: emulsification, functionalization, etc. CHARACTERIZATION An experiment performed to determine the distinctive characteristics (property/behaviour) or essential features of a material entity Subcat: physicochemical, biologically, etc. BIOLOGICAL PROCESS: Any process specifically pertinent to the functioning of integrated living units: cells, tissues, organs, and organisms. A process is a collection of molecular events with a defined beginning and end Subcat: anti-angiogenic, anti-proliferative, etc.	Biomaterial is not defined, no hierarchy between these classes

Medical Subject Headings (MeSH)	Medical Subject Headings, National Library of Medicine	2022	349K	MEDICAL OR DENTAL MATERIAL: Substances used in biomedicine or dentistry predominantly for their physical, as opposed to chemical, properties. Subcat: alloys, cements, dental materials, membranes, etc.	Subcategories of biomaterial mixed between composition and form
Computer Retrieval of Information on Scientific Projects Thesaurus (CRISP)	Computer Retrieval of Information on Scientific Projects	2022	9039	BIOMATERIAL: synthetic or industrial materials intended for use in contact with human tissues. Subcat. Biodegradable, dental material, oral facial restoration material, tissue support frame, etc. BIOMATERIAL COMPATIBILITY: compatibility and incompatibility of biomaterials depends on a number of factors, including elements of toxicology, immunology, surgical technique, implant design, motion, mechanics, porosity, material surface properties, and biorecognition. Subcat: interface interaction, antithrombotic surface, etc. BIOMATERIAL DEVELOPMENT: synthesis or manufacturing of synthetic or industrial materials intended for use in contact with human tissues. BIOMATERIAL EVALUATION: evaluation of synthetic or industrial materials intended for use in contact with human tissues.	Subcategories of biomaterial mostly by application, separate classes for compatibility, development and evaluation
National Cancer Institute Thesaurus (NCIT)	Reference terminology that includes broad coverage of the cancer domain, including cancer related diseases, findings and abnormalities.	2022	172K	BIOMEDICAL MATERIAL Any substance other than pharmacologic substance that can be applied in biomedical research or in constructing artificial organs, devices, or prostheses that can be introduced into the human body. Subcat: Ocrytale, mecrylate, etc. PROSTHESIS A device which is an artificial substitute for a missing body part or function; used for functional or	Subcategories of biomaterial by raw material, separate classes for prosthesis

				cosmetic reasons, or both. Sucat: Implants, stents, etc.	
Biological and Environmental Research Ontology (BERO)	Biological and Environmental Research Ontology (BERO) is an application ontology developed by the combination of many ontologies (base or subsets).	2022	450K	BIOMEDICAL MATERIAL Any substance other than pharmacologic substance that can be applied in biomedical research or in constructing artificial organs, devices, or prostheses that can be introduced into the human body. Subcat: Ocrytale, mecrylate, etc. PROSTHESIS A device which is an artificial substitute for a missing body part or function; used for functional or cosmetic reasons, or both. Sucat: Implants, stents, etc.	Subcategories of biomaterial by raw material, separate classes for prosthesis

From these ontologies, we reviewed in detail three of them, the Devices, Experimental scaffolds and Biomaterials Ontology (DEB), the Bone and Cartilage Tissue Engineering Ontology (BCTEO), and the Nano-Particle Ontology (NPO). They have been selected because they not only contain classes relevant to the domain, but they provide a specific view and understanding of information in the field. All these three ontologies are available to download from Bioportal:

- The **DEB Ontology** is centred on the knowledge representation of devices, implants, and experimental scaffolds. DEB was designed using a bottom-up approach, relying on the content of randomly selected ~1200 biomaterials' abstracts [142]. The result was an iterative process that captured the language used by scientists in the domain to describe the objects they have created, their function and effect. The DEB ontology assumed that the final application of a biomaterial is in the form of a "manufactured object" and goes on to designate a 'medical application' and "features" of the object, as well as two classes related to biocompatibility. More detailed information on the DEB Ontology can be found in section 7.1.1.
- The **BCTEO Ontology** attempts to tackle the heterogeneity of the data types generated as an output of bone and cartilage tissue engineering research. It appears to have been the first attempt to provide means for data integration and standardisation in the field of tissue engineering. At the core of BCTEO are five main classes: Biomaterial, Experiment, Organism, Tissue, and Cellular response, and these classes interact at various levels to model tissue engineering knowledge. The class 'Biomaterials', which has six subclasses: 'Ceramic', 'Composite', 'Gel', 'Metal', 'Polymer', and 'Other biomaterials'. Under these classes there are more specific classes ('Chitosan gel', 'Bioglass'). There are also a few classes of attributes linked to these materials ('Biomaterial behaviour', 'Intrinsic property' and 'Total porosity').
- The **NPO Ontology** was developed to represent knowledge underlying the preparation, chemical composition, and characterization of nanomaterials involved in cancer research [141]. Similarly, to BCTEO and DEB, the creators of the NPO are acutely aware of the lack of controlled vocabularies in the area of cancer nanotechnology and created NPO with the aim to enable scientists to share, annotate, communicate and leverage data for tasks such as inference.

4.3 Biomaterials databases

As previously mentioned, data on biomaterials can generally be found in the form of publications and patents in general sources such as journal repositories and patent databases. However, when using these sources, relevant data in the field of biomaterials must be selected manually, which leads to considerable effort and difficulty in finding relevant information. The use of specialised databases can help in this process of finding relevant information. In addition to reducing the amount of data, specialised databases offer advanced search systems that help in the search process, or visualisation tools that help to interpret the information. In the biomaterials field, there is still a rather small number of specialised databases, and only a few open access tools can be found:

- The major effort for extracting information about biomaterials is the **Database of Experimental Biomaterials and their Biological Effect (DEBBIE)**. This EU Horizon 2020 funded project had the goal to develop an open access database of biomaterials automatically curated from the scientific literature using text mining tools. More detailed information on DEBBIE can be found in the section 7.1.1.
- The **Compendium for Biomaterial Transcriptomics (cBiT)** is the first repository that offers biomaterial-based transcriptomics data together with all relevant biomaterial metadata. cBiT was an initiative of the de Boer lab when still at the Merln Institute in Maastricht, and now at the department of BME at TU/e. cBiT is continuing to expand as part of Platform for Therapeutic Biomaterial Discovery at TU/e. cBiT allows to browse, download, and analyse data. An impression of the layout of the cBiT repository can be seen in Figure 57. Annex.
- The **Biomaterials Properties Database** provides a list of tables provided as a service by the University of Michigan-NIDR Materials Science Research Centre at the University of Michigan School of Dentistry. The tables are updated periodically from "Dental Materials and Their Selection", 2nd ed., 1997 edited by W.J. O'Brien and published by Quintessence Publishing which holds the copyright. Dr. O'Brien has been given permission to publish these tables electronically. An impression of the Biomaterials Properties Database can be seen in Figure 58. Annex.
- The **3D Printing Database** public repository/database of articles involving 3D printing in the field of tissue engineering and regenerative medicine that is easily searchable by any user who wishes to enter this field. This database is free for use and is aimed at systematically collating the complex set of parameters that dictate material 3D printing. An impression of the 3D Printing Database can be seen in Figure 59. Annex.

In addition to the free-access biomaterials databases, ASM International (an association of materials-centric engineers and scientists) provides the **ASM Medical Materials Database.** This is a database of materials associated with medical devices that have FDA approval (510(k) and PMA) or Emergency Use Authorization, as well as those approved prior to 1996. In this regard the database provides comprehensive coverage of medical device materials and coatings, as well as associated drugs in the case of drug delivery vehicles, over a wide range of applications, such as cardiovascular, urologic, and orthopaedic. This is advertised as the world's largest collection of information and data on the composition, structure, properties, processing, performance, and evaluation of engineering materials for medical purposes. Access to the ASM Medical Materials Database is obtained via annual, single-user subscription. The database is powered by **GRANTA ANSYS MI**, which is an enterprise-level solution providing >250,000 reference materials, along with tools for: 1) searching, filtering, and

viewing data; 2) generating charts, reports, and comparisons; 3) exporting data to CAD/CAM design and FE simulation software.

For the case of a material, one can access the FDA approved Medical Devices that use the material. Additionally, the database provides a wide range of quantitative and qualitative properties, from mechanical properties to physicochemical and biological properties.

For the case of a Medical Device, one can access FDA regulatory information, including classification and approval summary, and description of the device, as well as biocompatibility information, including which ISO 10993 assessments were conducted. Importantly, the Medical Device pages provide cross-referencing to the materials used in the device, as well as the device Producer.

An additional tool provided by the ASM Medical Materials Database is the ability to compare materials over a selected set of properties and generate charts and tables. Finally, the database provides a potentially powerful tool in the form of searching for substitute materials based on a set of criteria, resulting in tables with comparisons and distance scores from the reference material. However, it is important to note that the database is limited to materials used in FDA approved devices, so novel research materials are not included in the "search for substitute" results.

Additionally, there is a database developed specifically for biomaterials that is no longer active. Biomat _dBase [143] is a biomaterials database created using a relational database management system (RDBMS). It provided the following information on biomaterials: how the structure is solved experimentally (X-Ray crystallography, NMR spectroscopy or fibre diffraction method); resolution of the structure; group of the protein or polysaccharide (e.g., hydrolyses, celluloses); assembly type (e.g., DNA or RNA bound, protein chain, number of residues); and references of the structure [143].

Table 12. List of the available databases specialised in biomaterials.

Name	URL	Description	Size	Open	Limitations
DEBBIE	Link	First database performing biomaterials named entity recognition, biomaterials text classification and database deposition of information about scaffolds and implants. Enables free-text /keyword search and filters by top associated terms; filters narrowed by selecting annotation categories. Allows for study type information and abstract exportation.	**344K studies extracted from PubMed**	**Yes**	Limited to abstracts from PubMed.
cBiT	Link	Compiled transcriptomic data linked with biomaterial-cell interaction. Information can be annotated by material, biological or technical properties.	**28 studies = 17 biomaterials + 11 tendons**	**Yes**	Small dimension Limited to a specific field
Biomaterials Properties Database	Link	Database of various biomaterials properties, such as density, hardness, elastic modulus, etc. organised in a table of 45 properties	**244 studies**	**Yes**	Small dimension
3D Printing Database	Link	Public database of articles on 3D printing for tissue engineering and regenerative medicine, collating the parameters dictating material 3D printing (only to extrusion-based	**807 studies**	**Yes**	Small dimension

		3D printing). Selection of raw material to view publications, printing conditions, and heat maps to visualise 3D printing parameter space. Allows metadata download.			Limited to a specific field
ASM Medical Materials Database	Link	A commercial database featuring both material properties and biological response data, addressing Surgical, Cardiovascular, Orthopaedic and Neurological medical device designers. Allows free trial.		**No**	Restricted access upon annual payment subscription.

Data about materials composing medical devices can also be found in the corresponding associated regulatory documents. The FDA possesses several databases that collect information about classification of medical devices, pre-market approval and post-market surveillance, some of them being specific for one class of medical device, which are summarised in Table 24.

4.4 Related material databases not specialised in medical biomaterials

Physicochemical properties of raw materials can be found in conventional materials databases Table 23. Annex. Overall, this type of database provides information based on the chemical formula of the material. Databases like AFLOWlib or Electronic Structure Project among others calculate physical properties from the electronic structure inorganic compounds. Novel Materials Discovery allows to perform atomistic simulations for modelling. Some of them (i.e., Materials Project, Springer Materials) have a list of labels regarding several material properties, like electronic structure, phonon dispersion, diffraction patterns, aqueous stability. Magnetic properties, etc. On the other hand, several databases also possess data from both inorganic and organic materials (i.e., COMAR, Knovel, etc.). MATWEB presented a dataset of thermoplastics and thermoset polymers, metals ceramics, and fibres and a tool to compare several material properties. Sciginder collects chemical information from journals, patents, conference proceedings, and technical reports.

Interestingly, all of these material databases exclude information about biopolymers. In this sense, we have to go to more specialised material databases to find this kind of data. We only found 3 databases about polymers, being one open access (Polymer Database) and two restricted (Polymer Library and Polymers: A Property Database). The Polymer Database provides thermophysical properties of polymers, some of them being biopolymers (i.e., cellulose derivatives). Polymer Library includes references from relevant journals together with conference papers, specifications, and standards, books, reports, press releases, company literature, data sheets, and directories. This is an extensive collection of physical property data for polymers and monomers by CRC Press. The electronic handbook may be searched by keyword, or by ranges of property values. All these databases miss information regarding biocompatibility, biosafety, biological properties, etc.

To have information about polypeptide materials, common protein databases can be employed, like the Protein Data Bank (https://www.rcsb.org/), the Structural Classification of Proteins (https://scop.mrc-lmb.cam.ac.uk/), and CATHDB (https://www.cathdb.info/).

Data about materials composing medical devices can also be found in the corresponding associated regulatory documents. The FDA possesses several databases that collect information about classification of medical devices, premarket approval and post-market surveillance, some of them being specific for one class of medical device, which are summarised in Table 24. Annex.

In the European context, the new rules on medical devices (Regulation (EU) 2017/745) and *in vitro* diagnostic medical devices (Regulation (EU) 2017/746) have established the creation of EUDAMED. EUDAMED will provide a living picture of the lifecycle of medical devices that are made available in the European Union. It will integrate different electronic systems to collate and process information about medical devices and related companies (e.g., manufacturers). EUDAMED aims to provide better access to information for the public and healthcare professionals. It will include information about actor registration, unique device identification and device registration, notified bodies and certificates, clinical investigations and performance studies, vigilance and market surveillance.

As it is described in section 3.6, each region (Europe, U.S., China) has their own regulatory organisms, which makes it difficult to compare data between them. The International Consortium of Investigative Journalists (ICIJ) International Medical Devices Database (IMDD) solves that in part. The IMDD contains information on more than 120,000 Recalls, Safety Alerts and Field Safety Notices about medical devices distributed worldwide. The information connects with medical device companies and their subsidiaries. The database allows users to explore events associated with the same product in different parts of the world. It covers not only implants, but a wide range of devices that have been recalled by manufacturers and reported to local authorities — everything from condoms and gloves to complex high-risk devices like pacemakers and defibrillators. This database also used FDA Device Classification Panels to identify broad categories of medical specialties, such as cardiology and orthopaedics, that would use specific devices. Products that were part of class I recalls in the U.S. and their respective categories were used to match them with the same medical device in other countries and include their classification. The matches were not done against class II and class III recalls, which means not all devices outside the U.S. have a Device Classification linked to them. The IMDD also includes links to primary sources for reference purposes and an interactive map that allows exploration by country. For impressions of the IMDD see Figure 60. Annex and Figure 61. Annex.

Interestingly, we have not been able to find any kind of specialised database in any part of the lifecycle of ATMPs, apart from the research articles registered by the DEBBIE database about biomaterials intended to be used as part of an ATMP.

5 Intelligent data processing approaches

When examining the design of Intelligent Data Processing platforms and technical approaches applied to the field of biomaterials, it must be considered that there is no single technical solution or platform that serves as a commonly used technical framework for building specifically biomaterials databases or structure knowledge bases.

A diversity of systems, components, processing modules/platforms have been developed over the past years that are clearly relevant for biomaterials data processing, many of them were originally more focused on biomedical, clinical, chemistry, general material sciences or pharmacological data processing scenarios. Some of them are also general domain text data processing solutions that can be applied or adapted to process biomaterials data.

Thus, generating an exhaustive compilation of all potentially relevant technical resources and solutions that might be somewhat relevant for processing biomaterials data is unfeasible. We therefore will focus on providing a selected compilation and general characterization of platforms, components, and modules of relevance specifically for building biomaterials related data processing components/pipelines or that can be in principle adapted or tuned towards biomaterials data processing and data annotation/extraction.

The objective is to have a general vision of the current state of Intelligent Data Processing systems/resources, in particular of Natural Language Processing (NLP) technologies that can be applied to process content related to biomaterials or other somewhat relevant research domains.

5.1 GATE, General Architecture for Text Engineering

GATE is a Java framework for developing NLP pipelines, developed by the University of Sheffield, UK, which started in 1995 and is used by a wide community today, including applied scientific research like biology, biomedicine, chemistry, and material-sciences. GATE includes a number of NLP components and wrappers that allow developers to integrate non-native components. In the DEBBIE resource, annotations were performed using the Biomaterials Annotator, an instrument combining several open lexical resources which builds on the General Architecture of Text Engineering (GATE) software.

The GATE architecture enables the integration of a variety of linguistic text processing techniques that classify documents and extract relevant information such as mentions of particular predefined concept types or relations. GATE enables the integration and allows the construction of systems for a specific task, using a series of modules, each carrying out a specific data processing step.

GATE is based on a centralised batch execution architecture with its own scalability solution (GateCloud). GATE distinguishes between different types of components:

- Language Resources: Resources such as dictionaries and ontologies, necessary for the NLP components.
- Processing Resources: NLP processors.
- Visual Resources: Graphical tools, such as annotation editors or viewers.

The first versions of GATE, developed in 1997, allowed defining processing chains (pipelines) by selecting the NLP components on a graph that showed the dependencies between modules, according to the annotations they consumed and generated.

GATE, together with Natural Language Toolkit (NLTK), was historically one of the preferred tools used in NLP courses, because it has a graphical interface that makes it very intuitive for users without programming knowledge and it has a much less steep learning curve than other intelligent data processing frameworks like Unstructured Information Management Architecture (UIMA). The system uses JAPE (Java Annotation Patterns Engine) for interoperability between components with different input/output requirements.

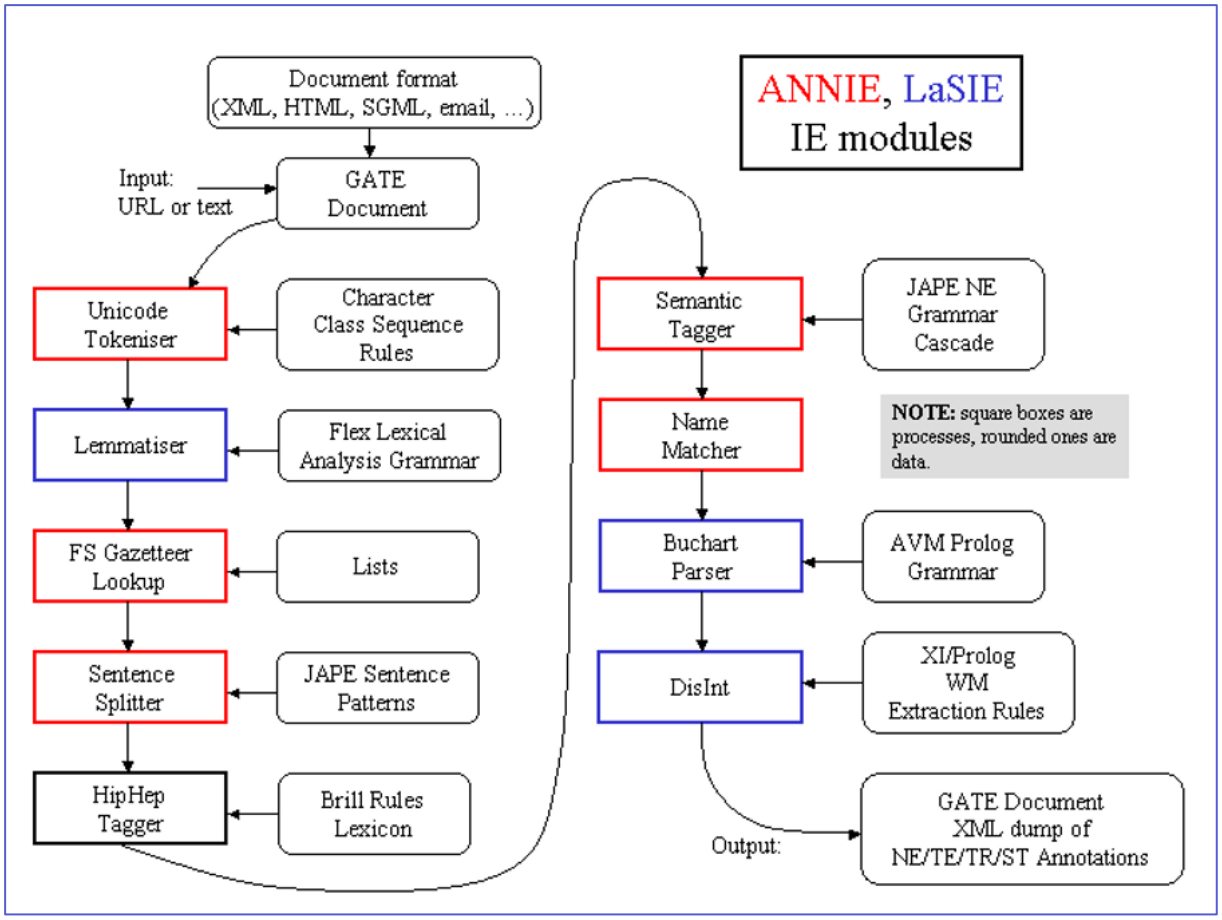


Figure 42. A typical processing chain using ANNIE and LaSIE components used in GATE

Some of these tools/components are no longer maintained and are out of date such as: ABNER, MiniChem/Drug Tagger, AbGene, Penn BioTagger, MutationFinder, Metamap.

The resources available for GATE that might be relevant for biomaterials data processing are explained below.

5.1.1 Native components (BADREX)

BADREX

BADREX is a GATE plugin that identifies abbreviation-definition pairs using dynamic regular expressions, extending the Schwartz & Hearts algorithm. It also uses a subset of the selection rules described in Ao & Takagi's ALICE algorithm. In addition to extracting terms and their abbreviations, it annotates them and adds their corresponding short and long forms as annotations. Abbreviation detection and resolution are relevant both for intelligent data processing of biomaterials content as

well as for improved search experience and user query disambiguation referring to biomaterials-relevant concepts.

There also exists the option to expand all the abbreviations in the text that match the most recently detected pairs or the option to annotate and classify common medical abbreviations pulled from Wikipedia.

5.1.2 Non-native components (GSpell, GENIA)

It is possible to adapt external processing resources and integrate them into GATE by creating a wrapper. A wrapper is a Processing Resource (PR) that is responsible for connecting an external resource with the GATE components allowing their communication and making them interoperable with each other. Rather than focus on providing support for a single external tagger, this plugin provides a generic wrapper that can be easily customised (no Java code required) to incorporate many different taggers within GATE.

The basic idea behind this plugin is to allow the use of many external taggers. Providing such a generic wrapper requires some assumptions. First, it is assumed that the external tagger will read from a file and that the content of this file will be one annotation per line (i.e., one token or sentence per line). Second, it is assumed that the tagger will write its response and that it will also be based on one annotation per line, although the input and output annotation types are not supposed to be the same.

Wrappers like the Tagger Framework are convenient for a startup phase, but are often not scalable. Thus, for each input the wrapper: (i) writes a file to disk with the input, (ii) launches a new annotation thread, (iii) writes the results back to disk, and (iv) finally retrieves the results for generating final logs and delete temporary files. Obviously, this system is not scalable and can hardly be implemented in a production environment.

GSpell

GSpell is a spelling suggestion tool developed by the Lexical Systems Group of the National Library of Medicine (NLM) to add suggestions to input and output annotations. The GSpell plugin has a lot of customization options when it comes to making suggestions. For example, you can ignore words and spelling suggestions smaller than a user-specified range, and use regular expressions to filter the words passed to the spelling analyser.

This component is of relevance in the context of biomaterials data annotation to improve mapping and normalisation of automatically detected biomaterials-relevant concepts to structured vocabularies, ontologies, metadata items. Moreover, it can also be used to enhance user experience for cases where no search hits are recovered to increase recall and enable more flexible query formulations.

GENIA

GENIA Tagger is an English tagger, specifically developed for biomedical text, including as well biomaterials research publications, that parses sentences and returns word forms, their parts of speech, word groups, and named entities. GENIA is included in GATE with all the features. GENIA requires downloading and installing the app externally, and then referencing it from within the app.

GENIA is the equivalent to ANNIE (a set of NLP modules integrated by default in GATE) for the biomedical domain.

5.2 UIMA, Apache Unstructured Information Management Architecture

UIMA (Unstructured Information Management Architecture) is a platform for NLP, originally developed by IBM and now maintained by the Apache Software Foundation. It has many similarities to the GATE architecture: it represents documents as text along with their annotations, and it allows users to define pipelines of parsing engines that look at the document in much the same way as the processing resources in GATE. The development kit supports creating analysis components in both Java and C++, and running them on both a local and remote machine. GATE and UIMA can be combined with each other.

Unlike GATE, UIMA uses strongly typed annotations (they assume fully domain dependent annotations). UIMA is based on having a common representation of the annotations (CAS, of the English Common Analysis System) with which the different components communicate.

UIMA distinguishes different types of components:

- CAS Initializer: Component to initialise the CAS.
- Collection Reader (CR): Component to read the documents of a collection.
- Analysis Engine (AE): NLP processor.
- CAS Consumer (CS): Component to serialise or present the results.

The UIMA architecture is one of the most important system-architectures in NLP, which has also been evolving since its inception and has been used for a variety of intelligent data processing application scenarios including content such as scientific publications and literature, patents, clinical documents, clinical trials, or web content. UIMA-AS allows executing UIMA processes asynchronously, thus offering greater scalability of NLP processes. UIMA-AS replaces the so-called Collection Processing Manager (CPM), which is now based on the Java Message Service (JMS) standard, an API MOM library (Message-Oriented Middleware, a queue management service using messages) for Java applications that implements the point-to-point and publish/subscribe implementation protocols (both models can be synchronous or asynchronous).

UIMA has been used in different domains, such as biology (bionlp-uima) or medical report processing (cTakes, clinical Text Analysis and Knowledge Extraction System).

New architectures have now appeared, such as Argo, based on UIMA, which work according to the NLP as a service model.

Resources included with or available to UIMA that focus exclusively on biomedical document processing are explained below. Some of these tools/components are no longer maintained and out of date, such as: ARGO, MedXN, Bluima.

5.2.1 Native components (cTAKES, JCoRe, MedKAT & CogStack, MedEX, AnatomyTagger)

cTAKES

cTAKES (Clinical Text and Knowledge Extraction System) is an NLP system for extracting information from electronic clinical texts. Originally developed by the Mayo Clinic, it has expanded to be used by several international institutions. cTAKES is developed by combining both UIMA and Apache OpenNLP. Some of the concept types as well as document types processed by cTAKES are also of relevance for biomaterials data processing, in particular under more clinical usage scenarios (implants and biomaterials, adverse events associated with a biomaterial's clinical use).

cTAKES makes a wide variety of components available to the user, each of them with unique qualities and capabilities. Each component includes at least one parsing engine (annotator), although some include more. Some of the most used are the following:

- Sentence Detection: A sentence detection model trained on manually annotated clinical data.
- Tokenization: rule-based tokenizer.
- Morphological Normalisation: A Lexical Variation Generation Tool from the National Library of Medicine
- Part-of-Party Labelling: A part-of-speech labelling model trained on manually annotated clinical data.
- Surface Analysis: A surface analysis model trained on manually annotated clinical data.
- Recognition of named entities:
- Mapping using dictionaries (lookup search algorithm).
- Semantic typing, based on these UMLS semantic types: diseases/disorders, signs/symptoms, anatomical sites, procedures, medications.
- Modifier detection module: negation detector, degree of certainty, and the subject experiencing the clinical event.
- Dependency Analyzer: Detects dependency relationships between words (machine learning with a model trained on manually annotated clinical data).
- Role Analyzer: A role analysis model trained on manually annotated clinical data.
- Semantic role tagger: assigns the predicate-argument structure of the sentence (who did what, to whom, when and where).
- Coreference resolution: Resolves coreference entities (machine learning with a model trained on manually annotated clinical data).
- Relationship Extractor: Discovers attributes such as the location and severity of a clinical condition (machine learning with a model trained on manually annotated clinical data).
- Drug Profiles Module: Discover specific drug attributes such as dose, duration, form, frequency, mode of administration, strength.
- Smoker Status Classification: Classifies the document/patient as ex-smoker, smoker, non-smoker, or unknown.

The components included in cTAKES can be used together, forming a pipeline, or independently. However, some of the components depend on other components; that is, the input of one component may require the output of a previous component. The cTAKES component dependencies are shown in Figure 43.

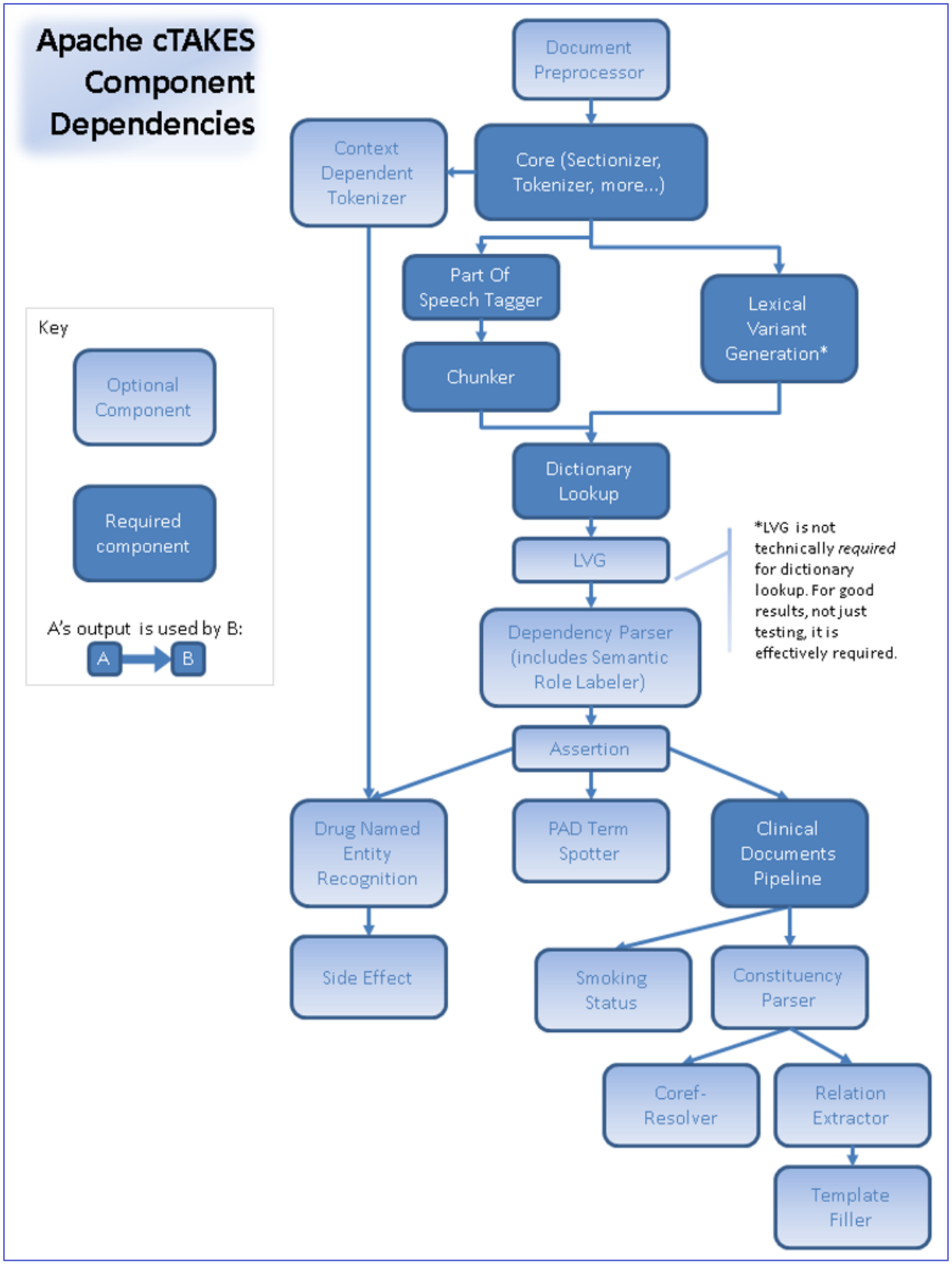


Figure 43. cTAKES Component Dependencies

JCoRe

JCoRe (JULIE Lab Component Repository) is an open repository for NLP based on UIMA. It offers a range of parsers developed in the JULIE group (University of Jena) for scientific texts written in English, both for abstracts and full articles in the domain of biology. Some of these components are also relevant to process biomaterials research content, in particular scientific publications and clinical trials.

The main components integrated in JCoRe are the following:

- Type systems: form a complete annotation type definition schema:
  - JULIE Type System.
    - Mantra XML Types.
- Collection Readers (CR): allow users to access annotation information from other projects and corpus):
  - ACE Reader.
  - BioNLP ST Reader.
  - DTA Reader.
  - FileReader.
  - IEXML/Mantra Reader.
  - MUC7 Reader.
  - XMLReader.
- Analysis Engines (AE): they constitute the main part of the NLP pipelines:
  - JULIE Sentence Segmenter (JSBD).
  - OpenNLP Sentence Segmenter.
  - JULIE Token Segmenter (JTBD).
  - OpenNLP Token Segmenter.
  - Acronym Resolution.
  - Gazetteer (Lingpipe).
  - Stanford Lemmatizer.
  - JULIE POS Tagger (JPOS).
  - OpenNLP POSTagger.
  - OpenNLP Chunker.
  - MST Dependency Parser.
  - OpenNLP Constituency Parser.
  - JULIE Named Entity Tagger (JNET).
  - JULIE Coordination Baseline.
  - Relationship Extractor.
- CAS Consumers (CS): export annotations to various formats:
  - BioNLP ST Consumer.
  - CAS2IOB Consumer.
  - IEXML/Mantra Consumer.
  - XMIWriter.
- Additional components: predefined pipelines for specific NLP tasks:
  - BioSEM Event Annotation (ST11 Model).
    - Named Entity Recognition (biomedical).
    - Part-of-Speech Tagger (Medical).

MedKAT and CogStack

Medical Knowledge Analysis Tool (MedKAT) is a tool for UIMA adapted to the pathological domain, prepared to extract information from a diversity of medical texts such as oncology. It makes use of patterns to detect negations and resolve coreferences. Some of the relationships to be extracted are based on the Cancer Disease Knowledge Model (CDKM) knowledge base. It offers a range of components types including:

- Document ingest: determine the structure of the document and extract the implicit meaning of that structure.
- Natural language processing: tokenization, sentence detection, part-of-speech tagging, and surface parsing.
- Concept Search: Search for concepts based on terminology (dictionaries) or specific patterns. Includes denial detection.
- Search for relationships: components that populate the CDKM and resolve co-references.
- Software tools for retrieval of medical information can also be found on the CogStack platform

MedEX

The MedEX system extracts drug information from electronic clinical records. It is integrated into UIMA and contains an information extraction module and a normalizer that assigns Concept Unique Identifier (CUI) codes from the Unified Medical Language System (UMLS) to the drugs found.

AnatomyTagger

AnatomyTagger is a tool for recognizing named medical entities that is very easy to use. The tagger has several lexical and corpus resources and is easy to train and apply. Includes support for UIMA.

5.2.2 Non-native components (MetaMap, LINNAEUS)

UIMA allows you to integrate external components through wrappers. To create a wrapper for UIMA, four main steps must be followed:

1. Create a type system: The type system has representations of the CAS feature structure. The type system specifies what type of data is available.
2. The parsing engine descriptor: The parsing engine descriptor defines the capabilities of the NLP service, especially with respect to input/output. It should be based on the type system from the previous step.
3. Generate Java classes: Having the necessary descriptor files, the UIMA JCasGen tool can be used to generate the required classes.
4. The annotator class: The annotator class guides the construction of an annotation object. It has to implement the functions of the initialization, processing, and destruction interfaces.

Some of the most relevant non-native components in biomedicine available in UIMA through wrappers are described below.

MetaMap

MetaMap is a highly configurable program developed by the National Library of Medicine (NLM) to map a biomedical text to the UMLS Metathesaurus or, equivalently, to discover the Metathesaurus concepts mentioned in the text. MetaMap is one of the foundations of NLM's Medical Text Indexer

(MTI), which is used for semi-automated and fully automatic indexing of NLM's biomedical literature. This logger encodes MetaMap named entities into a format interoperable with UIMA components. The annotator is available in UIMA through a wrapper (http://sourceforge.net/projects/metamap-uima/).

The main components integrated in MetaMap are the following:

- Lexical/syntactic analysis:
  - Tokenization.
  - Sentence detection.
  - Identification of acronyms/abbreviations.
  - Labelling of grammatical categories.
  - Syntactic analysis.
- Each sentence found by the pre-parsing is further parsed by the following processes:
  - Generation of variants: using variants of all the words in the sentence.
  - Identification of candidates: the extent to which the intermediate results or candidates coincide with the input text is evaluated.
  - Mapping - The candidates found in the previous step are combined and evaluated to produce a final result that best matches the input text.
  - Word Sense Disambiguation (WSD): Concepts that are semantically consistent with the surrounding text are prioritised.
- Licence: UMLS Metathesaurus.
- Basic processing components integrated or supported by the system:
  - Programming language: Java.
  - Languages supported by the tool: English.
  - Input formats supported by the tool: Text.
  - Output format supported by the system: Text.

LINNAEUS

LINNAEUS is a general-purpose dictionary search software capable of processing multiple types of document formats from the biomedical domain (MEDLINE, PMC, BMC, OTMI, text, etc.). It produces multiple types of output (XML, HTML, TSV, or export to a database). It also contains methods to act as a server (including managing load balancing across multiple simultaneous servers), allowing clients to request lookups over a network.

LINNAEUS can be run in two different ways: using an internal dictionary or using an external dictionary. The internal dictionaries (subsets of the external dictionaries, contain the 10,000 most frequently mentioned species in MEDLINE and represent approximately 99% of the mentions) are contained in the Java JAR file and do not require configuration. Due to the small size of the internal dictionaries, they require very little memory.

Additionally, we have also generated a collection of components, tools and systems covering a variety of Intelligent Data Processing strategies for biomedical content of relevance for biomaterials-related concepts and content analysis:

Table 13. Components, tools and systems for Intelligent Data Processing strategies

Name	Component/task	Domain	Format	Original URL (some are obsolete/not maintained)
Ab3P	Abbreviations	Biomedicine	Text	https://github.com/ncbi-nlp/Ab3P
Acromine	Abbreviations	Biomedicine	Text	http://www.nactem.ac.uk/software/acromine/
AcroTagger	Abbreviations	Biomedicine	Text	ftp://ftp.ebi.ac.uk/pub/software/textmining/abbreviation_resolution/
BADREX	Abbreviations	Biomedicine	Text	https://github.com/philgooch/BADREX-Biomedical-Abbreviation-Expander
BioText SH	Abbreviations	Biomedicine	Text	http://biotext.berkeley.edu/code/abbrev/ExtractAbbrev.java
ChemDataExtractor	NER	Drugs and chemical compounds/ substances	Text	http://chemdataextractor.org/
ChemicalTagger	NER	Drugs and chemical compounds/ substances	Text	http://chemicaltagger.ch.cam.ac.uk/
ChemSpot	NER	Drugs and chemical compounds/ substances	Text	https://www.informatik.hu-berlin.de/de/forschung/gebiete/wbi/resources/chemspot/chemspot
Chemxseer-Tagger	NER	Drugs and chemical compounds/ substances	Text	https://github.com/SeerLabs/chemxseer-tagger
Oscar4	NER	Drugs and chemical compounds/ substances	Text	https://github.com/BlueObelisk/oscar4
tmChem	NER	Drugs and chemical compounds/ substances	Pubtator	https://www.ncbi.nlm.nih.gov/research/bionlp/Tools/tmchem/
Neji	NER	Genes	Text/BioC/ XML/HTML	https://github.com/BMDSoftware/neji/wiki
SR4GN	NER	Genes	Pubtator	https://www.ncbi.nlm.nih.gov/research/bionlp/Tools/sr4gn/
Linnaeus	NER	Organisms/species	Text	http://linnaeus.sourceforge.net/
Micropie2	NER	Biomedicine	Text	https://github.com/biosemantics/micropie2/tree/0.1.0
OrganismTagger	NER	Biomedicine	Text	http://www.semanticsoftware.info/organism-tagger
SPECIES	NER	Biomedicine	Text	http://species.jensenlab.org/
GNormPlus	NER	Proteins/Genes	BioC/ Pubtator	https://www.ncbi.nlm.nih.gov/research/bionlp/Tools/gnormplus/
Annotator	NER	General	Text	http://bioportal.bioontology.org/annotator
BECAS	NER	General	Text	http://bioinformatics.ua.pt/becas/
Bluima	NER	General	Text	https://github.com/BlueBrain/bluima
Casper	NER	General	Text	http://biosemantics.org/index.php/software/casper
ChemdNER	NER	General	Text	https://bitbucket.org/tsendeemts/chemdner-demo

CliNER	NER	General	Text	http://text-machine.cs.uml.edu/cliner/
LeadMine	NER	General	Text	https://www.nextmovesoftware.com/leadmine.html
DTMiner	Search/ retrieval	Diseases	Text	http://gdr-web.rwebox.com/public_html/index.php
Ferret	Search/ retrieval	Genes	Text	https://mullai.cs.uiowa.edu/ferret3/genesearch/
ORGANISMS	Search/ retrieval	Organisms	Text	http://organisms.jensenlab.org/Search
Meshable	Search/ retrieval	General	Text	https://www.ncbi.nlm.nih.gov/CBBresearch/Wilbur/IRET/MESHABLE/
SeMedico	Search/ retrieval	General	Text	http://www.semedico.org/
BioMedICUS	General	Biomedicine	Text	https://github.com/nlpie/biomedicus3
cTakes	General	Biomedicine	Text	http://ctakes.apache.org/
DNorm	General	Biomedicine	Text	https://www.ncbi.nlm.nih.gov/research/bionlp/Tools/dnorm/
HITEx	General	Biomedicine	Text	https://www.i2b2.org/software/projects/hitex/hitex_manual.html
MedTagger	General	Biomedicine	Text	https://github.com/OHNLP/MedTagger
MedXN	General	Biomedicine	Text	https://github.com/OHNLP/MedXN
Meshy	General	Biomedicine	Text	https://github.com/infspiredBAT/MeSHy
Metamap	General	Biomedicine	Text	https://metamap.nlm.nih.gov/
Laitor	Other	Coreference	Text	https://sourceforge.net/projects/laitor/
MedTime	Other	Temporal expressions	Text	http://ohnlp.org/index.php/MedTime
Peregrine	Other	Multiword expressions	Text	http://biosemantics.org/index.php/software/peregrine
SimConcept	Other	Simplification	Pubtator	https://www.ncbi.nlm.nih.gov/research/bionlp/Tools/simconcept/
TaxonGrab	Other	Organisms/species	Text	https://sourceforge.net/projects/taxongrab/

5.3 Technological advances and deep-learning based intelligent data processing resources

There have been significant recent advances in the development, quality and use of intelligent data processing systems due to the improvements made by deep learning technologies and the exploitation of language models to process textual data for a variety of tasks, including document classification, retrieval, semantic annotation as well as question answering or even machine translation. These methodologies are being integrated also into technical solutions, which are clearly of relevance to process automatically biomaterials-related content with the aim of extraction biomaterials database annotation items. Most of these technologies make use of manually labelled or annotated data

collection which serve as example cases to train or learn automatically data processing models by means of machine learning technologies. Some of the more relevant recent AI-based content processing resources of relevance for processing biomaterials content will be briefly introduced.

5.3.1 SpaCy

spaCy is an open-source software library for advanced natural language processing, written in Python and Cython which is increasingly being used for production usage both in academic environments as well as by companies. It supports deep learning workflows that allow connecting models trained by machine learning libraries like TensorFlow or PyTorch. It also features neural network models for text classification and named entity recognition (NER) tasks, thus being clearly relevant for application scenarios such as classifying content for biomaterials relevance or detecting automatically predefined concept types or entities of relevance for biomaterials annotation extraction.

spaCy has also prebuilt neural network models for 23 languages, including English, Portuguese, Spanish, Russian and Chinese, as well as multi-language NER models. It allows users to train custom models on their own datasets as well, which is particularly relevant for developing new biomaterials-relevant entity detection components.

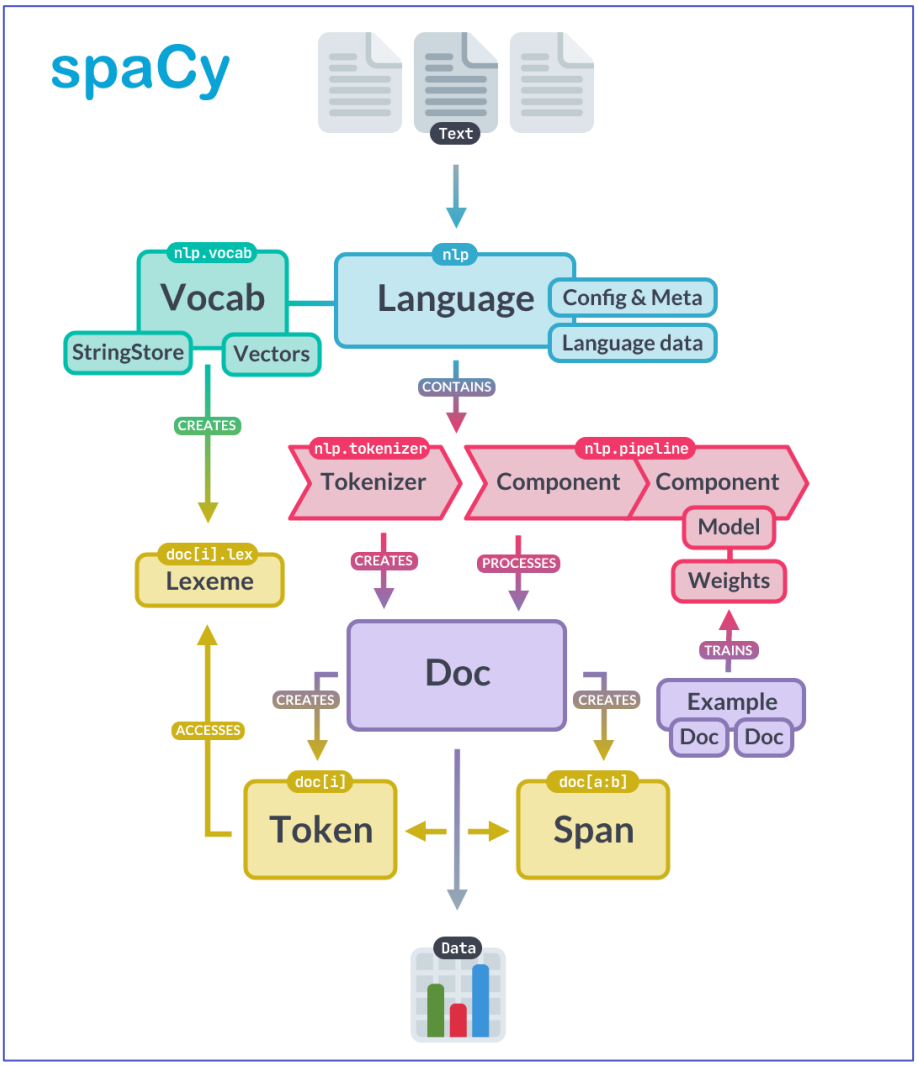


Figure 44. General overview of the spaCy resource architecture

5.3.2 ScispaCy

Due to the relevance of scientific content as an application domain of NLP technologies, and the importance of text mining and intelligent content processing for building data analytics and knowledgebase, several spaCy projects have been initiated specifically for processing scientific data. Among these projects, scispaCy has attracted particular attention.

It was created as a reliable, effective, and fast NLP package to meet the key text-processing requirements in the biomedical field, and is therefore also useful to automatically extract key information elements of relevance for biomaterials content processing. It provides several entity and biomedical concept extraction spaCy models relevant to biomedical literature mining.

Since ScispaCy was created to help research in the biomedical field, it has multiple pipelines that can be used to recognize ontologies like Gene Ontology, Human phenotype ontology, RxNorm, MESH, UMLS and more.

Apart from detecting ontologies and mapping vocabularies, machine learning models were trained as part of the library to be able to detect diseases, chemical components, proteins, cellular components, organs/tissues, and more.

5.3.3 BRAT

In order to carry out efficient text annotation tasks with the aim of generating training data for advanced text data analytics systems, text annotation tools are key. They allow not only to speed up the data annotation/data labelling process, but also facilitate annotation visualisation, editing, corrections, and consistency/quality comparisons. Brat is one of the most widely used tools for web-based text annotation allowing users to annotate (label) manually existing text documents as well as adding remarks/additional comment fields.

Brat is specifically made for generating machine-readable highly interoperable text annotations. In the example below, a sentence has been annotated to label and visualise mentions for certain biomaterial-related concepts.

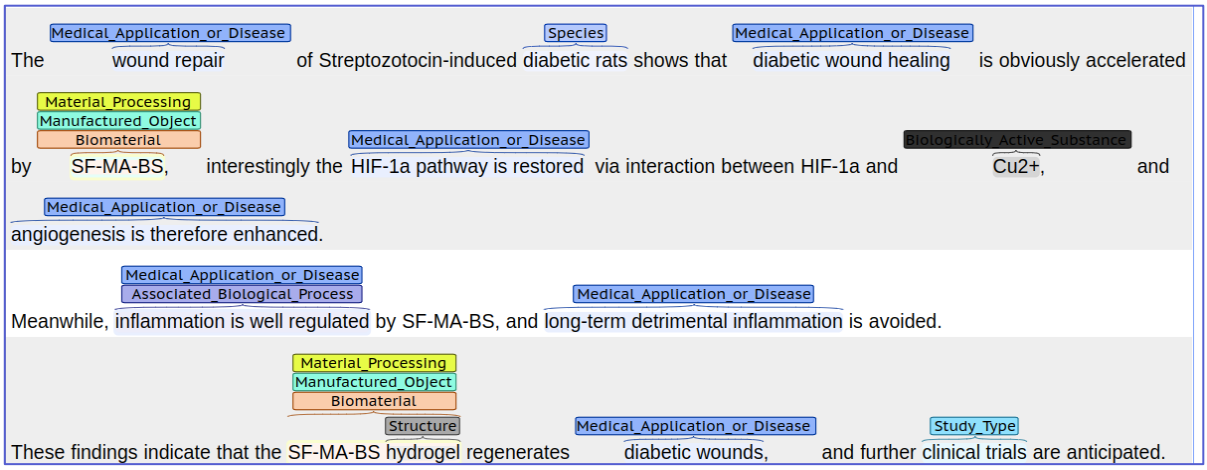


Figure 45. Annotated sentence

Brat creates a separate file for each text document file that was annotated. This separate file annotation metadata file has an ".ann" extension, and it is inside this file where all the manually annotated entities and relations between them are recorded. It can in principle be considered as a sort

of meta-date file that stores the information associated with the labels or annotations referring to the input document or text.

```
T32     Biologically_Active_Substance 688 690  BS
T33     Biologically_Active_Substance 708 829  bioceramics with a coupled network of interconnected [BO3] and [
T34     Biomaterial 708 829    bioceramics with a coupled network of interconnected [BO3] and [SiO4] which can
T35     Medical_Application_or_Disease 559 582        angiogenesis inhibition
T36     Medical_Application_or_Disease 587 611        inflammatory dysfunction
T37     Biomaterial 878 880    SF
T38     Biologically_Active_Substance 878 880  SF
T39     Structure 899 925      natural amino acid polymer
T28     Structure 1075 1083    hydrogel
T40     Biomaterial 1066 1083  SF-MA-BS hydrogel
T41     Material_Processing 1066 1083  SF-MA-BS hydrogel
T42     Material_Processing 0 36       In Situ Photo-Cross-Linking Hydrogel
T2      Medical_Application_or_Disease 358 394        inhibits the subsequent angiogenesis
T43     Medical_Application_or_Disease 415 475        function and phenotype transition of macrophage are impai
T44     Material_Processing 708 829    bioceramics with a coupled network of interconnected [BO3] and [SiO4] wh
T45     Biologically_Active_Substance 1107 1161       methacryloyloxy (MA) groups modified on both BS and SF
T47     Medical_Application_or_Disease 1231 1244      wound surface
T48     Tissue_Type 1231 1244  wound surface
T49     Material_Processing 1252 1316  in situ photo-cross-linked to form an integral SF-MA-BS hydrogel
T50     Structure 1299 1316    SF-MA-BS hydrogel
T51     Biomaterial 1252 1316  in situ photo-cross-linked to form an integral SF-MA-BS hydrogel
T52     Medical_Application_or_Disease 1345 1350      wound
T53     Medical_Application_or_Disease 1352 1398      protects the wound from external contamination
T54     Medical_Application_or_Disease 1435 1453      wound regeneration
T55     Biologically_Active_Substance 1468 1484       therapeutic ions
T56     Medical_Application_or_Disease 1490 1502      wound repair
T57     Medical_Application_or_Disease 1555 1577      diabetic wound healing
T58     Material_Processing 1606 1614  SF-MA-BS
```

Figure 46. Example annotation file in BRAT format.

5.3.4 Prodigy

Another commercial text annotation resource is Prodigy, a tool for efficiently creating labelled training sets and evaluation data for supervised machine learning models to process texts (classification and mention labelling). Prodigy can also be used to help scientists inspect and clean data, do error analysis, and develop rule-based systems to use in combination with statistical models.

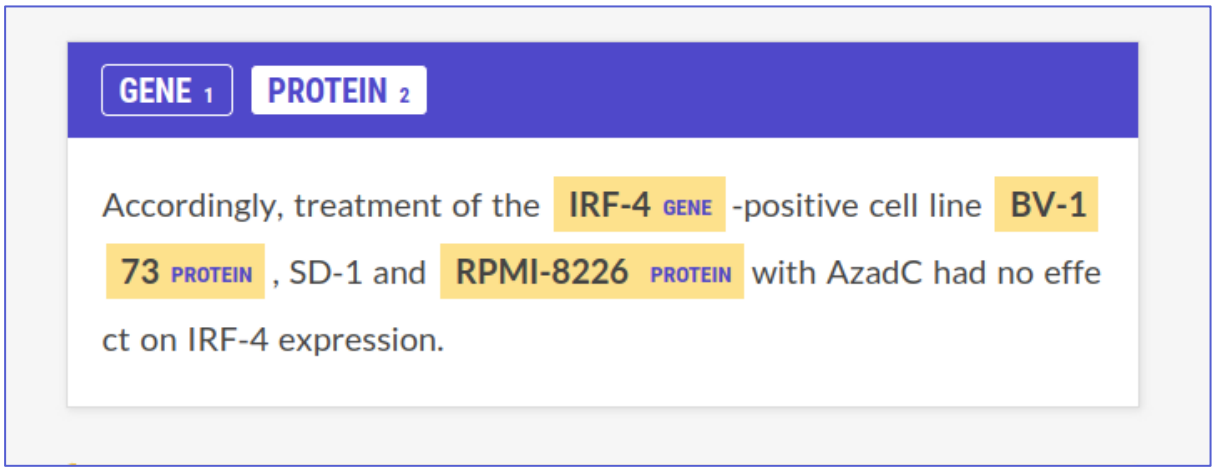


Figure 47. Example of annotating text on Prodigy

Since Prodigy is part of the spaCy ecosystem, it is easy to train a machine-learning model from the database created by Prodigy. This makes the training process straightforward.

6 Marketplaces

6.1 Biomaterials marketplaces

The BIOMATDB project aims to create an advanced database for biomaterials providing information on their properties and a marketplace to support companies offering their products and match the suppliers and the demanders. A desk search for raw biomaterial-specialised marketplaces provided only two results, the Biomaterial Store and BONEZONE (Table 14). The Biomaterial Store provides quality grafting materials, sutures, and instruments for dental professionals (Figure 62. Annex). The marketplace provides access to arrays of information sheets and brochures relating to some of their best products. To make a purchase from the store it is necessary to be a General Dental Council registered dental practitioner. BONEZONE is a network of orthopaedic-focused suppliers. Engineers, manufacturing executives, supply chain managers, and all those who seek to commercialise innovative, life-changing products can use the Supplier Directory to identify and validate quality partners. BONEZONE presents more than 200 companies, more than 100 capabilities and more than 17 countries involved. It connects with supplier companies, but it does not provide information about their products, though their product catalogues can be downloaded (Figure 63. Annex). Then, despite not being exclusively for biomaterials, Knowde provides a filtration by application field, limiting the filtration to biomaterials. To this aim, it is possible to select "Healthcare & Pharma" and then "Medical" where there are subclasses like "dental", "implants", and "adhesives" among others, with biomaterials being then showcased. It provides a complete tagging system to collate the products, like type of material, end use, features and suppliers, a clear capture of physicochemical properties, and protocols represented in tables and linking to datasheets. Interestingly, some of these materials are identified as biomedical grade, but the product dataset only provides information about physicochemical characteristics (as described in previous sections, biosafety is only evaluated once the biomaterial is incorporated in a medical device/ATMP). The main limitation of Knowde, apart from the number of included companies, is that the filtration of material is not able to completely exclude materials that are employed for medical applications but are not biomaterials (for example, materials that are used in external or not implanted prosthesis).

Table 14. Biomaterials marketplaces

Name	Description	Size	Open	Limitations
The Biomaterial Store	Grafting materials, sutures & instruments for dental professionals, set up to supply implant, surgical and perio practices.	-	Yes	Targeting dental practitioners. Limited to UK dental products
BONEZONE	Database of orthopaedic-focused suppliers, offering free test introduction + labels like market segments, capabilities, certifications and geographic region.	+200 companies	Yes	Supplier directory, not information about products. Restricted to orthopaedic field.

Knowde	Marketplace for ingredients, polymers and chemistry; allows for search, comparison, sample, quote and purchase products; global suppliers.	+8000 suppliers	Yes	Research limited to the registered companies. The filters are not able to distinguish biomaterials from medical materials

6.2 Related marketplaces

In the absence of specialised biomaterials marketplaces, this kind of products can be founded in general material marketplaces (Table 15). They usually offer different label systems like properties, certification, composition, among others, to filter the kind of products pursued and provide the connection with corresponding suppliers (i.e., Prospector, Total Materia, ChemSpider). They also provide physicochemical information of the material, so in this sense they are also databases.

Table 15. Biomaterials-related marketplaces

Name	URL	Description
Prospector	https://www.ulprospector.com	Search for materials from global suppliers by keyword, property, certification, and more; technical data analysis, sample request, and contact suppliers with free accounts. Filtering industry type, followed by label filtering: functionality, chemical class, company, etc.
Total Materia	https://www.totalmateria.com/	It allows search for mechanical and physical properties of diverse materials, cross-referenced to materials and suppliers. Two labels: Type (bulk/3D materials, adhesives, etc.) and group (metal, ceramic, polymer, etc.) Advanced search: chemical composition, mechanical properties, physical properties, etc.) Sort survey about interests for registration.
ChemSpider	https://www.chemspider.com/	Free chemical structure database providing fast text and structure search access to over 100 million structures from hundreds of data sources.
Material Properties Database	https://www.makeitfrom.com/	Curated database of engineering material properties emphasising on comparison-ease of internationally recognized materials. Data sourced from published standards, academic literature, supplier documentation. Classification in: metals, ceramics and polymers.
MATDAT	https://www.matdat.com/	Database of Materials Properties; DIRECTORY of Labs, Services & Suppliers. REPOSITORY of Materials Research Data: not available yet
Matmach	https://matmatch.com/	Allows optimization based on required performance; additional info on materials and applications; advanced search capabilities for constraints.

Materials Marketplace	https://go.materialsmarketplace.org/	Materials Marketplace connects businesses and organisations to develop and scale new, reuse, and recycling market opportunities. Subscription required
Materials Exchange	https://material-exchange.com/	Material Exchange mission is to help make transactions between suppliers and buyers more efficient, transparent and cost effective.
PlastEurope	https://www.plasteurope.com/	Material databases of product characteristics and supplier contact regarding plastics, elastomers, and polymer additives.
Evonik	https://www.plastics-database.com/main	Offers customized high-performance polymers for various industries.

In addition, for the case of natural materials, some of them can be found in biological science-related marketplaces (Table 16). **All of these marketplaces are providers of products for research purposes**. Interestingly, Bioz allows users to connect the product with research publications where they have been used and filter by technique employed.

Table 16. Some of the available bioscience marketplaces

Name	URL	Description	Open
Bioz	https://www.bioz.com	AI search engine empowering scientists in biopharma and academia to accelerate their research.	Yes
Science Exchange	https://ww2.scienceexchange.com/s/	A cloud-based software company offering an R&D marketplace to buy and sell scientific services. Fully automated R&D outsourcing from source to pay.	No
Scientist	https://scientist.com/	Artificial intelligence (AI)-powered network of public and private e-commerce marketplaces that connects buyers and suppliers of research services.	No
Zageno	https://zageno.com/	Addresses research scientists through comprehensive product portfolio, website navigation and customer analytics.; > 8 million products from over 2,000 suppliers.	No
Quartzy	https://www.quartzy.com/	Online lab management platform and scientific research supply marketplace, featuring collaborative order requests and supply tracking, inventory management tools and product quotes for comparisons.	No Free trial
BioHippo	https://www.ebiohippo.com/	Aims to provide transparency in the life science market and to simplify the search and comparison process.	Yes
Biocompare	https://www.biocompare.com/	Combines in-depth knowledge of life science products and new technologies, offering dynamic, media-based marketplace for life science information.	Yes

As it is explained in previous sections, medical devices that are implanted or in close contact with the body need to be composed of biocompatible materials. In this regard, medical device marketplaces could be interesting tools and sources of data in the biomaterial environment. There is a huge amount of medical device marketplaces online providing a selection of products or advising about suppliers (Table 17). What could be interesting for the biomaterials community is to get information about the biomaterials composing the medical devices, but this information is severely limited among the several marketplaces that were found. For example, MedicalExpo is able to take with more or less specificity (and not always) the main material component of the medical device. Information about material composing the medical device is sometimes also found in the description of the product or in the product dataset (when available). Biological testing information is not found in this database. Secondly, Qmed is a marketplace that collects suppliers (not products) and interestingly, presents a section with medical materials from qualified industry suppliers. Despite being a really useful tool to find suppliers of biomaterials, the information about the available products and the biomaterials properties is not well connected.

Table 17. Medical device marketplaces

Name	URL	Description
MedicalExpo	https://www.medicalexpo.com/	The business-to-business (B2B) marketplace for *medical* equipment, connecting buyers and sellers globally.
Oisto	https://oisto.com/	An online product marketplace that allows users to choose goods or services, create a purchase order, select a payment method and delivery.
Omnia Health	https://www.omnia-health.com/	A digital platform connecting the global healthcare marketplace**;** global directory of *medical* equipment, devices and companies, directly connecting the suppliers of *healthcare* products and services.
MediBid	https://www.medibid.com/	Offers self-paying patients options to find the best-fit to criteria medical practitioner; criteria can include price, location, time-to-treatment & professional credentials.
Chamfr	https://chamfr.com/	Accelerating medical device development; offers option to order components choosing from >1000 components across >15 suppliers; updating new medical device component options; offers 24 hour shipment.
Wound Reference	https://woundreference.com/	Self-funded startup building a decision support platform to facilitate cost-effective, patient-centric and evidence-based clinical and reimbursement decisions in HBO and wound care, aiming to empower clinicians.
ESutures	https://www.esutures.com/	Wholesale liquidator of surgical disposables & sutures from top brands such as Arthrex, Bard, Medtronic, Stryker, etc; users have access to brand name surgical supplies at discounted prices and quantity options.

QMed	https://directory.qmed.com/	Qmed is the world's only directory of pre-qualified suppliers to the medical device and in vitro diagnostics industry.
MedicaEx	https://medicaex.com/	Leverage on the B2B marketplace to generate leads and maximise brand awareness within the medical equipment and technology; global, open 24/7.

6.3 Decision Support Processes (Digital Advisors)

In order to help stakeholders to identify the biomaterials solution they are interested in, the biomaterials marketplace will adopt decision support processes, namely digital advisors, to accompany these organisations in the process. Intelligent digital advisors help the user to gather the desired information about products, services, technologies or any other entity they are looking for. In a first step, it presents the user with scenarios of situations in which the user might be. These situations are described and list the product categories that are related to these situations. The user is then able to choose the product category that is most relevant to their need and is then asked a set of questions by the digital advisors in order to funnel the search process. The digital advisors' questions are simple questions related to specific characteristics and attributes of the product category and can be answered by the user in a simple choice manner. Once the user navigates through the digital advisors' questionnaire, the system presents the user with the result of the products of the certain product category that match the requirements set by the user. The digital advisors are able to assist the user in the search for biomaterial products and services, especially when the user is not exactly aware of what he or she is looking for. Thus, it makes the process of searching for a solution much easier, resulting in a more friendly user experience in the biomaterials marketplace. Additionally, the digital advisor helps the user to better understand which types of products (product categories) may solve their needs in a specific situation.

As it can be seen in the table below, currently there are not many marketplaces that provide digital advisors or a functionality with a similar service. Three marketplaces were identified so far. Note that the third identified marketplace has the characteristics of an e-commerce platform that provides customers with their own marketplace setup, including a digital advisoring module. Thus, it can also be said that the biomaterials marketplace that is to be designed, developed and tested in BIOMATDB will focus on tackling this gap in the current marketplace ecosystem by providing a decision support process (digital advisors) that will assist the user to find the best solutions for them according to their needs.

Table 18. Marketplaces with digital advisors

Name	URL	Description
Medizinio	https://www.medizintechnikmarkt.de/	Medizinio GmbH facilitates the procurement of medical technology for physicians
Solved	https://www.solved.fi/	Marketplace for sustainability related products and knowledge
inventory	https://inventory.com/	e-commerce platform that facilitates the creation of marketplaces. It also includes a module for digital advisors that can be setup.

7 Existing technologies and project assets

Existing technologies and project assets represent resources in the form of experts, experiences gained, and technical components which the BIOMATDB project consortium can build upon. The resources can either be used to further develop already existing technical components, to exploit experience in developing and creating marketplaces and databases, e.g., for the creation of meaningful categories or the acquisition of exhibitors and users, or to draw on experts for validation and demonstration of the developed solutions.

Project or technology assets can either stem from previous projects of consortium partners (internal project and technology assets) or from projects similar to the BIOMATDB project or resources made available by the EU (external projects and technology assets). In the next chapter we will describe the projects and technologies that were identified as project assets by the consortium and we will describe how they might be of use for the BIOMATDB project.

7.1 Main project and technology assets

This chapter will introduce existing technologies and assets of previous consortium partner projects whose results and experiences gained the BIOMATDB Consortium can build upon for the development of the biomaterials database and the informational marketplace.

7.1.1 DEBBIE

The Database of Experimental Biomaterials and their Biological Effect (DEBBIE) is an open access database of biomaterials automatically curated from the scientific literature. DEBBIE was designed to facilitate a more efficient access to the large amount of literature in the field, generate a comprehensive map of research activity and findings, and enable evidence-based selection of materials for medical applications.

The DEBBIE system was built using two key resources developed by the team: the Devices, Experimental scaffolds and Biomaterials Ontology (DEB) and the Biomaterials Annotator.

Beyond the development of the database, the project was dedicated to the creation, adaptation, and optimization of text mining tools for the biomaterials domain. These tools (Figure 48), including the DEBBIE retrieval and annotation pipeline, are openly available for download and use through the project's GitHub repositories.

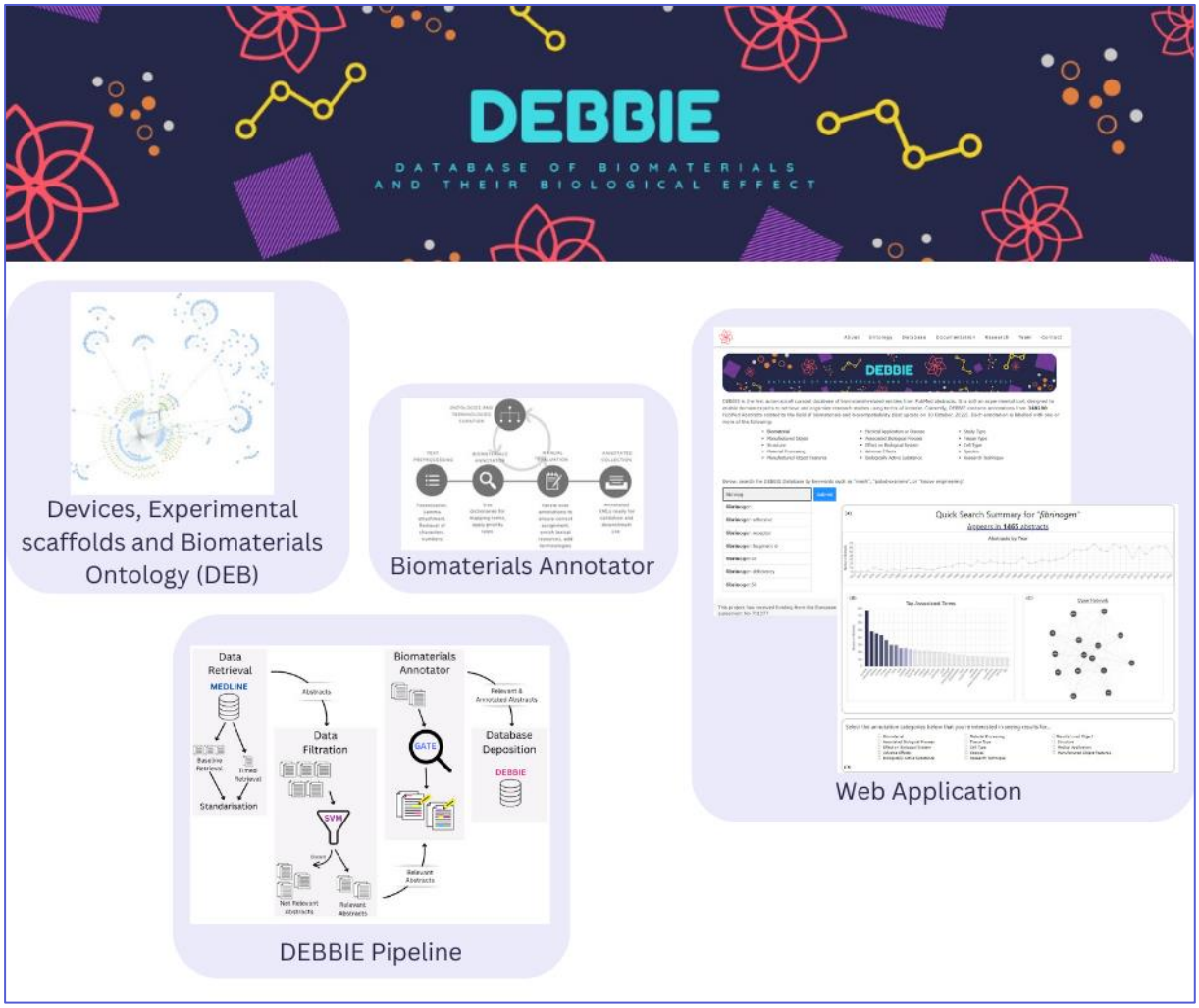


Figure 48. Overview of key assets developed as part of the DEBBIE project

Biomaterials Ontology (DEB)

The Devices, Experimental scaffolds and Biomaterials Ontology (DEB) is an open resource for organising and linking information about biomaterials, their design, manufacture and biological testing. It was developed using text analysis for identifying ontology terms from a biomaterials gold standard corpus, systematically curated to represent the domain's lexicon. DEB links biomaterial objects (e.g., scaffolds, stents) to concepts related to their design, manufacture, and biological testing.

A range of biomaterials-related concept types (Table 19) were created as classes and used to organise and provide further information related to a biomaterial. DEB has fifteen categories from various fields (e.g., biology, engineering, medicine, chemistry), highlighting the interdisciplinarity of the biomaterials field. Topics covered by DEB were validated by members of the biomaterials research community. The biomaterials-related concept types listed in alphabetical order in Table 19, were defined in the DEBBIE data model and recognised by the Biomaterials Annotator.

DEB may be used for searching terms, performing annotations for machine learning applications, standardised meta-data indexing, and other cross-disciplinary data exploitation.

Table 19. Biomaterials-related concept types defined in the DEBBIE data model

Category*	Definition
Adverse Effects*	An unfavourable or unintended disease, sign, or symptom (including an abnormal laboratory finding) that is temporally associated with the use of a medical device or biomaterial.
Associated Biological Process	A cellular or biological process that the manufactured object is designed to cause or support, or is measured to affect.
Biologically Active Substance	Substance, often a peptide or protein included in a manufactured object in order to impart a biological activity.
Biomaterial	A non-drug raw material or substance suitable for inclusion in systems which augment or replace the function of bodily tissues or organs.
Biomaterial Type	Classification or nature of biomaterials.
Cell Type*	The reported cell line or primary cell type.
Effect on Biological System	Biological effect associated with the manufactured object in a specific test system (cells, tissue or organism).
Manufactured Object	A physical object created by hand or machine.
Manufactured Object Component	A part, region or component referred to as a distinct unit, such as a surface or a layer.
Manufactured Object Features	Characteristics inherent or given during processing to a manufactured object or its component.
Material Processing	A planned process which results in physical changes in a specified input material.
Medical Application, Disease or Condition	Intended use, function or outcome of the manufactured object.
Research Technique	A laboratory or clinical technique used to evaluate a biomaterial (or implant/device) and their effect.
Species*	The species and/or breed used in the study.
Structure*	The configuration, form or texture associated with a manufactured object or its components.
Study Type	The set-up of the study (in vitro, in vivo, etc).
Tissue*	A tissue or an organ mentioned in the study as the target or test system for the biomaterial object or medical device.

***Categories nested as a subclass within another category.**

DEBBIE technical assets

Alongside DEB, additional assets were developed as part of the DEBBIE project. These include the DEBBIE Text Mining Pipeline, including the Biomaterials Annotator; and the web application.

The DEBBIE Text Mining Pipeline is a novel automated text mining pipeline [144] that facilitates the acquisition, filtration, concept recognition, and storage of annotated biomaterials publications using Natural Language Processing (NLP). The pipeline comprises four key steps and was developed to

detect, extract, and store relevant biomaterials information. It is open source and publicly available and can be downloaded. Figure 49 (based on Corvi, J. et al, submitted manuscript, 2023) shows a schematic illustration of the DEBBIE Text Mining Pipeline outlining these four key steps for annotating biomaterials-related concepts on scientific texts using the Biomaterials Annotator.

The pipeline currently indexes MEDLINE abstracts with fifteen relevant concepts related to the biomaterials domain using the Biomaterials Annotator. This pipeline is automatically executed once a month to be continuously updated, in an incremental manner.

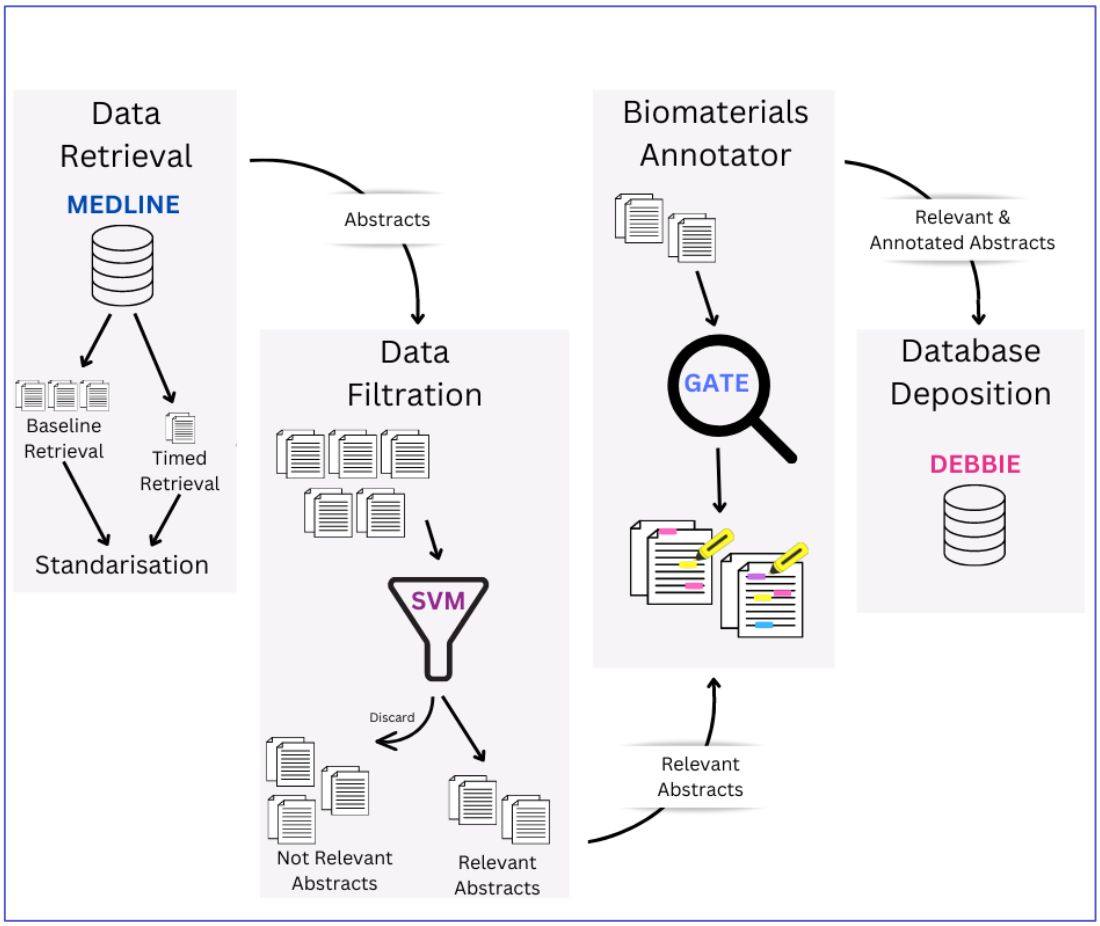


Figure 49. A schematic illustration of the DEBBIE Text Mining Pipeline

The Biomaterials Annotator [145] is a Named Entity Recognition (NER) tool specifically developed for the biomaterials field. It tackles the challenge of mining highly interdisciplinary scientific texts with fifteen relevant concepts (Table 19). This is done through the combination of multiple semantic resources that were selected, customised, and combined for recognising concepts in research abstracts (e.g., *in vitro, in vivo,* clinical studies) where experimental or commercially available materials were tested or used in a biological system or in physiological conditions. Lexical resources include DEB, the United Medical Language System (UMLS), Uber-anatomy ontology (UBERON), National Cancer Institute Thesaurus (NCIT) and the Chemical Entities of Biological Interest (ChEBI).

Figure 50 shows a screenshot of the homepage of the DEBBIE web application that displays a brief introduction to DEBBIE, the list of categories and their definition (these appear when hovering over a category), the date the system was last updated, the number of abstracts in DEBBIE at the time of access, as well as an auto-complete search box for keyword input (e.g., 'fibrinogen').

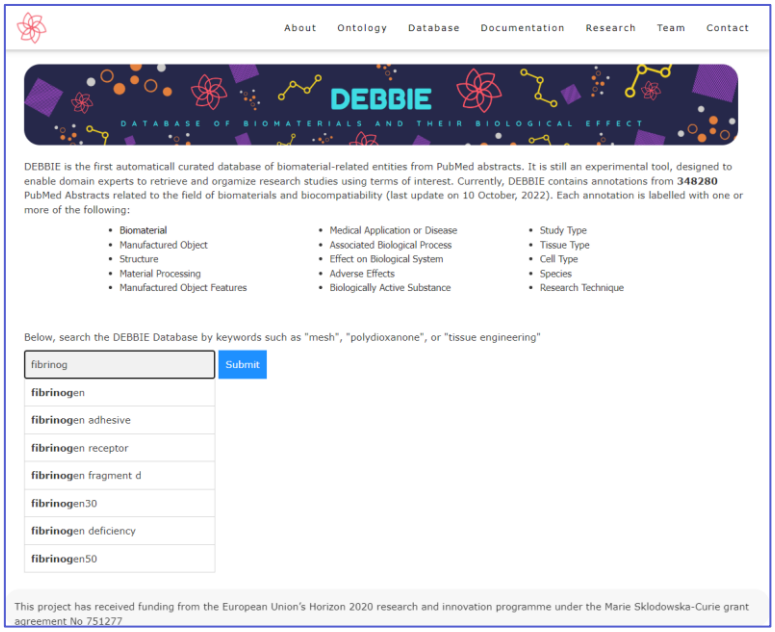


Figure 50. Screenshot of the DEBBIE web application (homepage)

Once the query is submitted, the user is redirected to the results page (Figure 51). Here, dashboards providing graphic depictions of the results are available and include a quick search summary with (A) the term's frequency over the years; (B) top associated terms; (C) a network graph, which can be expanded to a full-page view (Figure 52); and (D) a panel with different biomaterials-related categories. Figure 52 shows the full-page view of the network map produced by DEBBIE. The network map allows the user to customise edge length and node spacing, as well as the size of the network and position of each of the nodes. The full-page view can be accessed by clicking on the 'Open Network' panel title in the results page of the web application of DEBBIE.

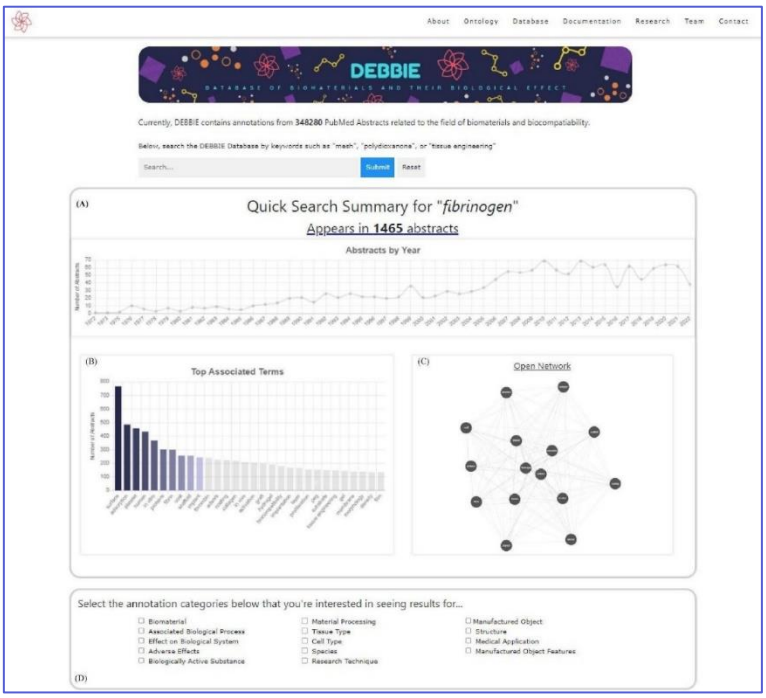


Figure 51. Screenshot from the DEBBIE web interface (results page)

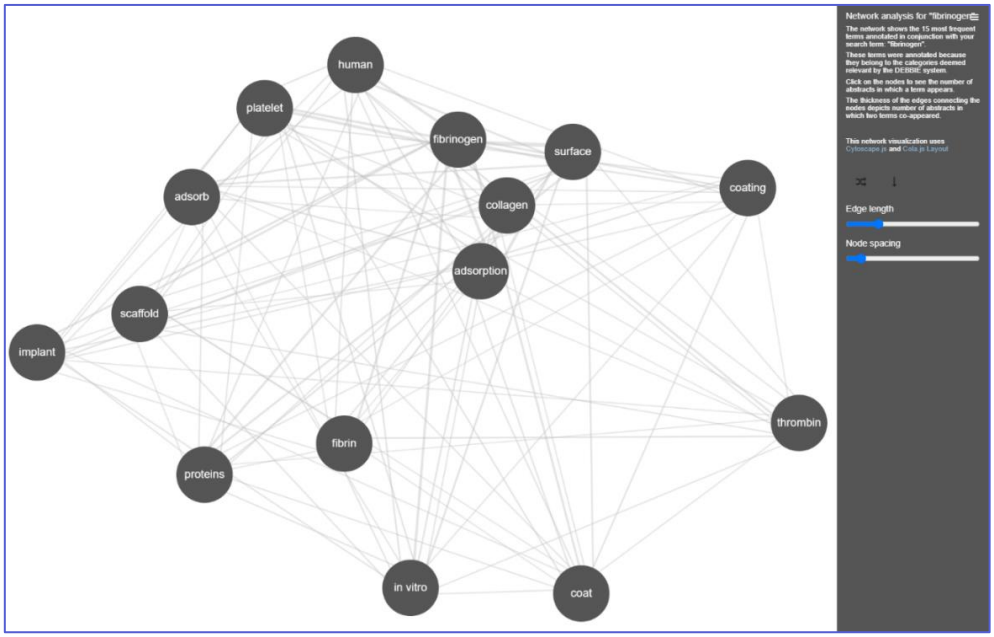


Figure 52. A full-page view of the network map produced by DEBBIE

An experimental version of DEBBIE is publicly available at https://debbie.bsc.es/search/. It contains abstracts automatically retrieved from PubMed, which were classified as 'relevant' to the areas of implants, medical devices, and experimental scaffolds. The abstracts are then annotated using a novel data model which includes multiple lexical resources. The annotations are finally stored in a NoSQL database, with each of the annotated concepts labelled by one or more of the categories outlined in Table 19.

7.1.2 eTOX (BSC)

Technical Framework and Re-Use of Components: Technically, components developed by the consortium partner (BSC, previously at CNIO) of the former eTOX project, an Innovative Medicines Initiative funded project related to the development of strategies and software tools to predict toxicology of molecular entities, will be re-used for the intelligent data processing and biomaterials database implementation of BIOMATDB. Computational infrastructures that will be adapted and serve as a technical base relate to database building and management resources, ontologies, and text mining techniques developed during the eTOX project for facilitating knowledge extraction from scientific literature, legacy preclinical reports, and public safety assessment reports (EU-EPAR and FDA-NDA). Specifically, content retrieval, preprocessing, text classification and data management resources (MongoDB) as well as data curation modules from the LimTox online database and semantic search application for chemically induced adverse effects [146] will be exploited and retrained/adapted to the BIOMATDB needs. Moreover, the labelled data collection, i.e., CHEMDNER corpus and components for chemical entity detection from text are specifically relevant for the extraction of biomaterials and their chemical composition in the context of the BIOMATDB database development. The transformer based chemical tagger (online demo at: (https://textmining.bsc.es/drugprot/chemical) will serve as a content pre-annotation tool for BIOMATDB. Figure 53 shows example results of the biomaterials chemical composition extraction by the chemical tagger system, to be further adapted to biomaterials content. The transformer-based chemical mention detection system was developed during the eTOX project and was applied to biomaterials related literature abstracts.

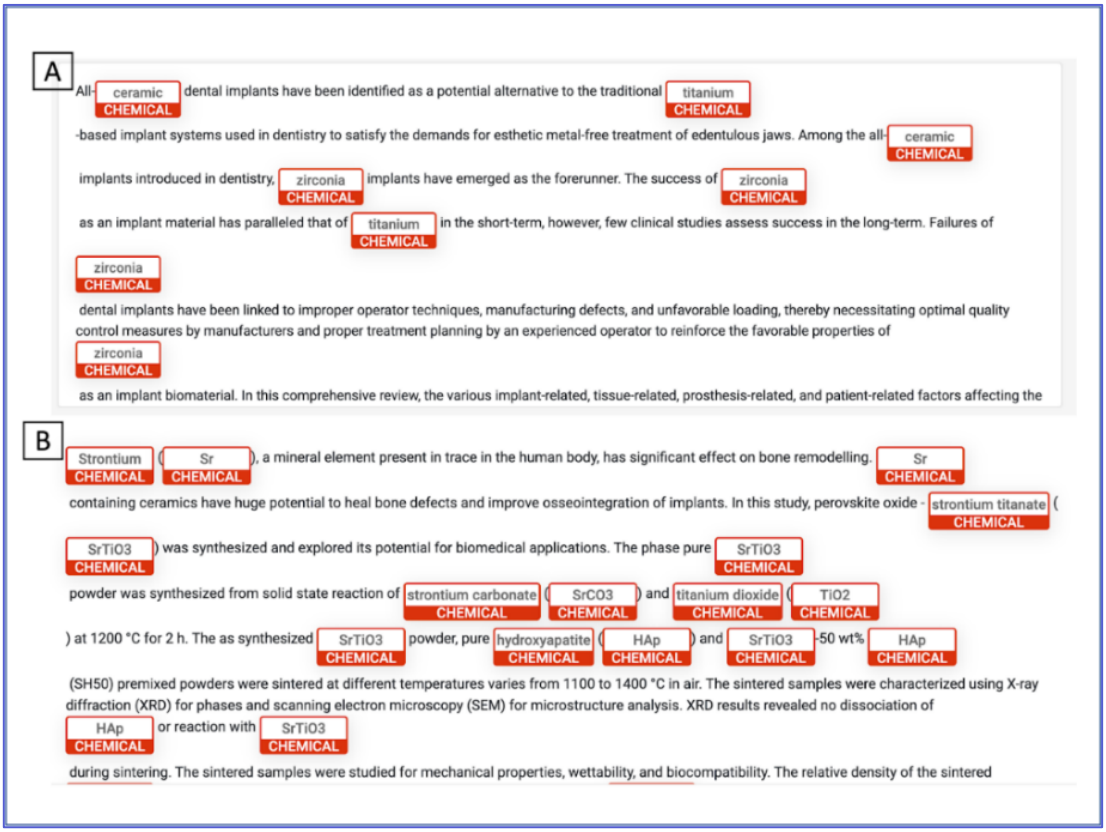


Figure 53. Example results of the transformer-based chemical mention detection system

7.1.3 OpenMinTed

Furthermore, BSC will explore the usefulness and adaptability to biomaterials content processing of several technical components created/wrapped for the OpenMinTed project to retrieve (OpenMinTeD content aggregator), harmonise and process text-based scientific and scholarly content. Moreover, the metadata - schema definitions originally developed for OpenMinted will be analysed as a base to serve for metadata definition of document content to be hosted by the BIOMATDB database.

7.1.4 SmartDataLake

BIOMATDB will use knowledge gathered and technical components developed by SYNYO in the SmartDataLake project to develop the biomaterials database and marketplace. The SmartDataLake project designed, developed, and evaluated approaches and techniques for extreme-scale analytics over Big Data Lakes, in order to facilitate the journey from raw data to actionable insights. These techniques have been tested and improved inside the project in an iterative manner with several feedback loops. The data analytics and data visualisation components developed by SYNYO can be integrated, further extended, and tested in the biomaterials database and biomaterials marketplace.

The data analysis and visualisation components will be the starting point for the data analysis tools that will be developed as the frontend of the biomaterials database. The knowledge gathered while designing and implementing the SmartDataLake components will assist SYNYO and the BIOMATDB consortium in identifying requirements and use cases when analysing the needs of the biomaterials database user and planning the processes of transforming extracted raw data to be presented in the data analysis tools (frontend).

The data analysis and visualisation framework developed by SYNYO in SmartDataLake is built upon industry leading technologies and frameworks that will be also used in the BIOMADB project. For example, ELK Stack (ElasticSearch, Logstash, Kibana) for data analysis, OpenLayers, D3.js, amCharts,js and anyChart for data visualisation, and Laravel, Bootstrap, and React JS for the development of the web based data analysis tools.

7.1.5 PHArA-ON – CATAALOG

To create the biomaterials marketplace, BIOMATDB will leverage the knowledge obtained as well as the technical elements created by MINDS & SPARKS in the PHArA-ON project. The PHArA-ON project addresses the problem of the highly fragmented and rapidly growing Healthy Ageing market, driven by recent technological advancements as well as digitalisation in the health sector. Therefore, the PHArA-ON project aims to support Europe's ageing population by providing integration of digital services, devices, and tools into open platforms.

Furthermore, the aim of the PHArA-ON project is to increase the exploitation prospects by involving key market and innovation actors and providing information about their existing or planned products and services in a curated way. In this way, it is possible to make a comprehensive assessment of best practices, ongoing activities as well as the EU's capabilities in the healthy ageing market. Such a holistic market overview creates new opportunities for innovation while ensuring that the solutions developed can be applied in practice and meet the market demand of the growing ageing population.

As part of this objective, Minds and Sparks has developed the CATAALOG solution. CATAALOG is a curated catalogue for Ambient Assisted Living (AAL) and smart health solutions and technologies. It provides an overview of existing and future smart solutions for active and healthy ageing. Stored in a powerful backend, CATAALOG contains a comprehensive collection of AAL products and solutions as well as relevant providers. For the development of the biomaterials marketplace, the core of the CATAALOG Marketplace can be reused and adapted according to the needs of BIOMATDB. This includes, for example, the modules Products, Services, Suppliers, Documents and Tenders, as well as various intelligent functionalities such as the Digital Advisors.

7.1.6 ActiveAdvice

The ActiveAdvice project aimed to deliver a fully functional ICT environment with specific web and mobile services for older adults and their relatives, for professionals in inclusive design and construction engineering across Europe, as well as for governments and municipalities involved in AAL. The ICT environment offers a ***holistic market overview***, presenting regional, national, and international AAL products and services in accordance with the needs of the end users, and combines it with a strong and integrated focus on the target market.

ActiveAdvice sought to create a novel ICT environment compromised from ***digital and human advisors***, enhancing the information exchange and expert dialogue, as well as the technology and service uptake in the field of AAL. Through the creation of three service models tailored to the specific needs of the identified target groups, combined with the creation of an international network of Authorised Active Advisors from various business sectors related to AAL, an increased rate of awareness for and implementation of AAL solutions was reached across Europe.

In the context of the biomaterials marketplace's development the following project's assets will be replicated in an adapted form and according to the requirements of the biomaterials marketplace end users:

Personas as a central concept representing the target groups of the project

Based on the gained experience in ActiveAdvice, the BIOMATDB project consortium might seek to visualise the different requirements and optimise developments by creating personas representing the needs of the target groups. In order to visualise the predispositions and needs of each of the target groups, an initial collection of the main stakeholder groups representing the potential end users of the biomaterials marketplace has been already initiated.

Digital Advisory

Aimed at the target groups of BIOMATDB, digital advisors will be designed and developed to provide knowledge that enables informed decision-making. In order to address the different needs for consultation, the digital advisors might be divided into different groups, each with a different focus. A problem-centred search function will provide guidance for specific areas of application of biomaterials. A product advisor informs all target groups about biomaterials based medical instruments, products and services, based on product attributes and specifics for each product category presented in the product search.

7.1.7 OpenDataMonitor

In addition, the consortium can build on the technical components for data analysis and data visualisation that SYNYO developed in the course of the FP7 project OpenDataMonitor. The OpenDataMonitor project created a platform that provides users with an overview of existing open data resources and at the same time visually displays the metadata of these data. For this purpose, the metadata is first processed, structured, and harmonised and then visualised using scalable analytics and visualisation methods.

While these data analysis and data visualisation techniques were used in the OpenDataMonitor project to support users in identifying different potentials or gaps in regional, national, or pan-European open data repositories, similar techniques can be used by BIOMATDB to analyse and visualise biomaterials data.

7.1.8 SmartCareBase

The SmartCareBase project established a platform to connect suppliers of AAL solutions with end users. For that purpose, the platform provides information about Smart Care solutions, an overview of suppliers, individual expert support for competence transfer, news feeds, discussion features, and opportunities for knowledge exchange in the area of smart care solutions. A core feature that supports the matching of end users with suppliers is the database consisting of supplier profiles and their offered solutions. Users can navigate this database using search features and sorting options based on criteria such as the location. With the main target group of the SmartCareBase project being older adults looking for knowledge on home optimization to their age, specific focus was placed on making the platform easy to use for end users.

Therefore, the technical components and the experiences gained from the SmartCareBase project can be exploited to create a user-friendly and easily searchable biomaterials marketplace for the

BIOMATDB project that, similar to the SmartCareBase project, aims at providing a platform where demanders of biomaterials find information about biomaterials suppliers and products.

7.1.9 iProcureSecurity

Against the need for strengthening the resilience of European societies in the light of multiple man-made and natural hazards the iProcureSecurity project sought to identify the major issues the diversity of the emergency medical ecosystem in Europe poses to the capability of working together. As a part of its activities, the project consortium created the open www.iprocuresecurity.com web platform, which is based on multifunctional modules and channels including several information and collaboration services. The project platform includes materials in multiple European languages as well as additional tools such as input forms.

In the context of the biomaterials marketplace's development, the BIOMATDB project will consider the implementation of the abovementioned input forms. As such they will allow end users to contribute to the extension of the marketplace knowledge database. The implementation of the input forms will also allow the consortium to control the quality of the data being collected. New data will be then checked by a person, having the responsibility of supervising and approving the new content. The person will be notified that a new entry requires their attention and the task can be completed, online, from any location.

7.1.10 PlatformUptake.eu

The PlatformUptake.eu project delivered an inventory of platforms in the Active and Healthy Ageing (AHA) and Ambient Assisted Living (AAL) domains and assessed the use of such platforms, covering both open - such as UniversAAL - and partly-open/proprietary platforms developed by the industry.

Under the lead of SYNYO, the PlatformUptake.eu consortium created the PlatformUptake.eu Open Information Hub. The Hub aggregated all relevant project findings, including video recordings of eight webinars and matchmaking events, uptake materials such as video tutorials and interactive presentations, and a MOOC (Massive Open Online Course) to explain to potential end users how to identify, select and implement open platforms services into their organisations process and structures.

The BIOMATDB consortium would consider capitalizing on the abovementioned experience to create intuitive training manuals and compact online video tutorials and support the use of the database, marketplace and biocompatibility label.

7.2 Additional project and technology assets

To our knowledge, currently there are a few similar European and EU-funded projects, which also aim to develop advanced web tools to curate data in related fields. The development of the BIOMATDB could benefit immensely from the early identification of these projects, turning the seemingly overlapping liability into an asset that will further enable dissemination and success of the project. We enlist below such relevant projects, some enablers of which we have already contacted or aim to reach out to, in the near future, and the BIOMATDB consortium is involved in network building activities. The aim here is not only to exploit the networking opportunities and relevant outcomes for our own timely success. We aim to facilitate cross-linking and functional intersections among platforms when possible, and as instructed by the founding FAIR principles, we will advance the EU biomaterials landscape to the benefit of EU digitalisation. This effort goes beyond the state of the art of the BIOMATDB proposal,

as described in the proposal and further addresses transparency in research, R&D, healthcare and health services and market sustainability challenges.

In brief, the main asset platforms and projects BIOMATDB intersects with are:

7.2.1 EUDAMED

The creation of the European database on medical devices (**EUDAMED**) is one of the key aspects of the new rules on medical devices (Regulation (EU) 2017/745) and *in vitro* diagnostic medical devices (Regulation (EU) 2017/746), to ensure transparency and traceability regarding medical devices and to improve health and safety. EUDAMED represents a live map of medical devices made available in the EU. Integrating different electronic systems to collate and process information about medical devices and related companies (e.g., manufacturers), EUDAMED aims to enhance overall transparency. This will facilitate easy and better access to information for the public and healthcare professionals and will enable and enhance coordination between the different EU Member States. To address all the above EUDAMED is designed to be composed of six modules. These are related to actor registration, unique device identification (UDI) and device registration, notified bodies and certificates, clinical investigations and performance studies, and finally vigilance and market surveillance [147].

BIOMATDB will seek to capitalise on the available Product Information System (PIM) and related medical device metadata, which represent a comprehensive overview of approved medical devices according to the MDR from across Europe and beyond. The project consortium plans to use all available information in order to support the growth of both technical solutions, the biomaterials database, and biomaterials market, in terms of reliable information on biomaterials suppliers and medical devices vendors, decision makers such as certification and standardisation bodies and agencies. Moreover, all collected contacts will be used in a later phase of the project's activities to raise awareness on the developed solutions and ensure the validation of their market relevance and future application.

7.2.2 OntoCommons

The standardisation of data documentation across all domains related to materials and manufacturing will be addressed by the H2020 CSA project **OntoCommons**. OntoCommons aims to set the foundation for interoperable, harmonised, and standardised data documentation through ontologies. The main outcome of this project is to facilitate data sharing and pushing data-driven innovation, to enable a truly Digital Single Market for the new business models for European industry.

Based on the current achievements and gained knowledge by OntoCommons, BIOMATDB will seek to explore the project's established ontologies in the field of nanotechnologies with relevance to the production of biomaterials. Any other available concepts or methods of categorization concerning relevant biomaterials fields of application will be further considered as additional input into the BIOMATDB biomaterials database. Beyond that, BIOMATDB will seek to facilitate knowledge exchange with the OntoCommons consortium and explore possible networking opportunities to support the planned dissemination, communication, and exploitation actions [148].

7.2.3 eNanoMapper

The toxicological data management of engineered nanomaterials (ENMs) will be supported by **eNanoMapper** (ENM). This project proposes to address the challenge with a computational infrastructure based on open standards, ontologies, and an interoperable design. This will enable an

effective and integrated approach to European research in nanotechnology. eNanoMapper will further support the collaborative safety assessment for ENMs by creating a modular, extensible infrastructure for transparent data sharing, data analysis, and the creation of computational toxicology models for ENMs. That consortium thus aims to develop the resources, tools, and standards for a scientifically sound risk assessment of ENMs. This will support both the design of new safe and environment-friendly ENMs, but also the assessment of existing materials.

BIOMATDB will aim to explore the established computational toxicology models and modelling tools aimed for integration of nanosafety data from various sources and identify approaches, which can be eventually used and extended within the framework of the BIOMATDB biomaterials database. Another point of interest and possible exploration represents the data management and ontology platform, which is developed to capture data and knowledge along the full lifecycle of ENMs. Any extraction methods, which can be applied in the case of the biomaterials database will be considered. Last but not least, BIOMATDB plans to identify potential collaboration opportunities within the established network of eNanoMapper with industry organisations, regulators, and end users in order to boost the project's engagement activities [149].

7.2.4 BIORIMA

The Biomaterial Risk Management (**BIORIMA)** aims to develop an integrated risk management (IRM) framework for nano-biomaterials (NBM) used in Advanced Therapeutic Medicinal Products (ATMP) and Medical Devices (MD). The IRM framework will consist of: risk management strategies and systems, validated methodologies and tools to identify the potential Exposure and Hazard posed by NBM to humans and the environment and a strategy for Intelligent Testing (ITS) and Tiered Risk Assessment for NBM used in ATMP and MD. The BIORIMA framework toolbox will consist of validated methods/tools for materials synthesis and a reference materials bank, and others. Among the outcomes of BIORIMA is to deliver a web-based Decision Support System to help users, especially SMEs, evaluate the risk/benefit profile of their NBM products. This will also be critical for NBM products in the context of shortening the time to market [150].

BIOMATDB plans to analyse the established BIORIMA IRM and related tools and methods for assessing hazards and risk identification specific to nano-biomaterials and their application in medical products. Focus will be put on any relevant materials such toxicology testing protocols, papers and other scientific materials that can be used to support the growth and acceptance of the BIOMATDB biomaterials database among its potential end users. Another subject of potential exploration will be the created web-based Decision Support System and its services aimed towards SMEs and other industry organisations for shortening the time to market for NBM products. Last, collaboration with relevant stakeholders from the consortium of BIORIMA will be sought, whereas paths for exploitation of the BIOMATDB technical solutions will be identified.

7.2.5 Open Innovation Test Beds

Still in the context of shortening the time to market, and even more importantly advancing the process of validation in a laboratory to prototypes in industrial environments, the need for **Open Innovation Test Beds** was identified. Furthermore, another objective of the Open Innovation Test Beds is to bring nanotechnologies and advanced materials within the reach of companies and users. According to the EU Commission, Open Innovation Test Beds are entities, established in at least three Member States

or Associated Countries, offering access to physical facilities, capabilities and services required for the development, testing and upscaling of nanotechnology and advanced materials in industrial environments.

7.2.6 MDOT

As the new Medical Device Regulation (MDR) requires costly testing that may threaten the competitiveness of Europe's innovation SMEs, the **Medical Device Obligations Taskforce (MDOT)** project will develop a series of coordinated procedures to support SMEs to bring test beds and device innovations to the level of clinical evaluation. This will enable conformity assessment using a database procedure and access to medical device testing data through a secure and transparent platform. MDOT will perform joint evaluations of commonly used parts and devices and develop advanced testing methods focusing on inhalation technology, neural implants and orthopaedic devices.

Based on the conditions laid down in the proposal text, BIOMATDB is expected to facilitate cooperation with, among others, relevant ongoing Open Innovation Test Beds and capitalise on their results, insights, networks, and developed innovation. Hence, the BIOMATDB project plans to engage with MDOT. Thus, the project consortium will seek to explore the specifications of the envisioned data platform, which has the goal to simplify the assessment procedures for MedTech SMEs and start-ups against the complexity and connected costs of the Medical Device Regulation (MDR). Further, BIOMATDB will aim to tap into the established network of suppliers of biomaterials and biomaterial based medical solutions and collect feedback regarding the planned BIOMATDB biomaterials marketplace as well as induce the identified organisations to register and use the marketplace's services.

7.2.7 TBMED

The **TBMED** project also aims to support med-tech companies in the development of high-risk medical devices by reducing their time to market for the European sector. The overall objective here is easy accessibility of patients to medical devices accessible, increasing quality and reducing risk, and meanwhile facilitating clinical testing. More specifically, it will assist European SMEs to maintain their competitiveness and innovation capacity in the face of global competition. This will further assist to promote real benefits of new devices, be it value or final outcomes. Also, by establishing an open innovation test bed with a connected network of labs, it could minimise time to market and facilitate efforts for reimbursement.

Against the background and achievements of TBMED, the BIOMATDB consortium will seek to build upon the created project's high-quality services and set of tutorials aimed towards SMEs and tackling their need of support throughout the different phases of the medical device development. Moreover, based on the established Open Innovation Test Bed (OITB) and connected network of entities, BIOMATDB plans to explore any collaboration and knowledge exchange activities, which should help the consortium validate insights gained in WP2 as well as design and develop outcomes in WP4 and WP5.

7.2.8 SAFE-N-MEDTECH

Nanotechnology is increasingly being utilised for the development of medical devices. As with all technological innovations that find applications in the healthcare sector, there is a need for careful

assessment of potential risks and benefits. This is where **SAFE-N-MEDTECH** enters the equation. This project will develop an open access platform to provide the required knowhow, networks, and services required for the development of nanotechnology-based medical and diagnostic devices. The SAFE-N-MEDTECH platform will address companies and laboratories and offer an integrated approach for assessing qualification, regulation, biocompatibility, and the properties of nanomaterials. Similar to other projects, this platform will expedite the transition of nanotechnology-based medical technologies to the market.

BIOMATDB plans to explore the established network of SAFE-N-MEDTECH consisting of industry organisations, laboratories, networks, and service providers. These entities will be mapped and presented on the SAFE-N-MEDTECH open access platform. Thus, potential collaborations can be identified and utilised to ensure the sustainable exploitation of the project's results. Further on, the BIOMATDB consortium will seek to gain knowledge on available best practices regarding the adoption and upscale of medical devices and implement relevant insights in the context of the design and development of the BIOMATDB biomaterials marketplace [151].

In conclusion, Open Innovation Test Beds are of particular importance to the BIOMATDB project since the consortium plans to utilise these projects for the testing and validation of the database and marketplace to ensure that all technical outcomes and data processing methods developed by the BIOMATDB project are tested and approved by practitioners.

8 Gaps and limitations

This deliverable aims to create a comprehensive document which will enable to correctly identify biomaterials data and constitute a source of relevant information for upcoming steps and tasks of the BIOMATDB project.

To define the main elements that BIOMATDB should focus on, we first selected the main resources in the field of biomaterials in Table 20 and summarized their main features.

Table 20. Main features of the most relevant resources in the biomaterials field

Type of data	DEBBIE	ASM Medical Materials	International Medical Devices Database	BONEZONE	Knowde
Free access	Yes	No	Yes	Yes	Yes
Physicochemical properties	Yes	Yes	No	No	Yes
Biocompatibility	Yes	Yes	No	No	Yes
Clinical data	No	Yes	No	No	No
Material composition	Yes	Yes	No	Yes	Yes
Medical devices	No	Yes	Yes	No	No
Marketplace/ Suppliers	No	Yes	Yes	Yes	Yes
Regulation	No	Yes	Yes	Yes	Yes
Source	Pubmed	Ansys Granta MI	International regulatory agencies	Suppliers' datasheets	Product datasheets and suppliers' webs
Curation	text mining pipeline	Manual	Manual	No	?
Numerical data	No	Yes	No	No	Yes
Other relevant limitations	Only analysis of abstracts	Only materials in FDA approved medical devices Seems to be manually curated	Limited to regulatory information Seems to be manually curated	Low number of companies	Not accurate filtering of biomaterials Restricted to included companies

First, the definition of biomaterial is a crucial step to capture those types of mentions that are of practical relevance in the biomaterials field among the wide range of documents and data sources with biomaterials information. The biomaterials field is an evolving discipline which depends on new applications, new compositions, fabrication processes, and discoveries. An actualized overview of the definition is required to establish annotation guidelines to capture biomaterials concepts. Currently, we have annotation guidelines related with the biomaterials field, like CHEMDNER, ChemProt and

DrugProt corpora, annotation guidelines to capture chemical entities and drugs, which can be modified and adapted to construct specific annotation guidelines for biomaterials. One objective of the next stages of the BIOMATDB project is to elaborate biomaterials annotation guidelines for the detection of relevant concepts in this field.

In practice, knowledge representation often takes the shape of one or several ontologies. Ontologies enable common understanding of the structure of information and establish relation within classes by hierarchy. It provides a common terminology that can be shared by researchers. Building ontologies is difficult and time consuming, and therefore often a better approach is the reuse of existing ontologies. Existing ontologies and their limitations are collected in Section 4.2.; specially DEB ontology will constitute a basis to automatically mine information from the biomedical literature and standardisation of data documentation across all domains related to biomaterials. DEB was designed using a bottom-up approach, relying on the content of randomly selected abstracts text.

A key disadvantage of the DEB ontology is that it relies on text from research article abstracts, and as such it is limited by the terminology included in that part of articles.

Existing biomaterials ontologies contain deficiencies and limitations in numerous areas. One drawback is that many ontologies are insufficiently thorough, failing to encompass all elements of biomaterials. Some ontologies, for example, may exclusively focus on a single class of biomaterials, such as polymers or ceramics, and not include other classes, such as metals or composites, limiting ontologies' comprehensive capability. Many ontologies are poorly organised and may contain overlapping or inconsistent terminology, making it difficult to browse and successfully use the ontology. This can also make it difficult to integrate and transfer information between multiple ontologies.

Current biomaterials-related ontologies are not well-curated and may contain errors or inaccuracies. This can lead to confusion and miscommunication among researchers and can also negatively impact the reliability and reproducibility of research results. Many ontologies are not designed to be easily extensible, which can make it difficult to add new terms or update existing terms to reflect new developments in the field.

Ontologies are often static and do not accurately reflect the dynamic character of the biomaterials sector, which is continually developing with new discoveries and advancements. Existing biomaterials ontologies include shortcomings such as a lack of coverage, poor structure, errors, a lack of extensibility, and a failure to represent the field's dynamic character.

The development and lifecycle of biomaterials and related products produced a vast amount of heterogeneous data that is distributed among different documents and sources. A main objective in this deliverable is to identify the kind of relevant data that the database needs to capture and the sources where they can be obtained. Considering the lifecycle of a biomaterials-related product that has been described in Chapter 3.6, we can distinguish the main types of information related with biomaterials:

- **Preclinical data**, which concerns all the evidences of the intended medical application of a biomaterial at different stages (under the corresponding form/shape, forming part of a more complex device, etc.), regarding mechanical and physicochemical properties and biological data taken by *in vitro* and *in vivo* evaluation by a wide range of models and assays.

- **Clinical data**, related with data obtained from clinical trials of a biomaterials-related product, like toxicological data, incidences, disease or condition, trial technical data (number of patients, if completed or not, etc.), etc.
- **Premarket reports**, including data and documents required to have the approval of the corresponding region, which includes protocols, preclinical, and clinical safety data.
- **Raw material data**, which implies data from the raw biomaterial employed to produce a biomaterials-related approved product, like supplier, if it is medical grade, manufacturing specifications, physicochemical characteristics, etc.
- **Biomaterials-related product data**, concerning data related to approved products like medical devices or ATMPs, such as components, medical use, mechanical properties, toxicological data, etc.
- **Post-market surveillance**, which includes data taken from following the post-market life of the product, basically safety data related to incidents and/or failures of the product.

Preclinical data could be obtained from research articles in journals or in patents, and both can be searched in general journal repositories described in Section 4.1.1 (Pubmed, Scopus, Web of Science, etc.) or patent databases described in Section 4.1.4 (Google Patents, ESPACENET, Patent Scope, etc.). Although they have different tools to filter information (combined terms, search by year, best match, etc.), they cover a wide range of fields that can lead to a more comprehensive and complete view of existing information on biomaterials. Some efforts tried to construct a biomaterial-specific database, for example the Biomaterials Properties Database, cBiT and 3D Printing Database (Section 4.3). These databases enable more comprehensive understanding of some aspects related with the biomaterials field (physicochemical properties, transcriptomics and 3D printing respectively), but they cover a few numbers of studies which limits their reach. We identified another two biomaterials-specific databases covering a wide amount of information, the DEBBIE database and the ASM Medical Materials Database.

DEBBIE curates biomaterials-related entities from PubMed abstracts. DEBBIE has several limitations that should be noted:

1. It relies on PubMed abstracts only, and as such has a limited depth of information.
2. Concept recognition in DEBBIE is built upon an annotation system called the Biomaterials Annotator. It uses dictionary mapping and rule-based annotation, greatly limiting the terms it can identify. For example, if terms have not been originally included in the annotator dictionary they will not be recognized. In practice, it means new emerging terms or terms not included in the language resources will not be annotated.
3. DEBBIE does not go further than simple annotations - it does not extract relations nor detects context. That means if two terms appear in the same abstract and are annotated, DEBBIE is not able to discern the meaning of that co-occurrence. That greatly limits the quality of the knowledge and its use. One can imagine a situation where collagen is mentioned in the same abstract as scaffold. DEBBIE cannot indicate if the collagen is part of the scaffold, a coating, or the cells growing on the scaffold have secreted collagen - important distinction as to how collagen should be annotated.
4. DEBBIE's language resources are borrowed from varied disciplines and have gaps and contradictions.

5. DEBBIE's search engine presents results as the metrics from found relevant documents. This is useful for general mapping, but harder to extract insights from.
6. DEBBIE does not curate any numerical information related to the entities it recognizes. (Example: tensile properties may be annotated, but not the values attached to them).

ASM Medical Material Database is an important resource for the biomaterials community that provides unique capabilities in terms of searching and comparing biomaterials used in US FDA approved medical devices. However, it is not without limitations. First, the single-user, non-transferrable, annual payment subscription ($750) model is a major limitation to access, particularly for researchers and SMEs in less economically developed countries, such as the Global South. Additionally, while comprehensive, the fact that the database only includes materials used in US FDA approved devices is also a major limitation, because in this way, novel research biomaterials are not included. Thus, while the ability to search for substitute materials is powerful, by excluding research biomaterials the database does not foster innovation or progress beyond the current status quo, in terms of translation of research to the clinic and market.

Clinical data are found in clinical trials registered in free access corresponding repositories (ClinicalTrials.gov, ECRIN, EU Clinical Trials Register, etc.) that are described in Section 4.1.2. Despite collecting the technical setup of the clinical trial with detail and presenting the results, the clinical trial repositories present limited information of the medical product employed in the clinical trial (regarding mechanical and physicochemical characteristics, composition, etc.), which makes it difficult to relate the safety results with biomaterial characteristics.

This project aims to provide information on approved biomaterials for clinical use. The main type of documents regarding specific information of medical products (more relevantly implantable Class III devices) are the premarket documents like PMA and post-market surveillance document, that can be found in specific databases from FDA (USA) or in EUDAMED (EU) as collected in Section 4.4. The limitation in these kinds of sources is the lack of specifications of the biomaterial components found in these medical devices, which makes it difficult to connect them with the medical application and safety data of the final products. An objective of the BIOMATDB project will be to try to relate these medical products with the biomaterials that they are composed of. Another disadvantage is the fragmentation of data related with the different regulatory systems per country and the connection with manufacturers. The International Medical Devices Database (IMDD) tries to resolve these issues, collecting more than 120,000 Recalls, Safety Alerts and Field Safety Notices of medical devices and their connections with their manufacturers. However, biomaterials composing medical devices are not well specified in any case, which makes it really difficult to understand the performance results of the device. In our database, we will try to correlate the preclinical data with the performance results from medical devices in order to establish an indirect relation of them with possible biomaterials.

Similarly to what happens with biomaterials data, biomaterials suppliers and products are really fragmented and are not well centralised. When you search for marketplaces specifically of biomaterials, only two results are obtained, the Biomaterials Store with dental materials for clinicians, and the BONEZONE with orthopaedic-focused suppliers. These two marketplaces are really niche-specific, collecting only suppliers and products from two sectors within the biomaterials field. To find more biomaterials products and suppliers, research within general materials marketplaces collected in section 6.2 can be done, however, they cover materials for a wide range of applications and rarely they include tools for search biomaterials. We only find one marketplace, named Knowde, which

presents a separate section for materials employed for medical applications. It presents interesting tags to filter the research of products and suppliers, like the chemistry of the material, end-uses or features related with physicochemical properties and biocompatibility. The main limitations of this source are that it is mostly focused on polymers, and it does not collect key aspects of the materials like if they are medical grade or the sterilisation process, among others. The BIOMATDB project will centralise a wide range of biomaterial suppliers and raw materials covering the main sectors in the market (metals, ceramics and polymers) and will facilitate finding relevant information for companies, like physicochemical properties, manufacturing process, medical grade and related biological data.

Intelligent data processing tools.

Current intelligent analysis tools for biomaterials databases have several limitations. One of the main drawbacks is the lack of ability to effectively handle a large amount of data, making it difficult to analyse and interpret complex biomaterials datasets, as well as making the integration of data from multiple data sources not effective, which could lead to inconsistencies and errors in the final analysis.

Many data processing tools cannot effectively handle different types of biomaterials data, such as imaging data or genetic data. This can make it difficult to fully understand and analyse complex biomaterials systems, since we cannot get many of the crucial metadata available for analysis due to the different data sources.

Performing advanced statistical analyses, such as multivariate analyses or machine learning techniques, can be a challenge using current data processing tools, limiting the ability to uncover complex relationships and patterns within different biomaterials databases. In the same note, when combining many data sources, there is no standardisation in the field of biomaterials database analysis, which makes comparing findings and results from different studies very difficult.

The absence of user-friendly interfaces in existing analytical tools for biomaterials databases is another challenge. Many analytic tools need a high degree of technical ability and knowledge to use, making them unavailable to researchers lacking a solid foundation in bioinformatics or computational biology. This can impede researchers' capacity to access and use the large volumes of data accessible in biomaterials databases, as well as prevent new researchers from entering the area.

In addition, many current analysis tools do not have the capability to visualise data in a meaningful and intuitive way. This can make it difficult to identify patterns and trends in large datasets, and can also limit the ability of researchers to communicate their findings to others in the field.

Another limitation is the integration with other resources and tools. For example, many biomaterials databases are not linked with other databases, such as gene expression databases or protein interaction databases, which can make it difficult to perform integrative analyses. Additionally, many analysis tools do not have the capability to perform functional annotation of biomaterials, which can complicate the comprehension of the biological function of different biomaterials.

In conclusion, while existing biomaterials database analysis tools have achieved great advances in the field of biomaterials research, there are still numerous gaps and restrictions that must be addressed. These include the inability to manage huge datasets, the lack of interaction with other resources and tools, the lack of user-friendly interfaces, and the inability to perform real-time analysis. To address these restrictions, it is critical to continue developing and improving analytic tools for biomaterials databases, as well as to stimulate collaboration between bioinformatics and biomaterials experts.

Biomaterials marketplaces and Digital Advisors

While collecting and analysing existing biomaterials and biomaterials-related marketplaces, it was identified that there are no biomaterials specific marketplaces currently available that offer biomaterials-specific services, products and features. As can be seen in chapter 6, there are only two marketplaces that seem to focus solely on biomaterials—Biomaterial Store and BONEZONE. However, both cover only a section of the biomaterials market. The Biomaterial Store targets dental practitioners and is limited to dental biomaterials and products. On the other hand, the BONEZONE is not only an online store but also a network of suppliers, institutions that focus on commercialising innovative orthopaedic related products. Thus, its biomaterial focus is solely on orthopaedic related biomaterials. See Table 14 for more detailed information about both marketplaces. There are other marketplaces that offer some biomaterials as a category, but are not marketplaces or online stores focused on biomaterials. Table 15 gives a short summary of the most relevant marketplaces available and the biomaterials they offer.

Moreover, in section 6.3 available digital advisors have been collected and analysed. It was identified that currently there is no biomaterials or even biomaterials-related marketplace offering such a functionality to assist users and buyers to find the best solution for their situation and need.

Therefore, the BIOMATDB project aims to tackle this gap and provide a marketplace in which biomaterials suppliers may list their products, services and resources related to biomaterials. A biomaterials-specific categorisation tree will assist the suppliers, buyers and marketplace users to navigate through the listed products and services and identify relevant solutions. Automatic digital advisors will also assist the buyers and users to find the best solution for their situation and need.

9 Conclusions

Research and development in the field of material science has led to the production of thousands of novel biomaterials. This represents an opportunity for suppliers of medical devices and advanced therapies to create novel solutions, which can help governments meet the demand for medical implants as well as tackle the challenge of ever rising incidence of cardiovascular diseases. However, centralized, easily accessible and well-structured data of biomaterials for researchers, companies, laboratories, and suppliers of biomaterials and biomaterials based medical instruments are needed. To approach the solution of these issues and support the design and development of the planned project's technical solutions, BIOMATDB initiated, as a part of T2.1 comprehensive research and analysis of existing knowledge and materials about biomaterials databases, data structures, solutions and intelligent data processing approaches, biomaterial terminologies and decision-support processes. The outcomes of this process constitute an important milestone in the project's efforts towards the identification of existing gaps and innovation needs in the field and the definition of the main end user groups of the BIOMATDB technical solutions and their related requirements and needs.

In concrete terms BIOMATDB managed to establish a structured approach, which allowed the individual consortium organisations to collect, among others, 404 suppliers of biomaterials and biomaterials based medical devices, 338 demanders organisations, 434 biomaterials or biomaterial-based products, 82 enabler organisations and networks, 64 relevant events in the field of biomaterials, 52 related projects and initiatives with outcomes to be considered as potential assets for BIOMATDB, 26 research institutions and 252 individual researchers, 135 policy makers and regulation organisations, 46 investor companies and individuals, 41 online platforms and marketplaces with relevance to the promotion of biomaterials and biomaterials based medical instruments, and 640 biomaterials journals, books and other publications relevant to the ongoing analysis and upcoming development activities in BIOMATDB. The main kind of documents and sources of biomaterials data, which have been identified during the process of compiling knowledge materials will help the consortium construct the BIOMATDB biomaterials database and marketplace and include preclinical, clinical, regulatory data, product data (raw materials and medical products) and post-market surveillance.

Additionally, the project elaborated on the definition of biomaterials, as well as on intelligent data processing approaches, which are required for the design and development of the biomaterials database and marketplace. This will allow both solutions to capture biomaterial concepts from relevant sources.

Based on the analysis, which was carried out by the consortium it was further found that an updated biomaterial ontology would be useful in order to hierarchically organize biomaterial concepts and overcome the limitation from existing ontologies. However, the content from existing ontologies in this process can be reused.

It was also established that a relevant departing point for the design and development of the project's technical solutions represent the DEBBIE and ASM Medical Materials databases and their related limitations. Based on the analysis of the DEBBIE database, the project consortium will consider the establishment of features and functionalities, which will ensure the competitive advantage of the BIOMATDB biomaterials database, including among others but not limited to full test analysis,

inclusion of terms from relevant sources, context detection, establishment of relation between data and numerical curation. Regarding the BIOMATDB biomaterials marketplace, the project consortium will consider the implementation of EU regulation coverage and inclusion of research and clinical data.

Further insights, which were collected within D2.1, which potentially can be implemented into the upcoming development activities include the detection of the biomaterial composition of medical products from clinical trials and regulatory documentation, as well as the establishment of relations with preclinical data. Additionally, it was also highlighted that the integration of relevant tools with regard to information such as gene expression, protein expression, cell lines, animal models would be desirable.

Furthermore, improved data processing tools, user-friendly interfaces and data visualisations were defined as mandatory in the biomaterials field, in order for solutions providers to meet the current demand and remain competitive on the market. This includes also the centralization of raw materials suppliers and products, as well as the capture of relevant data from products and clear presentation to the buyers. Last but not least, the development of digital advisors as a part of the infrastructure of the planned biomaterials marketplace was considered as necessary in order to assist potential end users with their purchasing decisions.

All outputs from the conducted knowledge aggregation will be consequently structured and fed into the upcoming design and development activities in WP2 and WP3 on the basis of which the path for the specification of the technical and user requirements for the BIOMATDB biomaterials database and marketplace will be set.

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Annex

Journal ranking and biomaterials books

Table 21. Annex - First quartile of the SJR journal ranking for the biomaterials category

Rank	Title	ISSN	SJR	H index	JIF	Ctry.	Publisher	Categories
1	Nature Reviews Materials	20588437	23,876	131	66,308	UK	Nature Publishing Group	Biomaterials (Q1); Electronic, Optical and Magnetic Materials (Q1); Energy (miscellaneous) (Q1); Materials Chemistry (Q1); Surfaces, Coatings and Films (Q1)
2	EnergyChem	25897780	7,488	21	11,62	NL	Elsevier BV	Biomaterials (Q1); Chemistry (miscellaneous) (Q1); Energy (miscellaneous) (Q1)
3	Advanced Functional Materials	1616301X	5	349	19,924	DE	Wiley-VCH Verlag	Biomaterials (Q1); Chemistry (miscellaneous) (Q1); Condensed Matter Physics (Q1); Electrochemistry (Q1); Electronic, Optical and Magnetic Materials (Q1); Materials Science (miscellaneous) (Q1); Nanoscience and Nanotechnology (Q1)
4	Small	16136829, 16136810	3,225	259	13,281	DE	Wiley-VCH Verlag	Biomaterials (Q1); Biotechnology (Q1); Chemistry (miscellaneous) (Q1); Engineering (miscellaneous) (Q1); Materials Science (miscellaneous) (Q1); Medicine (miscellaneous) (Q1); Nanoscience and Nanotechnology (Q1)

5	Materials Today Nano	25888420	2,691	24	13,364	UK	Elsevier Ltd.	Biomaterials (Q1); Condensed Matter Physics (Q1); Electronic, Optical and Magnetic Materials (Q1); Materials Chemistry (Q1)
6	Biomaterials	01429612, 18785905	2,678	397	15,304	UK	Elsevier BV	Bioengineering (Q1); Biomaterials (Q1); Biophysics (Q1); Ceramics and Composites (Q1); Mechanics of Materials (Q1); Nanoscience and Nanotechnology (Q1)
7	Journal of Bioresources and Bioproducts	23699698	2,466	20	16,82	CA	KeAi Communications Co.	Biochemistry (Q1); Biomaterials (Q1); Forestry (Q1); Materials Chemistry (Q1); Organic Chemistry (Q1)
8	Bioactive Materials	2452199X	2,281	43	14,119	NL	KeAi Communications Co.	Biomaterials (Q1); Biomedical Engineering (Q1); Biotechnology (Q1)
9	Biomaterials Research	20557124	2,235	32	9,719	UK	BioMed Central Ltd.	Biomaterials (Q1); Biomedical Engineering (Q1); Ceramics and Composites (Q1); Medicine (miscellaneous) (Q1)
10	Smart Materials in Medicine	25901834	2,023	7	11,267	CN	KeAi Communications Co.	Bioengineering (Q1); Biomaterials (Q1); Biomedical Engineering (Q1)
11	Advanced healthcare materials	21922640, 21922659	2,015	105	11,092	UK	John Wiley and Sons Ltd	Biomaterials (Q1); Biomedical Engineering (Q1); Pharmaceutical Science (Q1)
12	Biofabrication	17585082, 17585090	1,697	92	11,267	UK	IOP Publishing Ltd.	Biochemistry (Q1); Bioengineering (Q1); Biomaterials (Q1); Biomedical Engineering (Q1); Biotechnology (Q1); Medicine (miscellaneous) (Q1)

13	Acta Biomaterialia	17427061	1,661	207	8,947	NL	Elsevier BV	Biochemistry (Q1); Biomaterials (Q1); Biomedical Engineering (Q1); Biotechnology (Q1); Medicine (miscellaneous) (Q1); Molecular Biology (Q1)
14	Materials Today Bio	25900064	1,555	15	10,761	NL	Elsevier BV	Bioengineering (Q1); Biomaterials (Q1); Biomedical Engineering (Q1); Biotechnology (Q1); Cell Biology (Q1); Molecular Biology (Q1)
15	Journal of Colloid and Interface Science	10957103, 00219797	1,397	247	9,965	US	Academic Press Inc.	Biomaterials (Q1); Colloid and Surface Chemistry (Q1); Electronic, Optical and Magnetic Materials (Q1); Surfaces, Coatings and Films (Q1)
16	Journal of the Royal Society Interface	17425689, 17425662	1,381	147	4,118	UK	The Royal Society	Biochemistry (Q1); Bioengineering (Q1); Biomaterials (Q1); Biomedical Engineering (Q1); Biophysics (Q1); Biotechnology (Q1)
17	Biochar	25247867	1,365	14	11,452	DE	Springer Science and Business Media B.V.	Biomaterials (Q1); Environmental Science (miscellaneous) (Q1); Pollution (Q1); Soil Science (Q1)
18	Biomacromolecules	15264602, 15257797	1,359	232	6,978	US	American Chemical Society	Bioengineering (Q1); Biomaterials (Q1); Materials Chemistry (Q1); Polymers and Plastics (Q1)
19	APL Bioengineering	24732877	1,332	19	5,7	US	American Institute of Physics	Bioengineering (Q1); Biomaterials (Q1); Biomedical Engineering (Q1); Biophysics (Q1)
20	Tissue Engineering - Part B: Reviews	19373368, 19373376	1,287	100	7,376	US	Mary Ann Liebert Inc.	Biochemistry (Q1); Bioengineering (Q1); Biomaterials (Q1); Biomedical Engineering (Q1)

21	Materials Today Chemistry	24685194	1,271	36	7,613	UK	Elsevier Ltd.	Biomaterials (Q1); Colloid and Surface Chemistry (Q1); Electronic, Optical and Magnetic Materials (Q1); Materials Chemistry (Q1); Polymers and Plastics (Q1); Catalysis (Q2)
22	Food Packaging and Shelf Life	22142894	1,232	45	8,749	NL	Elsevier BV	Biomaterials (Q1); Food Science (Q1); Microbiology (medical) (Q1); Polymers and Plastics (Q1); Safety, Risk, Reliability and Quality (Q1)
23	Materials Science and Engineering C	09284931, 18730191	1,191	145	7,328	NL	Elsevier BV	Bioengineering (Q1); Biomaterials (Q1); Condensed Matter Physics (Q1); Materials Science (miscellaneous) (Q1); Mechanical Engineering (Q1); Mechanics of Materials (Q1)
24	Journal of Tissue Engineering	20417314	1,157	36	7,94	UK	SAGE-Hindawi Access to Research	Biomaterials (Q1); Biomedical Engineering (Q1); Medicine (miscellaneous) (Q1)
25	Multifunctional Materials	23997532	1,06	11	4,54	UK	IOP Publishing Ltd.	Biomaterials (Q1); Materials Science (miscellaneous) (Q1); Surfaces, Coatings and Films (Q1)
26	International Journal of Nanomedicine	11782013, 11769114	1,032	145	7,419	NZ	Dove Medical Press Ltd.	Bioengineering (Q1); Biomaterials (Q1); Biophysics (Q1); Drug Discovery (Q1); Medicine (miscellaneous) (Q1); Organic Chemistry (Q1); Pharmaceutical Science (Q1); Nanoscience and Nanotechnology (Q2)

27	Interface Focus	20428898, 20428901	1,01	57	4,661	UK	The Royal Society	Biomaterials (Q1); Biomedical Engineering (Q1); Biophysics (Q1); Biotechnology (Q1); Biochemistry (Q2); Bioengineering (Q2)
28	Engineering Science and Technology, an International Journal	22150986	0,983	62	5,155	NL	Elsevier BV	Biomaterials (Q1); Civil and Structural Engineering (Q1); Computer Networks and Communications (Q1); Electronic, Optical and Magnetic Materials (Q1); Fluid Flow and Transfer Processes (Q1); Mechanical Engineering (Q1); Metals and Alloys (Q1); Hardware and Architecture (Q2)
29	Journal of Science: Advanced Materials and Devices	24682284, 24682179	0,98	31	7,382	NL	Elsevier BV	Biomaterials (Q1); Ceramics and Composites (Q1); Electronic, Optical and Magnetic Materials (Q1); Materials Science (miscellaneous) (Q1)

Table 22. Annex - Relevant books to understand the field of biomaterials

Subject area; Book series	Title	Author/Editor	Year	Description (as cited in Ref.)	Ref.
Biomaterials in general	Definitions of Biomaterials for the Twenty-First Century (Materials Today)	Xingdong Zhang, David Williams	2019	Definitions of Biomaterials for the Twenty-First Century is a review of key, critical biomaterial terms and definitions endorsed by the International Union of Societies for Biomaterials Science and Engineering. The topics and definitions discussed include those in general biomaterials and applications, biocompatibility, implantable and interventional devices, drug delivery systems, regenerative medicine and emerging biomaterials. The book reviews the discussion of these terms by leaders in the global biomaterials community and summarizes the agreed upon definitions.	[1]
Biomaterials in general; Biological and Medical Physics, Biomedical	Biomaterials: A Tantalus Experience	Jozef A. Helsen , Yannis Missirlis	2010	Comprehensive survey of biocompatible materials with special focus on metallic and ceramic biomaterials In this book, the properties and selection of materials for such `spare parts' are deduced from case studies at the start of each chapter.	[152]

Engineering (BIOMEDICAL)				Hard tissue replacements (joints, long bones, dental), soft tissue (heart valves) and tissue engineering are included. The chapters also detail the three generic classes of materials: alloys (including shape memory alloys), ceramics & glasses and polymers. Separate chapters are devoted to the toxicity of implants, the metals zirconium (-zirconium oxide), tantalum, niobium and metallic glasses, soluble metals and Rapid Prototyping techniques for the fabrication of custom-made prostheses. The book concludes by a chapter on water as water is always 'there' and conditions the interaction between body and implant. Water is the very matrix of life on earth. A peculiarity of the book is its 'perspective view', meaning that the authors looked behind the present biomaterials' décor and included historical backgrounds (real and mythological), future developments, and the relation to nature (plants and geology).	
Biomaterials in general	Biomaterials Science: An Introduction to Materials in Medicine 4th Edition	William Wagner, Shelly Sakiyama-Elbert, Guigen Zhang, Michael Yaszemski	2020	The revised edition of the renowned and bestselling title is the most comprehensive single text on all aspects of biomaterials science from principles to applications. Biomaterials Science, fourth edition, provides a balanced, insightful approach to both the learning of the science and technology of biomaterials and acts as the key reference for practitioners who are involved in the applications of materials in medicine. This new edition incorporates key updates to reflect the latest relevant research in the field, particularly in the applications section, which includes the latest in topics such as nanotechnology, robotic implantation, and biomaterials utilized in cancer research detection and therapy. Other additions include regenerative engineering, 3D printing, personalized medicine and organs on a chip. Translation from the lab to commercial products is emphasized with new content dedicated to medical device development, global issues related to translation, and issues of quality assurance and reimbursement. In response to customer feedback, the new edition also features consolidation of redundant material to ensure clarity and focus. Biomaterials Science, 4th edition is an important update to the best-selling text, vital to the biomaterials' community.	[7]
Biomaterials in general	Engineering of Biomaterials (Topics in Mining, Metallurgy and Materials Engineering)	Venina dos Santos, Rosmary Nichele Brandalise, Michele Savaris	2017	Presents case studies on different applications of biomaterials. Provides a complete review on biomaterials in a clear and objective text Based on the authors' experience with the manufacturing processes of polymer and ceramic artifacts. Includes supplementary material.	[13]
Biomaterials in general	Fundamentals of Biomaterials	Vasif Hasirci, Nesrin Hasirci	2018	True, fully integrated teaching text presented in a single, coherent voice. Integrates materials	[14]

	– An Introduction			and biological properties to understand biomaterials function and design. Covers metals, ceramics, polymers, carbon-derived materials, materials of a natural origin, and composites as biomaterials. Includes hot topics from tissue engineering and guided tissue regeneration to nanoarchitecture of biomaterial surfaces. Contains a number of perspectives/ case studies from widely-recognized experts in the field. Includes chapter ending summaries to help students to identify the key, take-home messages	
Biomaterials in general	Biomaterials: An Introduction, 2007	Joon Bu Park; Roderic S. Lakes	2007	Emphasizes fundamentals as a basis for understanding biomaterials and their applications Extensively revised from the previous edition including a new chapter on materials for tissue engineering and regenerative medicine Includes new digitally redrawn artwork Written as a true teaching instrument by two authors with sixty years of combined experience	[16]
Biomaterials in general	Biomaterials and Medical Devices: A Perspective from an Emerging Country	Ferdiansyah Mahyudin, Hendra Hermawan	2016	Offers an introduction to biomaterials and medical devices. Focuses on the latest advances in research and development in Indonesia. Presents contributions written by selected experts.	[19]
Biomaterials in general	Materials for Biomedical Engineering: Bioactive Materials, Properties, and Applications	Valentina Grumezescu, Alexandru Mihai Grumezescu	2019	Materials for Biomedical Engineering: Bioactive Materials, Properties, and Applications introduces the reader to a broad range of the different types of bioactive materials used in biomedical engineering. All the main types of bioactive materials are discussed, with an emphasis placed on their synthesis, properties, performance, and potential for biomedical applications. Key chapters on modeling and surface modification and methods provide the step-by-step information needed by researchers. Important applications of bioactive materials, such as drug delivery, cancer therapy and clinical dentistry are also highlighted in detail. Final sections look at future perspectives for bioactive materials in biomedical engineering.	[153]
Biomaterials in general	Foundations of Biomaterials Engineering	Maria-Cristina Tanzi, Silvia Fare, Gabriele Candiani	2019	Foundations of Biomaterials Engineering provides readers with an introduction to biomaterials engineering. With a strong focus on the essentials of materials science, the book also examines the physiological mechanisms of defense and repair, tissue engineering and the basics of biotechnology. An introductory section covers materials, their properties, processing and engineering methods. The second section, dedicated to Biomaterials and Biocompatibility, deals with issues related to the use and application of the various classes of materials in the	[9]

				biomedical field, particularly within the human body, the mechanisms underlying the physiological processes of defense and repair, and the phenomenology of the interaction between the biological environment and biomaterials. The last part of the book addresses two areas of growing importance: Tissue Engineering and Biotechnology. This book is a valuable resource for researchers, students and all those looking for a comprehensive and concise introduction to biomaterials engineering.	
Biomaterials in general	Introduction to Biomaterials: Basic Theory with Engineering Applications	C. Mauli Agrawal, Joo L. Ong, Mark R. Appleford, Gopinath Mani	2014	This textbook gives students an introduction to the world of biomaterials, linking the fundamental properties of metals, polymers, ceramics and natural biomaterials to the unique advantages and limitations surrounding their biomedical applications. Clinical concerns such as sterilization, surface modification, cell-biomaterial interactions, drug delivery systems, and tissue engineering are discussed in detail, giving students practical insight into the real-world challenges associated with biomaterials engineering; key definitions, equations and concepts are concisely summarised alongside the text, allowing students to quickly and easily identify the most important information; and bringing together elements from across the book, the final chapter discusses modern commercial implants, challenging students to consider future industrial possibilities. Concise enough to be taught in a single semester, and requiring only a basic understanding of biology, this balanced and accessible textbook is the ideal introduction to biomaterials for students of engineering, materials science and medicine.	[154]
Biomaterials in general	Biomaterials: From Theory to Applications	Shay Fisher	2020	Biomaterial is a substance that is engineered to interact with biological systems for medical purposes. These purposes can either be therapeutic or diagnostic. The study of biomaterials is called biomaterial science or biomaterial engineering. Biomaterial science makes use of elements from medicine, biology, chemistry, tissue engineering and material science. Biomaterials can be derived from nature. They can also be synthesized in the laboratory by using varieties of chemical approaches such as utilizing metallic components, ceramics or composite materials and polymers. Biomaterials comprise a part or a whole of living structure or biochemical device which performs, augments or replaces a natural function. They are used for various medical purposes such as joint replacements, bone plates, intraocular lenses, bone cement, artificial ligaments and tendons, blood vessel prostheses, dental implants, heart valves, etc. The ever-growing need of advanced technology is the reason that has fueled the research in the field of biomaterials in recent times. Most of the	[155]

				topics introduced in this book cover new techniques and the applications of biomaterials. The extensive content of this book provides the readers with a thorough understanding of the subject.	
Biomaterials in general	Biomaterial Science	Ludwig Erik Aguilar	2022	This book bridges the gap between a clinician's and material scientists' knowledge by elucidating upon the different biomaterials used in anatomical systems and how those materials react to the human body. It explores both established and future prospective of biomaterial types/designs, and considerations in material selection and synthesis, to guide students from non-clinical background in understanding the relations of material science and the human body. This book covers Anatomy and Physiology, Synthesis and Characterization of biomaterials, the immune response to biomaterials, Biomaterials used for Cancer; Drug Delivery and Tissue Engineering, as well as the role of artificial intelligence.	[15]
Biomaterials in general	Biomaterials Science and Technology: Fundamentals and Developments	Yaser Dahman	2019	Biomaterials Science and Technology: Fundamentals and Developments presents a broad scope of the field of biomaterials science and technology, focusing on theory, advances, and applications. It reviews the fabrication and properties of different classes of biomaterials such as bioinert, bioactive, and bioresorbable, in addition to biocompatibility. It further details traditional and recent techniques and methods that are utilized to characterize major properties of biomaterials. The book also discusses modifications of biomaterials in order to tailor properties and thus accommodate different applications in the biomedical engineering fields and summarizes nanotechnology approaches to biomaterials.	[20]
Biomaterials in general	Biomaterials: A Basic Introduction	Qizhi Chen, George Thouas	2015	Biomaterials: A Basic Introduction is a definitive resource for students entering biomedical or bioengineering disciplines. This text offers a detailed exploration of engineering and materials science, and examines the boundary and relationship between the two. Based on the author's course lecture notes and many years of research, it presents students with the knowledge needed to select and design biomaterials used in medical devices. Placing special emphasis on metallic, ceramic, polymeric, and composite biomaterials, it explains the difference between materials science and materials engineering, introduces basic concepts and principles, and analyzes the critically important properties of biomaterials. This text provides an appropriate balance between depth and broadness of coverage, and offers an understanding of the most important concepts and principles to students from a wide	[156]

				academic spectrum. It delivers the science of biomaterials in laymen terms, from a material standpoint, as well as a clinical applications point of view. It equips students majoring in materials science/engineering with knowledge on the fundamentals of how biomaterials behave at a biological level, and provides students majoring in medicine with information that is generally unavailable in traditional medical courses. The authors incorporate learning objectives at the beginning of each chapter, as well as chapter highlights, problems, and exercises at the end of each chapter. In addition, they present objectives, suggested activities, and reference material for further reading.	
Special area; Woodhead Publishing Series in Biomaterials	Structural Biomaterials: Properties, Characteristics, and Selection	Cuie Wen	2021	Structural Biomaterials: Properties, Characteristics, and Selection serves as a single point of reference to digest current research and develop a deeper understanding in the field of biomaterials engineering. This book uses a materials-focused approach, allowing the reader to quickly access specific, detailed information on biomaterials characterization and selection. Relevant to a range of readers, this book provides holistic coverage of the broad categories of structural biomaterials currently available and used in medical applications, highlighting the property requirements for structural biomaterials, their biocompatibility performance and their safety regulation in key categories such as metals, ceramics and polymers. The materials science perspective of this text ensures the content is accessible even to those without an extensive background in applied medicine, positioning this text not just for students, but as an overview and reference for researchers, scientists and engineers entering the field from related materials science disciplines.	[157]
Special area; Woodhead Publishing Series in Biomaterials	Biomaterials in Translational Medicine	Lei Yang, Sarit Bhaduri, Thomas J. Webster	2018	Biomaterials in Translational Medicine delivers timely and detailed information on the latest advances in biomaterials and their role and impact in translational medicine. Key topics addressed include the properties and functions of these materials and how they might be applied for clinical diagnosis and treatment. Particular emphasis is placed on basic fundamentals, biomaterial formulations, design principles, fabrication techniques and transitioning bench-to-bed clinical applications. The book is an essential reference resource for researchers, clinicians, materials scientists, engineers and anyone involved in the future development of innovative biomaterials that drive advancement in translational medicine.	[158]

Special area; Woodhead Publishing Series in Biomaterials	Biomaterials for Organ and Tissue Regeneration	Nihal Engin Vrana, Helena Knopf-Marques, Julien Barthes	2020	Biomaterials for Organ and Tissue Regeneration: New Technologies and Future Prospects examines the use of biomaterials in applications related to artificial tissues and organs. With a strong focus on fundamental and traditional tissue engineering strategies, the book also examines how emerging and enabling technologies are being developed and applied. Sections provide essential information on biomaterial, cell properties and cell types used in organ generation. A section on state-of-the-art in organ regeneration for clinical purposes is followed by a discussion on enabling technologies, such as bioprinting, on chip organ systems and in silico simulations.	[159]
Special area; Woodhead Publishing Series in Biomaterials	Characterization of Polymeric Biomaterials	Maria Cristina Tanzi, Silvia Farè	2017	Characterization of Polymeric Biomaterials presents a comprehensive introduction on the topic before discussing the morphology and surface characterization of biomedical polymers. The structural, mechanical, and biological characterization is described in detail, followed by invaluable case studies of polymer biomaterial implants. With comprehensive coverage of both theoretical and experimental information, this title will provide scientists with an essential guide on the topic of these materials which are regularly used for clinical applications, such as implants and drug delivery devices. However, a range of novel polymers and the development and modification of existing medical polymers means that there is an ongoing need to satisfy particular design requirements. This book explains the critical and fundamentals methods to characterize polymer materials for biomedical applications.	[160]
Special area; Woodhead Publishing Series in Biomaterials	Handbook of Biomaterials Biocompatibility	Masoud Mozafari	2020	Handbook of Biomaterials Biocompatibility is a systematic reference on host response to different biomaterials, taking into account their physical, mechanical and chemical properties. The book reviews recent progress in the design and study of biomaterials biocompatibility, along with current understanding on how to control immune system response. Sections provide the fundamental theories and challenges of biomaterials biocompatibility, the role of different biomaterials physicochemical surface properties on cell responses, cell responses to different physicochemical properties of polymers, ceramics, metals, carbons and nanomaterials, and biomaterials in different tissues, such as the cardiac, nervous system, cartilage and bone. This resource will be suitable for those working in the fields of materials science, regenerative engineering, medicine, medical devices and nanotechnology.	[161]

Special area	Smart Biomaterials	Mitsuhiro Ebara, Yohei Kotsuchibashi, Ravin Narain, Naokazu Idota, Young-Jin Kim, John M. Hoffman, Koichiro Uto, Takao Aoyagi	2014	This book provides comprehensive coverage of smart biomaterials and their potential applications, a field that is developing at a very rapid pace. Because smart biomaterials are an emerging class of biomaterials that respond to small changes in external stimuli with large discontinuous changes in their physical properties, they have been designed to act as an "on–off" switch for, among others, bio separation, immunoanalysis, drug delivery technologies, gene therapy, diagnostics, bio sensors and artificial muscles. After an introduction to the topic and the history of smart biomaterials, the author gives the reader an in-depth look at the properties, mechanics, and characterization of smart biomaterials including hydrogels, particles, assemblies, surfaces, fibers and conjugates. Information on the wide range of applications for these materials follows, including drug delivery, tissue engineering, diagnostics, biosensors, bio separation and actuators. In addition, recent advances in shape memory biomaterials as active components of medical devices are also presented.	[162]
Bioengineering	The Biomedical Engineering Handbook: Four Volume Set (English Edition) 4. Auflage	Joseph D. Bronzino, Donald R. Peterson	2015	The definitive "bible" for the field of biomedical engineering, this collection of volumes is a major reference for all practicing biomedical engineers and students. Now in its fourth edition, this work presents a substantial revision, with all sections updated to offer the latest research findings. New sections address drugs and devices, personalized medicine, and stem cell engineering. Also included is a historical overview as well as a special section on medical ethics. This set provides complete coverage of biomedical engineering fundamentals, medical devices and systems, computer applications in medicine, and molecular engineering.	[163]

List of ISO Standards

Table 3. International Organization for Standardization (ISO) Documents[a] Applicable to Biological Testing of Biomaterials and Medical Devices (Paid Access at https://www.iso.org).

ISO Series[b]	Part	Year Published/Revision or Update	Title of Standard	Current Status (As of March 2018)
Technical Committee ISO/TC 194 Biological and Clinical Evaluation of Medical Devices				
10993	1	2018	Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing within a Risk Management Process	Revision to 2009/Cor[c] published August 2018
10993	2	2006	Biological Evaluation of Medical Devices—Part 2: Animal Welfare Requirements	Reviewed and confirmed in 2015
10993	3	2014	Biological Evaluation of Medical Devices—Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity[d]	Published. See TR 10993-33:2015 genotoxicity supplement
10993	4	2017	Biological Evaluation of Medical Devices—Part 4: Selection of Tests for Interactions with Blood	Published
10993	5	2009	Biological Evaluation of Medical Devices—Part 5: Tests for in vitro Cytotoxicity	Reviewed and confirmed in 2017
10993	6	2016	Biological Evaluation of Medical Devices-Part 6: Tests for Local Effects after Implantation	Published
10993	7	2008/Cor 1:2009	Biological Evaluation of Medical Devices—Part 7: Ethylene Oxide Sterilization Residuals	Reviewed and confirmed 2016. ISO 10993-7:2008/ DAmd[c] 1 under development
10993	8		Withdrawn—Selection of Reference Materials	Not applicable
10993	9	2009	Biological Evaluation of Medical Devices—Part 9: Framework for Identification and Quantification of Potential Degradation Products	Replacement ISO/DIS[b,c] 10993-9 under development
10993	10	2010	Biological Evaluation of Medical Devices—Part 10: Tests for Irritation and Skin Sensitization	Reviewed and confirmed in 2016. Replacement ISO/AWI[c] 10993-10 under development
10993	11	2017	Biological Evaluation of Medical Devices—Part 11: Tests for Systemic Toxicity[d]	Published
10993	12	2012	Biological Evaluation of Medical Devices—Part 12: Sample Preparation and Reference Materials	Replacement ISO/AWI[c] 10993-12 under development
10993	13	2010	Biological Evaluation of Medical Devices—Part 13: Identification and Quantification of Degradation Products from Polymeric Medical Devices	Reviewed and confirmed in 2013
10993	14	2001	Biological Evaluation of Medical Devices—Part 14: Identification and Quantification of Degradation Products from Ceramics	Reviewed and confirmed in 2013
10993	15	2000	Biological Evaluation of Medical Devices—Part 15: Identification and Quantification of Degradation Products from Metals and Alloys	Reviewed and confirmed in 2013. Replacement ISO/DIS 10993-15 under development
10993	16	2017	Biological Evaluation of Medical Devices—Part 16: Toxicokinetic Study Design for Degradation Products and Leachables	Published
10993	17	2002	Biological Evaluation of Medical Devices—art 17: Establishment of Allowable Limits for Leachable Substances	Reviewed and confirmed in 2016. Replacement ISO/AWI 10993-17 under development
10993	18	2005	Biological Evaluation of Medical Devices—Part 18: Chemical Characterization of Materials—Check New Version under Development	Reviewed and confirmed in 2013. Replacement ISO/DIS 10993-18 under development
TS[a] 10993	19	2006	Biological Evaluation of Medical Devices—Part 19: Physicochemical, Morphological and Topographical Characterization of Materials	Replacement ISO/DTR[b,c] 10993-19-8 under development
TS 10993	20	2006	Biological Evaluation of Medical Devices—Part 20: Principles and Methods for Immunotoxicology Testing of Medical Devices	Replacement ISO/NP[b,c] TS 10993-20 under development
TR[a] 10993	22	2017	Biological Evaluation of Medical Devices—Part 22: Guidance on Nanomaterials	Published
WD[b,c] 10993	23		Biological Evaluation of Medical Devices—Part 23: Determination of Skin Irritation of Medical Device Extracts Using Reconstructed Human Epidermis (RhE)	Under development

Figure 54. Annex - Summary of the most relevant ISOs in medical devices (1)

Table 3. (continued)

ISO Series[b]	Part	Year Published/Revision or Update	Title of Standard	Current Status (As of March 2018)
TR 10993	33	2015	Biological Evaluation of Medical Devices—Part 33: Guidance on Tests to Evaluate Genotoxicity—Supplement to ISO 10993-3	Published
NP TR 10993	55		Round Robin on Cytotoxicity—Part 55: (No Title)	Under development
TR 37137		2014	Cardiovascular Biological Evaluation of Medical Devices—Guidance for Absorbable Implants	Replacement ISO/DTR 37137-2 under development
NP TS 37137	1	2014	Biological Evaluation of Medical Devices—Part 1: Guidance for Absorbable Implants	Under development
TR 37137	2	2014	Cardiovascular Biological Evaluation of Medical Devices—Guidance for Absorbable Implants. Part 2: Standard Guide for Absorbable Metals	Under development
DTS[bc] 21726			Biological Evaluation of Medical Devices—Application of the Threshold of Toxicological Concern (TTC) for Assessing Biocompatibility of Extractable Substances from Medical Devices	Under development
TR 15499		2016	Biological Evaluation of Medical Devices—Guidance on the Conduct of Biological Evaluation within a Risk Management Process	Published
CD 22442	1		Medical Devices Utilizing Animal Tissues and Their Derivatives—Part 1: Application of Risk Management	Under development; previously 22442-1:2015
NP 22442	2		Medical Devices Utilizing Animal Tissues and Their Derivatives—Part 2: Controls on Sourcing, Collection And Handling	Under development; previously 22442-2:2015
Technical Committee ISO/TC 150 Implants for Surgery				
5840	1	2015	Cardiovascular Implants—Cardiac Valve Prostheses—Part 1: General Requirements	Published
5840	2	2015	Cardiovascular Implants—Cardiac Valve Prostheses—Part 2: Surgically Implanted Heart Valve Substitutes	Published
5840	3	2013	Cardiovascular Implants—Cardiac Valve Prostheses—Part 3: Heart Valve Substitutes Implanted By Transcatheter Techniques	Under development
TS 17137		2014	Cardiovascular Implants and Extracorporeal Systems—Cardiovascular Absorbable Implants	Replacement ISO/NP TS 17137 under development
25539	1	2017	Cardiovascular Implants—Endovascular Devices—Part 1. Endovascular Prostheses	Published
NP 25539	2	2012	Cardiovascular Implants—Endovascular Devices—Part 2. Vascular Stents	Under development
25539	3	2011	Cardiovascular Implants—Endovascular Devices—Part 3. Vena Cava Filters	Published
14708	5	2010	Implants for Surgery—Active Implantable Medical Devices—Part 5: Circulatory Support Devices	Replacement ISO/CD 14708-5 under development
7197		2006/Cor 1:2007	Neurosurgical Implants—Sterile, Single-use Hydrocephalus Shunts and Components	Published
17853		2011	Wear of Implant Materials—Polymer and Metal Wear Particles—Isolation and Characterization	Reviewed and confirmed in 2016
21534		2007	Nonactive Surgical Implants—Joint Replacement Implants—Particular Requirements	Reviewed and confirmed in 2016
Technical Committee ISO/TC 172 Ophthalmic Optics and Instruments				
11979	5	2006	Ophthalmic implants—Intraocular Lenses—Part 5: Biocompatibility	Replacement ISO/WD 11979 under development
11979	8	2017	Ophthalmic Implants—Intraocular Lenses—Part 8: Fundamental Requirements	Published
9394		2012	Ophthalmic Optics—Contact Lenses and Contact Lens Care Products—Determination of Biocompatibility by Ocular Study with Rabbit Eyes	Reviewed and confirmed 2017
16671		2015/Amd 1:2017	Ophthalmic Implants—Irrigating Solutions for Ophthalmic Surgery	Published
16672		2015	Ophthalmic Implants—Ocular Endotamponades	Replacement DIS 16672 under development

Figure 55. Annex - Summary of the most relevant ISOs in medical devices (2)

Table 3. (continued)

ISO Series[b]	Part	Year Published/Revision or Update	Title of Standard	Current Status (As of March 2018)
15798		2013/Amd 1:2017	Ophthalmic Implants—Ophthalmic Viscosurgical Devices	Published
Technical Committee ISO/TC 106 Dentistry				
TS 22911		2016	Dentistry—Preclinical Evaluation of Dental Implant Systems—Animal Test Methods	Published
7405		2008/Amd 1:2013	Dentistry—Evaluation of Biocompatibility of Medical Devices Used in Dentistry	Replacement ISO/FDIS 7405 under development
22803		2004	Dentistry—Membrane Materials for Guided Tissue Regeneration in Oral and Maxillofacial Surgery—Contents of a Technical File	Published
Technical Committee ISO/TC 84 Devices for Administration of Medicinal Products and Catheters				
10555	6	2015	Intravascular Catheters—Sterile and Single-use Catheters—Part 6: Subcutaneous Implanted Ports	Published
Technical Committee ISO/TC 121 Lung Ventilators and Related Equipment				
18562	1	2017	Biocompatibility Evaluation of Breathing Gas Pathways in Healthcare Applications—Part 1: Evaluation and Testing within a Risk Management Process	Published
Technical Committee ISO/TC 210 Quality Management and Corresponding General Aspects for Medical Devices				
14971		2007	Medical Devices—Application of Risk Management to Medical Devices	Replacement ISO 14971 and DTR 24971 under development
DTR 24971			Medical Devices—Guidance on the Application of ISO 14971	Under development
TR 13121		2011	Nanotechnologies—Nanomaterial Risk Evaluation	Published
TR 16197		2014	Nanotechnologies—Compilation and Description of Toxicological Screening Methods for Manufactured Nanomaterials	Published
TS 80004	5	2011	Nanotechnologies—Vocabulary—Part 5: Nano/Bio Interface	Under development

[a]Documents are available in paper and PDF form, with some documents becoming available in ePub and ebook formats and available for Kindle and Apple devices.
[b]Standardized notation for referencing the ISO standards numerically should include the specifics of the document series, number, and year, for example, ISO 10993-6:2016 or ISO/TR 10993-33:2015. These standards are generally reviewed every 5 years.
[c]ISO Abbreviations: Amd = amendment; AWI = approved work item; CD = committee draft; Cor = corrigenda; DAmd = draft amendment; DIS = draft international standard; DTR = draft technical report; DTS = draft technical specification; FDIS = final draft international standard; NP = new project; WD = working draft.
[d]ICH guidelines (see Table 6) are also frequently consulted for these assays.
[e]ISO Technical Subject (TS) and Technical Reports (TR) provide technical information with no conformance required.

Figure 56. Annex - Summary of the most relevant ISOs in medical devices (3)

List of related material databases

Table 23. Annex - List of related material databases

Name	Website	Content	Size	Open	Notes
AFLOWlib	http://www.aflowlib.org/	Method for high-throughput computational materials design, calculating physical properties from electronic structure.	60K	Yes	API downloadable data No metadata download
ioChem-BD	http://www.iochem-bd.org/	Digital repository of computational chemistry files.	247K	Yes	Registration for downloading
Electronic Structure Project	http://gurka.fysik.uu.se/ESP/	Database including electronic structure related information for a large number of inorganic compounds.	61K	Yes	No API downloadable data No metadata download
Materials Project	https://www.materialsproject.org/	Database of computed information on known and predicted materials. It also provides powerful analysis tools.	1,45M	Yes Under registration	API downloadable data Metadata downloadable
Novel Materials Discovery	http://nomad-repository.eu/cms/	Database for atomistic simulations and multi-scale modelling.	2,9M	Yes	No API downloadable data No metadata download
MEMSnet	https://www.memsnet.org/material/	A complete list of MEMS materials and material properties.	>200	Yes	No API downloadable data No metadata download
Open Materials Database	http://openmaterialsdb.se/	An open database for calculated material properties.	205K	Yes	No API downloadable data No metadata download
Open Quantum Materials Database	http://www.oqmd.org/	Database contains DFT (density functional theory) calculated thermodynamic and structural properties.	1M	Yes	API downloadable data
COMAR	http://www.comar.bam.de/en/	International database for certified reference materials.	7389	Yes Under registration	No API downloadable data Metadata downloadable
MatWeb	http://www.matweb.com/	Searchable database of material properties, which can be exported to o.a. Comsol, SolidWorks. etc.	155K	Yes	Downloadable functions only under subscription
Knovel	https://app.knovel.com/	Database which covers mechanical to chemical properties data, corrosion data and material properties	160 Sources 98K Concepts	Yes	No API downloadable data No metadata download

			75M Data Points		
Crystallography Open Database	http://www.crystallography.net/	Open-access collection of crystal structures of organic, inorganic, metal-organic compounds and minerals excluding biopolymers.	493K	Yes	Metadata download
Springer Materials	https://materials.springer.com/	Provides curated data and advanced functionalities to support research in materials science, physics, chemistry, engineering, and other related fields.	-	Yes	No API downloadable data No metadata download
HybriD³ database	https://materials.hybrid3.duke.edu/	Comprehensive collection of experimental and computational materials data for crystalline organic-inorganic compounds, predominantly based on the perovskite paradigm. Search by formula.	-	Yes	Metadata download
Scifinder	https://libguides.mit.edu/scifinder	Information from Chemical Abstracts, CAS registry, and Medline. Search tool for chemical information from journals, patents, conference proceedings, and technical reports.	-	No	-
Polymer Library	https://www.ebsco.com/products/research-databases/polymer-library	Large abstracts database dedicated to plastics, rubber, polymer composites and adhesives. Published by the WTI-Frankfurt-digital team, contains information from journals, proceedings, books and reports.	1,4M	No	-
Polymer Database	https://polymerdatabase.com/	Built and maintained by group of accomplished polymer scientists, to assist chemists for formulation of industry-grade polymers and plastic products.	-	Yes	No API downloadable data No metadata download
Polymers: A Property Database	https://www.library.ucsb.edu/research/db/1206	Extensive collection of physical property data for polymers and monomers by CRC Press. The electronic handbook may be searched by keyword, or by ranges of property values.	-	No	-

Table 24. Annex - List of databases relevant to medical devices and radiation-emitting products

Title	Description	Updated	More information
522 Postmarket Surveillance Studies Program	Information about current 522 Postmarket Surveillance Studies; allows search by manufacturer or device information.	Weekly	More about 522
AccessGUDID (Global Unique Device Identification Database)	Key device identification information submitted to the FDA about medical devices that have Unique Device Identifiers (UDI).	Daily	More about GUDID
Advisory Committee/Panel Meetings - CDRH	Historical information about CDRH Advisory Committees and Panel meetings through 2008, including summaries and transcripts.	No longer being updated	FDA Advisory Committees and Meeting Materials
CDRH Export Certificate Validation (CECV)	Contains valid (not expired) export certificates submitted electronically via CECATS (CDRH Export Certification Application and Tracking System) and issued by the Center for Devices and Radiological Health. Display contains facility name, certificate type, expiration date, certificate number, and number of pages per certificate.	Weekly	
CFR Title 21 - Food and Drugs	Most recent revision from the Government Printing Office (GPO) of the Code of Federal Regulations (CFR) Title 21 - Food and Drugs.	Quarterly	More About 21CFR
Clinical Laboratory Improvement Amendments (CLIA)	Commercially marketed in vitro test systems categorized by the FDA since January 31, 2000, and tests categorized by the Centers for Disease Control and Prevention (CDC) prior to that date.	Weekly	Clinical Laboratory Improvement Amendments - Download Data
CLIA Currently Waived Analytes	Commercially marketed in vitro test systems categorized as CLIA waived by the FDA since January 31, 2000, and by the Centers for Disease Control and Prevention (CDC) prior to that date. CLIA waived test systems are waived from certain CLIA laboratory requirements (42 CFR Part 493).	Monthly	CLIA Waivers
De Novo	Classifying novel devices of low to moderate risk. This database contains de novo classification orders.	Weekly	
Devices@FDA	Catalog of cleared and approved medical device information from FDA. It includes links to the device summary information, manufacturer, approval date, user instructions, and other consumer information. Devices@FDA searches the following databases: Premarket Notifications (510(k)s) and Premarket Approvals (PMA).	Weekly	
FDA Certified Mammography Facilities	Listing by state and zip code of all mammography facilities certified by the Food and Drug Administration (FDA) as meeting baseline quality standards for	Weekly	

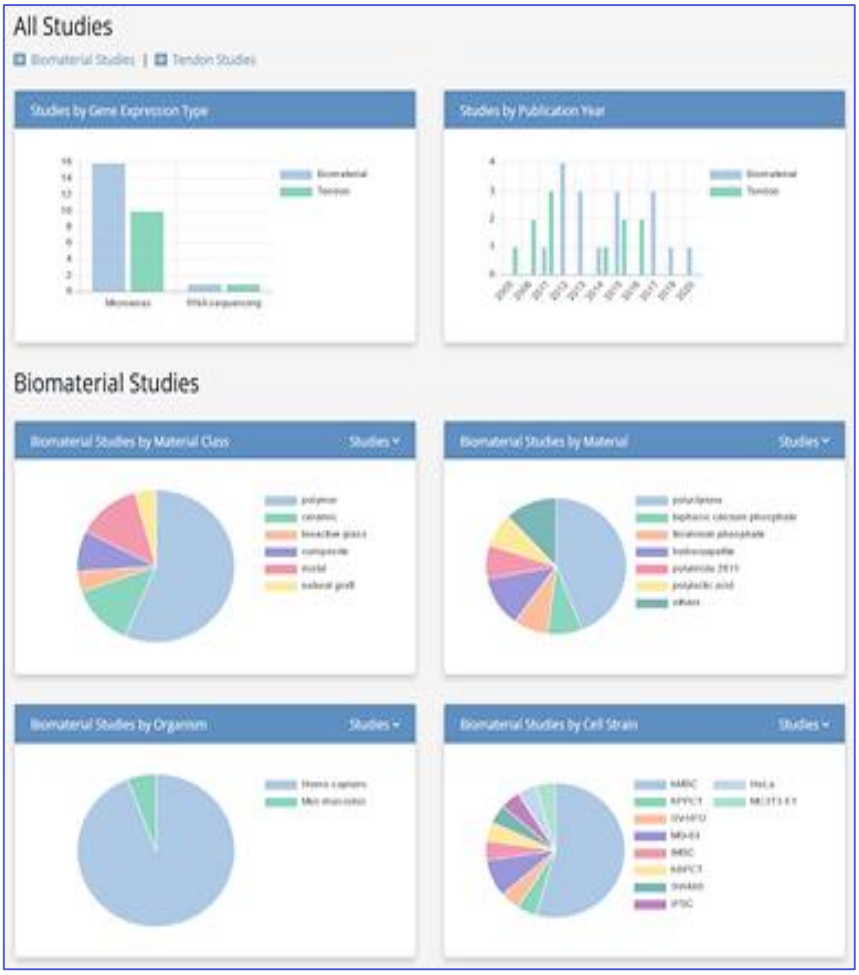
	equipment, personnel and practices under the Mammography Quality Standards Act of 1992 (MQSA).		
Humanitarian Device Exemption (HDE)	Searchable listing of Humanitarian Device Exemption (HDE) Class III medical devices.	Weekly	More about Humanitarian Device Exemption (HDE)
IVD Home Use Lab Tests (Over The Counter) Tests	Searchable listing of Over-the-Counter tests (OTC) and collection kits that have been cleared or approved by the FDA	Weekly	More about Home Use Lab Tests
MAUDE (Manufacturer and User Facility Device Experience)	MAUDE data represents reports of adverse events involving medical devices. The data consists of all voluntary reports since June, 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August, 1996.	Weekly	
MDR (Medical Device Reporting)	Search tool for the CDRH's database information on medical devices which may have malfunctioned or caused a death or serious injury for years 1992-1996.	No longer being updated	
MedSun Reports	The Medical Product Safety Network (MedSun) is an adverse event reporting program launched in 2002 by the U.S. Food and Drug Administration's Center for Devices and Radiological Health (CDRH). The primary goal for MedSun is to work collaboratively with the clinical community to identify, understand, and solve problems with the use of medical devices.	Daily	MedSun Homepage
Post-Approval Studies (PAS) Database	Information about current Post-Approval Studies (PAS). Manufacturers required to conduct PAS must complete the study as a condition of approval; allows search using PAS information by applicant or device information.	Weekly	More about PAS
Premarket Approvals (PMA)	Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of all devices classified as Class III devices. An approved Premarket Approval Application (PMA) is, in effect, a private license granted to the applicant for marketing a particular medical device.	Weekly	File Description for the CDRH Releasable (Approved) PMAs
Premarket Approval (PMA) Summary Review Memos for 180-Day Design Changes	A 180-day supplement is a request for a significant change in components, materials, design, specification, software, color additive, and labeling to an approved premarket application or premarket report. As a pilot program under the CDRH Transparency Initiative, FDA has begun releasing some summary review memos for 180-day PMA supplements relating to design changes.	Weekly	More about Premarket Approval (PMA) Summary Review Memos for 180-Day Design Changes
Premarket Notifications (510(k)s)	Medical device manufacturers are required to submit a premarket notification or 510(k) if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. This database	Weekly	

	of releasable 510(k)s can be searched by 510(k) number, applicant, device name or FDA product code. Summaries of safety and effectiveness information is available via the web interface for more recent records.		
Product Classification	Contains medical device names and associated information developed by the Center. It includes a three letter device product code and a Device Class that refers to the level of CDRH regulation of a given device.	Weekly	More about Product Code Classification Database
Radiation-emitting Electronic Product Codes	Contains product names and associated information developed by the Center for all products, both medical and non-medical, which emit radiation. It includes a three-letter product code, a descriptor for radiation type, applicable performance standard(s), and a definition for the code.	Weekly	
Radiation Emitting Product Corrective Actions and Recalls	Provides descriptions of radiation-emitting products that have been recalled under an approved corrective action plan to remove defective and noncompliant products from the market. Searches may be done by manufacturer name, performance standard, product name, description, or date range.	Weekly	More About Corrective Actions
Recalls of Medical Devices	Contains Medical Device Recalls classified since November 1, 2002. Beginning January 3, 2017, the database may also include correction or removal actions initiated by a firm prior to review by the FDA. The status of the action is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall and provides contact information for customers with questions. Therefore, the recall information posting date ("create date") indicates the date FDA classified the recall, it does not necessarily mean that the recall is new. CBER recall information also available.	Frequently as items become available	More About Recalls
Recognized Consensus Standards	Consists of FDA recognized national and international standards which manufacturers can declare conformity to and is part of the information the Center can use to make an appropriate decision regarding the clearance or approval of a submission. Information submitted on conformance with such standards will have a direct bearing on safety and effectiveness determinations made during the review of IDEs, HDEs, PMAs, and PDPs. Conformance with recognized consensus standards in and of itself, however, may not always be a sufficient basis for regulatory decisions.	Quarterly	
Registration & Listing	Contains establishments (engaged in the manufacture, preparation, propagation, compounding, assembly, or processsing of medical devices intended for human use and commercial distribution) and listings of medical devices in commercial distribution by both domestic	Weekly	More About Registration and Listing

	and foreign manufacturers. Generally, owners or operators of establishments that are involved in the production and distribution of medical devices intended for use in the U.S. are required to register annually with the FDA. Generally, establishments that are required to register with the FDA are also required to list the devices that are made there and the activities that are performed on those devices. If a device requires a premarket submission before being marketed in the U.S., then the owner/operator should also provide the FDA premarket submission number (510(k), De Novo, PMA, PDP, HDE).		
Total Product Life Cycle (TPLC)	The Total Product Life Cycle (TPLC) database integrates premarket and postmarket data about medical devices. It includes information pulled from CDRH databases including Premarket Approvals (PMA), Premarket Notifications (510[k]), Adverse Events, and Recalls. You can search the TPLC database by device name or procode to receive a full report about a particular product line.	Weekly	More about TPLC
X-Ray Assembler Data	Federal regulations require that an assembler who installs one or more certified components of a diagnostic x-ray system submit a report of assembly. This database contains the releasable information submitted including Equipment Location, General Information and Component Information. Note: Data does not include dental system installations.	No longer being updated	X-Ray Assembler Data File

Screenshots of the databases and marketplaces

cBIT



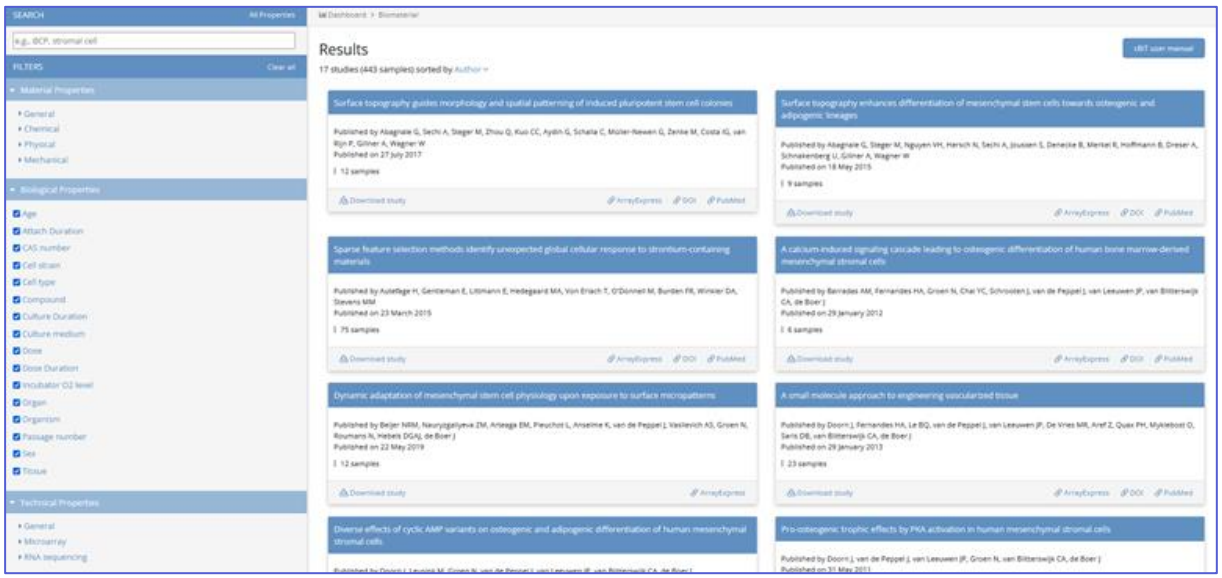
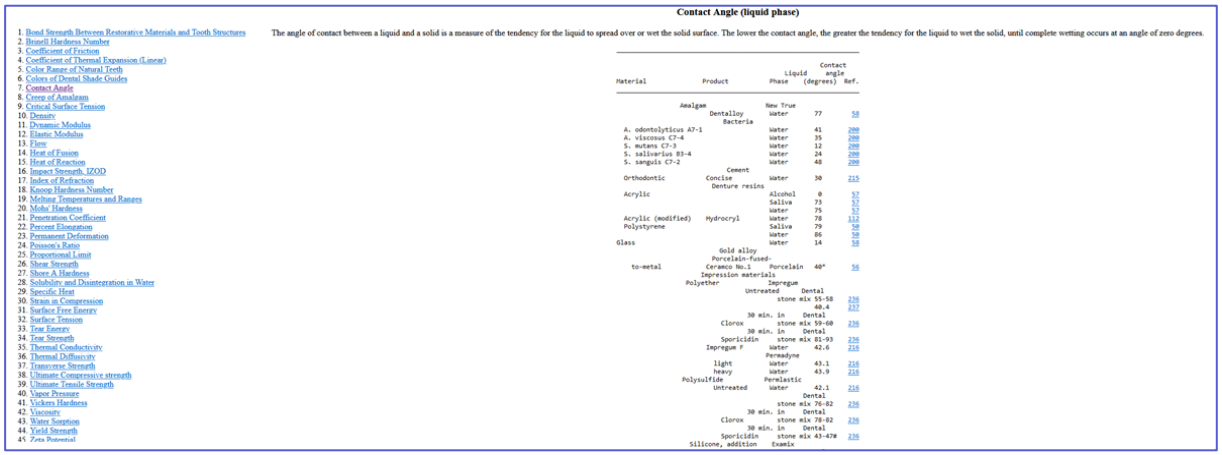


Figure 57. Annex - Screenshots of the cBiT repository

Biomaterial properties database



Contact Angle (liquid phase)

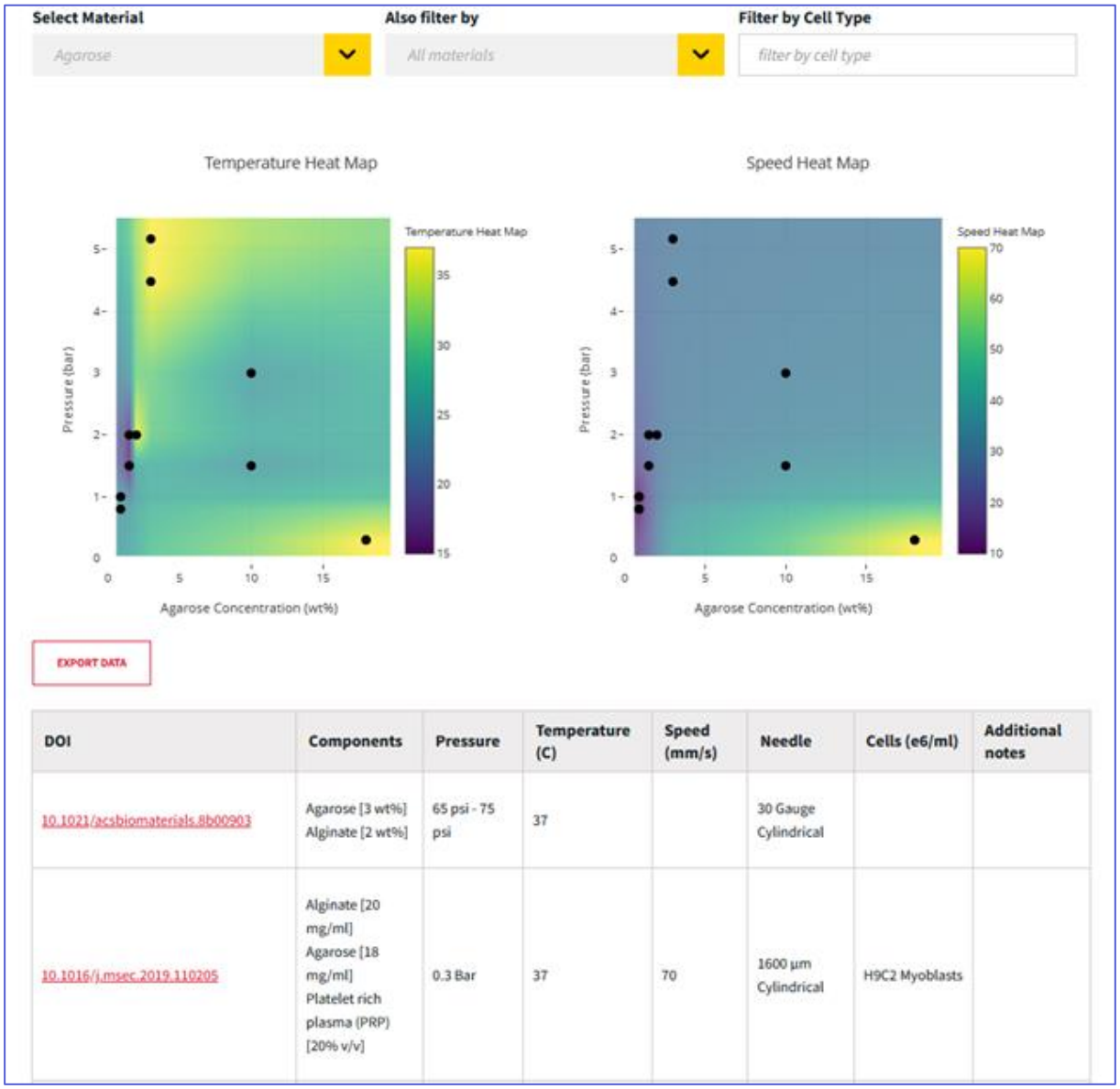
1. Bond Strength Between Restorative Materials and Tooth Structures
2. Brinell Hardness Number
3. Coefficient of Friction
4. Coefficient of Thermal Expansion (Linear)
5. Color Range of Natural Teeth
6. Colors of Dental Shade Guides
7. Contact Angle
8. Creep of Amalgam
9. Critical Surface Tension
10. Density
11. Dynamic Modulus
12. Elastic Modulus
13. Flow
14. Heat of Fusion
15. Heat of Reaction
16. Impact Strength, IZOD
17. Index of Refraction
18. Knoop Hardness Number
19. Melting Temperatures and Ranges
20. Mohs' Hardness
21. Penetration Coefficient
22. Percent Elongation
23. Permanent Deformation
24. Poisson's Ratio
25. Proportional Limit
26. Shear Strength
27. Shore A Hardness
28. Solubility and Disintegration in Water
29. Specific Heat
30. Strain in Compression
31. Surface Free Energy
32. Surface Tension
33. Tear Energy
34. Tear Strength
35. Thermal Conductivity
36. Thermal Diffusivity
37. Transverse Strength
38. Ultimate Compressive strength
39. Ultimate Tensile Strength
40. Vapor Pressure
41. Vickers Hardness
42. Viscosity
43. Water Sorption
44. Yield Strength
45. Zeta Potential

The angle of contact between a liquid and a solid is a measure of the tendency for the liquid to spread over or wet the solid surface. The lower the contact angle, the greater the tendency for the liquid to wet the solid, until complete wetting occurs at an angle of zero degrees.

Material	Product	Liquid Phase	Contact angle (degrees)	Ref.
Amalgam	New True Dentalloy	Water	77	58
Bacteria				
A. odontolyticus A7-1		Water	41	200
A. viscosus C7-4		Water	35	200
S. mutans C7-3		Water	12	200
S. salivarius B3-4		Water	24	200
S. sanguis C7-2		Water	48	200
Cement				
Orthodontic	Concise	Water	30	215
Denture resins				
Acrylic		Alcohol	0	57
		Saliva	73	57
		Water	75	57
Acrylic (modified)	Hydrocryl	Water	78	112
Polystyrene		Saliva	79	58
		Water	86	58
Glass		Water	14	58
Gold alloy				
Porcelain-fused-to-metal	Ceramco No.1	Porcelain	40°	56
Impression materials				
Polyether	Impregum Untreated	Dental stone mix	55-58	236
			40.4	237
	30 min. in Clorox	Dental stone mix	59-60	236
	30 min. in Sporicidin	Dental stone mix	81-93	236
	Impregum F	Water	42.6	216
Polysulfide	light	Permadyne Water	43.1	216
	heavy	Water	43.9	216
	Untreated	Permlastic Water	42.1	216
		Dental stone mix	76-82	236
	30 min. in Clorox	Dental stone mix	78-82	236
	30 min. in Sporicidin	Dental stone mix	43-47#	236
Silicone, addition		Examix		

Figure 58. Annex - Screenshot of the Biomaterial properties database

3D Printing Database



DOI	Components	Pressure	Temperature (C)	Speed (mm/s)	Needle	Cells (e6/ml)	Additional notes
10.1021/acsbiomaterials.8b00903	Agarose [3 wt%] Alginate [2 wt%]	65 psi - 75 psi	37		30 Gauge Cylindrical		
10.1016/j.msec.2019.110205	Alginate [20 mg/ml] Agarose [18 mg/ml] Platelet rich plasma (PRP) [20% v/v]	0.3 Bar	37	70	1600 µm Cylindrical	H9C2 Myoblasts	

Figure 59. Annex - Screenshot of the 3D Printing Database

IMDD

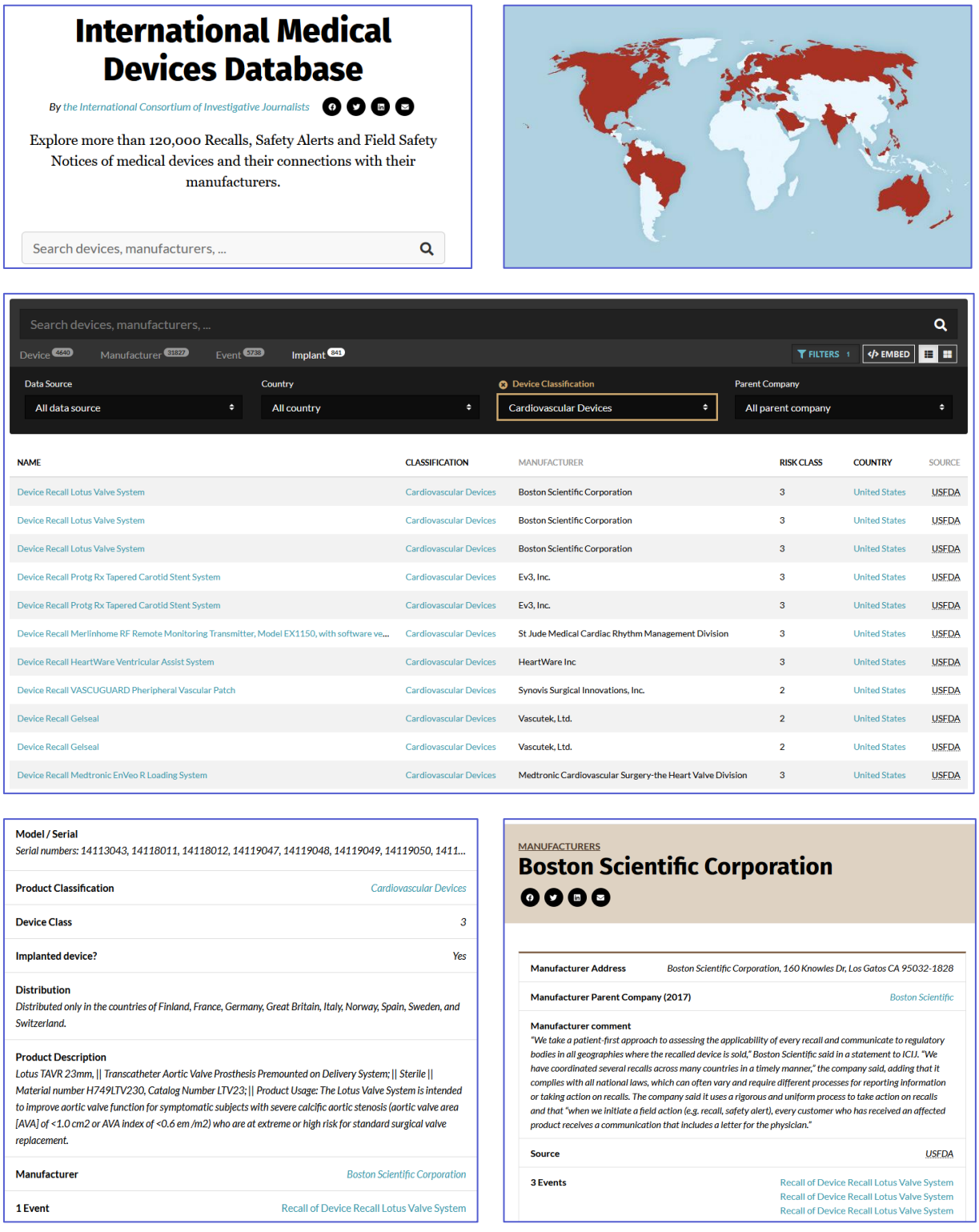


Figure 60. Annex - Screenshots from the International Medical Devices Database (1)

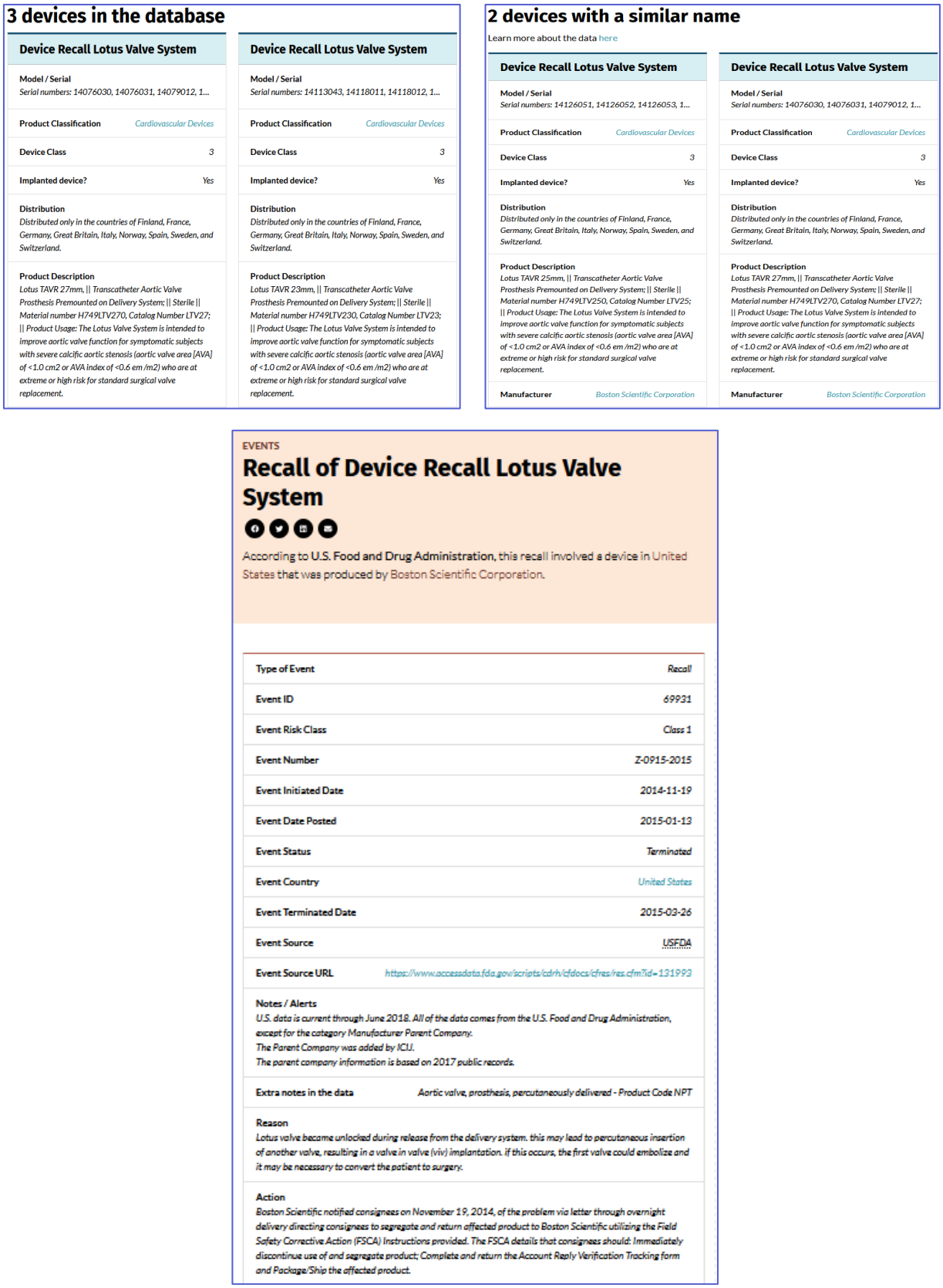


Figure 61. Annex - Screenshots from the International Medical Devices Database (2)

The Biomaterial Store

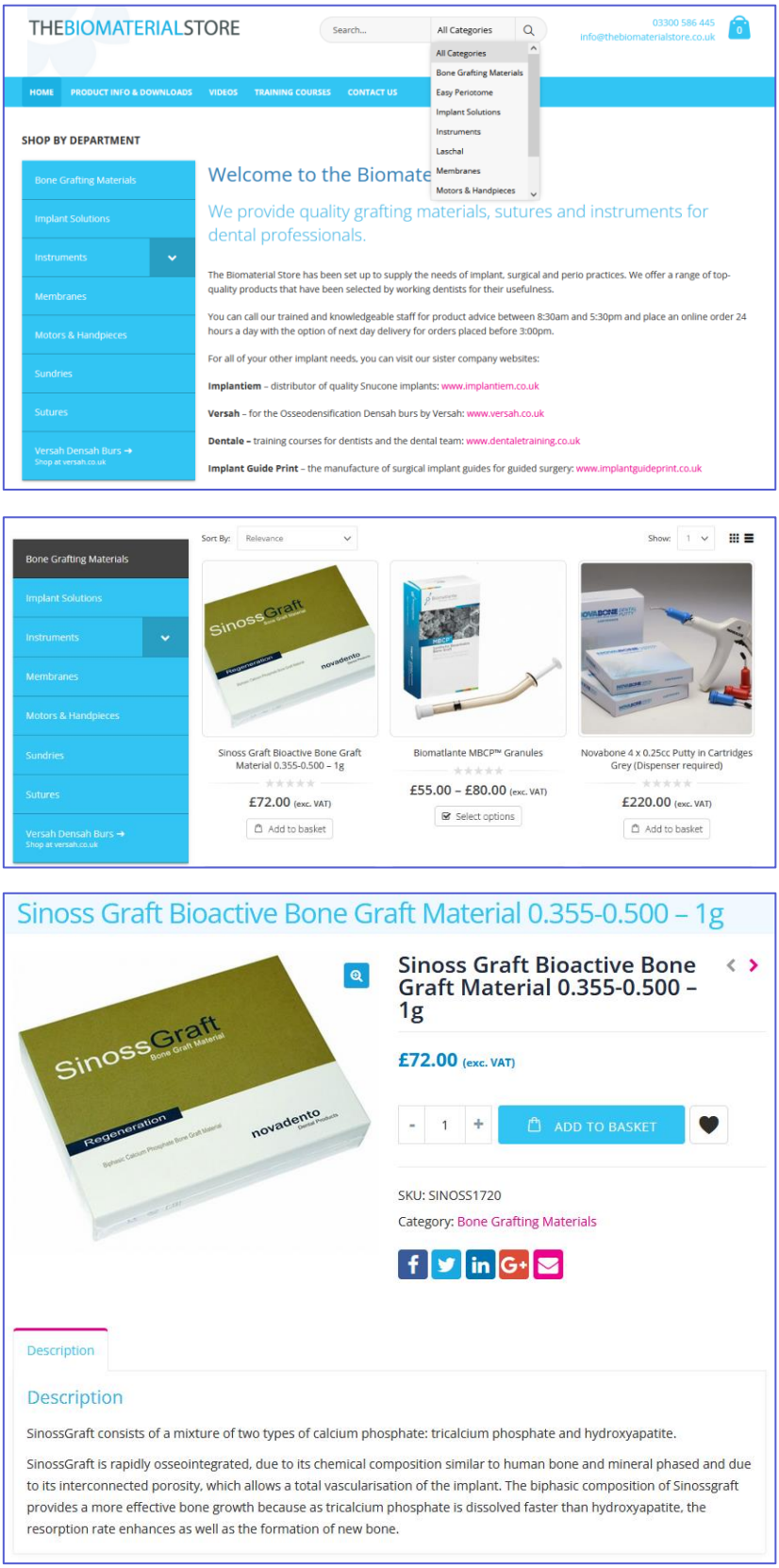


Figure 62. Annex - Screenshots from The Biomaterial Store

BONEZONE

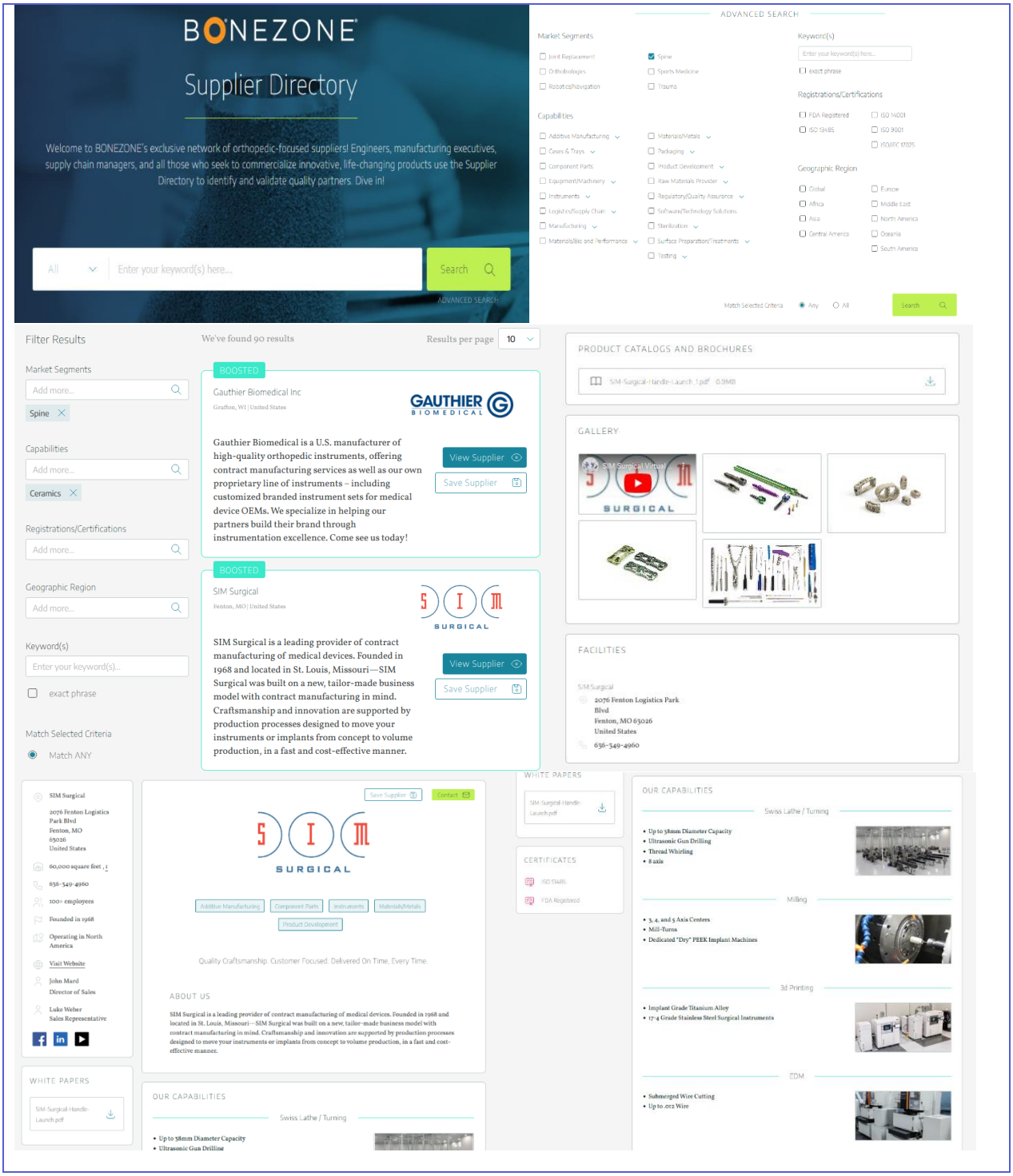


Figure 63. Annex - Screenshots from BONEZONE