European Commission

JRC TECHNICAL REPORTS

Mapping Nanomedicine Terminology in the Regulatory Landscape

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2018

Joint Research Centre

EUR 29291 EN

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JRC112224

EUR 29291 EN

PDF	ISBN 978-92-79-89872-3	ISSN 1831-9424	doi:10.2760/753829
Print	ISBN 978-92-79-89873-0	ISSN 1018-5593	doi:10.2760/404274

Luxembourg: Publications Office of the European Union, 2018

How to cite this report: Quirós Pesudo, L.; Balahur, A., Gottardo, S., Rasmussen, K., Wagner, G., Joanny, G. and Bremer-Hoffmann, S., *Mapping Nanomedicine Terminology in the Regulatory Landscape*, EUR 29291 EN; Publications Office of the European Union, Luxembourg, 2018, ISBN 978-92-79-89872-3, doi:10.2760/753829, JRC112224

Contents

Foreword

Highly innovative products resulting from emerging technologies are usually accompanied by the generation of new terms, concepts and definitions, which may be used ambiguously by various stakeholders having diverse interests, coming from different backgrounds and/or various regions in the world. A typical example of generation of a new and complex terminology is the application of nanotechnology in health. Such nanotechnology based products - often called nanomedicines - can be based on a variety of materials, are unique in their design and can have specific size related physicochemical properties and biological effects. In recent years, the growing number of submissions of nanomedicines to regulatory bodies has led to the development of a new vocabulary in the regulatory domain which has not yet been harmonised between the various competent authorities worldwide. This can cause difficulties regarding the mutual acceptance of data requiring a clear understanding of the scientific/technical vocabulary by the various parties.

The Nanomedicines Working Group of the International Pharmaceutical Regulators Forum (IPRF) acknowledged the relevance of terminology in the field and the need to map and compile the most relevant terms used in the regulatory domain. As a member of the working group, the European Commission's Joint Research Centre (JRC) has taken the lead to identify and describe the most relevant keywords used by various stakeholders. In order to obtain a bigger picture of currently used keywords in the field of nanomedicine, the JRC has applied automated text and tech mining tools for the identification of the relevant terms before manually extracting and compiling the most relevant terms used by the partners of the IPRF Nanomedicines Working Group in 2016. The present report aims to provide a useful basis for discussion among experts and efforts towards terminology harmonisation in the field of nanomedicine. It is outside the scope of this report to present an official terminology or glossary for nanomedicine.

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Abstract

A common terminology is essential in any field of science and technology for a mutual understanding among different communities of experts and regulators, harmonisation of policy actions, standardisation of quality procedures and experimental testing, and the communication to the general public. It also allows effective revision of information for policy making and optimises research fund allocation.

In particular, in emerging scientific fields with a high innovation potential, new terms, descriptions and definitions are quickly generated, which are then ambiguously used by stakeholders having diverse interests, coming from different scientific disciplines and/or from various regions. The application of nanotechnology in health -often called nanomedicine- is considered as such emerging and multidisciplinary field with a growing interest of various communities.

The Nanomedicines Working Group of the International Pharmaceutical Regulators Forum (IPRF) has been established in 2009 in order to discuss key issues related to the regulation of nanomedicines such as the definition of nanotechnology, standards, biocompatibility, risk/safety assessments and labelling. Since these objectives are also of interest for the European Commission's Joint Research Centre (JRC), the JRC has joint the group in 2015.

In order to support a better understanding of terms used in the regulatory domain, the IPRF has prioritised the need to map, compile and discuss the currently used terminology of regulatory scientists coming from different geographic areas. The JRC has taken the lead to identify and compile frequently used terms in the field by using web crawling and text mining tools as well as the manual extraction of terms. Websites of 13 regulatory authorities and clinical trial registries globally involved in regulating nanomedicines have been crawled. The compilation and analysis of extracted terms demonstrated sectorial and geographical differences in the frequency and type of nanomedicine related terms used in a regulatory context. Finally 31 relevant and most frequently used terms deriving from various agencies have been compiled, discussed and analysed for their similarities and differences. These descriptions will support the development of harmonised use of terminology in the future.

The report provides necessary background information to advance the discussion among stakeholders. It will strengthen activities aiming to develop harmonised standards in the field of nanomedicine, which is an essential factor to stimulate innovation and industrial competitiveness.

Glossary

Term	Definition
Author keywords	Author keywords are the keywords attributed by the authors to their publications and retrieved by the Tool for Innovation Monitoring (TIM) technology.
Automatic keyword	Automatic keywords are terms generated automatically by natural language processing algorithms from a bibliographic dataset created by the Tool for Innovation Monitoring (TIM) technology.
Automatic Term Recognition	Automatic Term Recognition focuses on the extraction of words and multi-word expressions that are significant for a given domain. The roots of Automatic Term Recognition date back to late 80s when the need for automatic extraction of terminological units from specialized texts became acute in various fields [4].
Bibliographic metadata	Bibliometric study involves the analysis of bibliographic metadata linked to scholarly publications. Such metadata, which include authors' affiliations, associated keywords, funding and citation information, can be used to monitor trends in the scientific development of a research domain, determine the impact of research funding, compare research performance across different institutions, document changes in the research workforce, identify emerging areas of research focus and predict future research success [7].
Bibliographic search engine	A bibliographic search engine is an information retrieval system designed to help find information stored on a bibliographic database.
Expanded lexical query	Expanded lexical query can help to identify records lying near the boundaries of emerging and legacy technologies. This step makes substantial use of precision and recall indicators rather than relying solely on expert judgment.
Natural Language Processing (NPL)	Natural Language Processing is a theoretically motivated range of computational techniques for analysing and representing naturally occurring texts at one or more levels of linguistic analysis for the purpose of achieving human-like language processing for a range of tasks or applications [3].
Publications dataset	Publications dataset is the name given in this report for the construction of a dataset of different types of publications (including article papers, grant reports and patents) related to a specific topic, e.g. nanomedicine, using the "Tools for Innovation Monitoring" (TIM) tool, developed by JRC.

Search string	A search string is a combination of keywords, truncation symbols, and Boolean operators you enter into the search box of a library database or search engine [6].
Term discrimination	The term discrimination value of an index term has been proposed as a quantitative measure of the extent to which that term can discriminate between documents in bibliographic databases. Indicates to what degree a set of terms can aid to distinguish one scientific domain from others.
Tech mining	Tech mining is the application of text mining tools to science and technology information, informed by understanding of technological innovation process. Tech mining has roots in content analysis, bibliometrics and text mining [2].
Text mining	Text mining is defined as the automatic discovery of new, previously unknown, information from unstructured textual data. This is often seen as comprising of three major tasks: information retrieval (gathering relevant documents), information extraction (extracting information of interest from these documents), and data mining (discovering new associations among the extracted pieces of information) [1].
Unstructured text	While structured data is readily available for information and knowledge extraction, unstructured information, for example obtained from a collection of text documents cannot be directly utilized for such purposes. Most text documents are written in an unstructured manner, so classification has to be done on the basis of attributes such as presence or absence of keywords and their frequency of occurrence [8].
Wildcard character	It is a term modifier that allows the user to introduce flexibility in the terms used for a search. The character for wildcard is an asterisk ("*") and it is used to substitute any other character(s) in a string.

1 Introduction

The application of nanotechnology in the health sector impressively demonstrates how new technologies can have an impact on society. The opportunities provided by nanotechnology in medicine were already envisaged by Richard Feynman in his lecture "There's Plenty of Room at the Bottom" given to the American Physical Society meeting at Caltech on December 29, 1959 [9]. Nanotechnology is now seen as an emerging tool in the health sector that offers many possibilities to revolutionize the healthcare sector through nanotechnology-enabled formulations in imaging, diagnostics, therapeutics, regenerative medicine and medical devices. There is an increasing trend of nanomedicines seeking for approval of clinical trials and market authorisations. Currently, the regulatory community is building expertise on how to best evaluate the next generation of nanomedicines and various regulatory bodies have published specific guidance. However, the terminology used in the various documents deriving from various regions is not always harmonised and as such can contribute to misunderstandings regarding the mutual acceptance of data in different countries [10]. A harmonisation of the regulatory practice for this new product class requires a common understanding of the terminology used by the various parties.

In 2013, the OECD published the results of a survey aiming to provide information on regulatory approaches, legislative regimes and government-sponsored regulatory-science research in food and medical products that involve the application of nanotechnology [11]. The report elucidates that nanotechnology based medical products are generally covered under existing national and/or regional legislative and regulatory frameworks for medical products. None of the 12 responding international regulatory authorities reported to have specific regulations for nanotechnology based medical products. However, some regulatory agencies, including the European Medicines Agency, have started to tailor the regulatory practice by publishing a variety of guidance for product developers addressing the evaluation of nanospecific properties in nanomedicines [12]. In addition, some regions are facing a substantial increase in the submission of nanotechnology based products aiming to enter into clinical applications or seeking market authorisation [13]. A harmonised terminology would facilitate the sharing of experiences and the development of common practices between authorities.

Moreover, a mutual understanding of terms is essential for the communication between various stakeholders in order to enable information sharing, collaborative scientific work and common standards, as well as to assist industry in the translation of research in nanotechnology into clinical applications [14]. Satalkar et al. (2015) concluded that a clear and consistent definition of terminology in this area would contribute to generate a trusted environment among stakeholders (researchers, industry, clinicians, regulators and patients) and would be critical to foster an ethical research and transparent translational nanomedicine [14]. Tinkle et al. (2014) explained how regulatory communities are challenged by a confusion of definitions for nanomaterials and nanotechnology-enabled products and by limited standard nomenclature and lack of reference materials, also highlighting the importance of a common terminology in a harmonised regulatory approach [15]. However, there are only few regulatory relevant documents available which consider the application of nanotechnology for medical products, and most of the available glossaries refer to technical terms. Several national and international organisations have contributed to the terminology and standards for the application of nanotechnology in the health care sector e.g. British Standards and ISO (see section 2.2.3). These terminologies, harmonised or not, are intended to be used in broad contexts by the health sector, but definition of general terms, which may be needed in the regulatory landscape, may be lacking and may not always reflect the increase of terms and synonyms, and diversity of descriptions that regulators may encounter.

The International Pharmaceutical Regulatory Forum (IPRF) has established a working group on nanomedicine to provide a platform for exchanging information and advance the regulatory science in this field. One objective of the IPRF working group is to establish a common understanding of the current terminology used by the involved regulatory bodies. The European Commission's Joint Research Centre has taken up the task to compile and map the terminology currently used by different stakeholders.

Usually the construction and expansion of terminology in emerging scientific fields, such as nanomedicine, begin in scientific publications with terms that represent basic elements of knowledge concepts, followed by other areas needing terminology for communication, such as manufacturing, marketing, clinical research, regulatory practice or information to the general public [16][17]. The multidisciplinary nature and rapid evolution of nanomedicine also lead to the continuous generation of new terms, which, however, leads to ambiguity and confusion for existing definitions, both in the scientific and regulatory landscape.

The aim of the JRC work was i) to develop an unbiased methodology allowing to monitor the growing terminology of an innovative field such as nanomedicine; ii) to describe in an unbiased manner the growing terminology in the emerging field of nanomedicine used by different stakeholders (scientists, regulators, industry) and iii) to select and describe the most frequently used terms by the various regulatory bodies.

This information may provide a basis for future discussion of a harmonised or convergent terminology.

In order to avoid any bias in the selection of the most relevant terms, tech and text mining methods, including the automatic extraction of terms used in the regulatory, clinical and patent landscape have been explored in this report. In addition, the report builds on previously developed methodologies, such as the use of modular keyword sets. These keyword[1] sets have been used in the field of bibliometrics to analyse emerging trends of nanotechnology, to identify trajectories of nanotechnology publications and research funding sponsorships, as well as active nanotechnology research in the scientific literature [7]. The established keyword training set that is specific to nanomedicine, is covering two categories of terms: 1) general terms describing the field, and 2) specific terms[1], describing scientific/technical terms for materials or final products used in the research or application of nanomedicine. The keywords were used as the main tool to identify the implementation of specific terminology and information on nanomedicine in relevant information sources, such as the regulatory authorities' websites.

Aims and Objectives of this compilation

Aims:

- Development of an unbiased methodology allowing the extraction of terms with regulatory relevance in the innovative field of nanomedicine

- Selection and description the most frequently used terms in regulatory documents

Objectives:

- Construction of a keyword set based on specialised scientific literature

- Mapping the nanomedicine keyword set in information sources of regulatory relevance

- Compilation of descriptions for a selection of terms from relevant documents

[1]The words keywords and terms are interchangeably words throughout this report.

2 Methodology

2.1 Information sources

2.1.1 Bibliographic databases

Scientific literature and related documents, such as scientific articles and project reports are an excellent source of data and knowledge to describe any given scientific field, and therefore to be used in a first attempt to identify and retrieve a field-related terminology. The following databases were analysed:

*Scopus from Elsevier, a large bibliographic database of peer-reviewed scientific publications including scientific articles, reviews, book chapters and conferences proceedings (**https://www.scopus.com/**). This database was automatically and manually queried using a specific bibliometric program and the website search engine, respectively.*

PubMed, a large citation database specialised in biomedical literature from the U.S. National Library of Medicine (MEDLINE), life science journals, and online books. This database was queried using a specific bibliometric program for automatic keyword extraction.

CORDIS, the European Commission's primary portal for results of EU-funded research projects published as briefs, report summaries and projects factsheets from Horizon 2020, Seventh Framework Programme and earlier funding programmes (http://cordis.europa.eu/). This database was queried using a specific bibliometric program for automatic keyword extraction.

2.1.2 Regulatory authorities' websites

The regulatory authorities' (RAs) websites are usually dedicated means of communication from regulators to health professionals and patients with the aim to inform on medical products. The medicines RAs websites have been also described as tools to contribute to the transparency of their procedures and activities to all stakeholders. These RAs websites provide access to diverse information on safety, efficacy, and quality of health care products, on regulatory requirements and guidance [22]. A complete understanding of the specific terminology used by these different organisations involved in the regulation of nanomedicine products is particularly important for a future harmonisation exercise, to enhance the discussion on this topic and strengthen a potential global regulatory convergence for nanomedicines. 14 websites of regulatory agencies participating in the IPRF working group Nanomedicine have been explored by regulatory authorities in order to analyse the content and the use of specialised nanomedicine terminology (**Table 1**).

Table 1. Regulatory authorities' websites explored in this study.

Country	Regulatory authorities	Website (English version)	Regulate or support regulation
Australia	Therapeutic Goods Administration (TGA)	www.tga.gov.au	**Medicines** **Medical devices** Cosmetics Biologicals Blood and tissues
Brazil	Brazilian Health Surveillance Agency (ANVISA)	portal.anvisa.gov.br/english	**Medicines** **Medical devices** Sanitizers Pesticides Food Cosmetics Blood, tissues and organs Tobacco
Canada	Health Canada, Health Products and Food Branch (HC)	www.canada.ca	**Drugs** **Health Products** Food
European Union	The European Medicines Agency (EMA) Directorate General for Health and Food Safety (DG SANTE)	www.ema.europa.eu/ ec.europa.eu/health/location_en	**Medicinal products** for human and veterinary use
	Directorate General for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW)	ec.europa.eu/growth/index_en	Medical devices
Japan	Ministry of Health, Labour and Welfare (MHLW)	www.mhlw.go.jp/english/	**Pharmaceuticals** **Medical devices**
	Pharmaceuticals and Medical Devices Agency (PMDA)	www.pmda.go.jp/english/	
Republic of Korea	Ministry of Food and Drug Safety (MFDS)	www.mfds.go.kr/eng	**Drugs** **Medical devices** Food Agro-Livestock and Fisheries Biologics Cosmetics
Russian Federation	Roszdravnadzor (Federal Service for Control over Healthcare and Social Development)	www.roszdravnadzor.ru/en	**Medicines** **Medical devices**
Singapore	Health Sciences Authority (HSA)	www.hsa.gov.sg/	**Western medicine** **Medical devices** Complementary Health Products Cosmetics Tobacco control
Switzerland	Swiss Institute of Therapeutic Products (Swissmedic)	www.swissmedic.ch/swissmedic/en/home.html	**Medicinal products** **Medical devices**
Taiwan	Taiwan Food and Drugs Administration (TFDA)	www.fda.gov.tw/EN/index.aspx	Human drugs Medical devices **Cosmetics** **Food**
United States of America	U.S. Food and Drug Administration (FDA)	https://www.fda.gov/	Drugs Medical devices **Food** **Radiation-emitting products** **Vaccines, blood and biologics** **Animal and Veterinary** **Cosmetics** **Tobacco Products**

2.1.3 Clinical trial registries database

Clinical trials are defined *as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.*[2]. Clinical trials are registered in specifically designed databases that serve as an information platform for researchers, clinicians, regulators, industry and patients. This information platform aims to improve transparency and data quality, avoid unnecessary duplication of studies, and foster collaboration.

In order to capture the terminology that describes the application of nanotechnology for health products in clinical trials, the International Clinical Trials Registry Platform (ICTRP) that is hosted by the World Health Organisation (http://www.who.int/ictrp/en/) has been analysed. This platform gathers datasets of clinical trials from 17 international registries including relevant sources such as ClinicalTrials.gov, the European Union Clinical Trials Register and the Japan Medical Association Clinical Trials Register (JMACTR) (**Table 2**).

Table 2. Registries and number of clinical trials containing nanomedicines

Registries	Websites	N° of clinical trials with nano-terms
Australian New Zealand Clinical Trials Registry	www.anzctr.org.au	19
Brazilian Clinical Trials Registry (ReBec)	www.ensaiosclinicos.gov.br	4
Chinese Clinical Trial Register	www.chictr.org.cn/abouten.aspx	47
ClinicalTrials.gov	www.ClinicalTrials.gov	464
Clinical Trials Registry - India	www.ctri.nic.in	28
EU Clinical Trials Register	www.clinicaltrialsregister.eu	96
German Clinical Trials Register	www.germanctr.de	9
Pan African Clinical Trial Registry	www.pactr.org	3
Thai Clinical Trials Registry	www.clinicaltrials.in.th	5
The Netherlands Trial Register (NTR)*	www.trialregister.nl/	23

Data retrieved in November 2016. *Clinical trials registered under NTR identification have been annotated under EudraCT registry after this analysis, where text mining for the prefix "nano*" was performed, including using term modifiers such as wildcard characters ("*" or "?") and Boolean operators (AND, OR, NOT).

This database offers information on clinical and interventional trials of several products including drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care or environmental epidemiological studies. Also, ICTRP uses an unambiguous trial identification to avoid duplication of the registration of results, i.e. trials that are registered in more than one registry database. Another reason for the selection of this database was the easiness to manually extract information using the website's search engine. ICTRP allows the manual search for the prefix *"nano*"* using term modifiers such as wildcard characters (*"**" or *"?"*) and Boolean operators (AND, OR, NOT). This facilitates the extraction of nano-prefixed terms and the exclusion of unwanted terms. The data from ICTRP was retrieved in November 2016.

2.1.4 Patent database

Patent databases are an important source of information as state-of-the-art information for the development of new products, for exploring responses to technical problems or

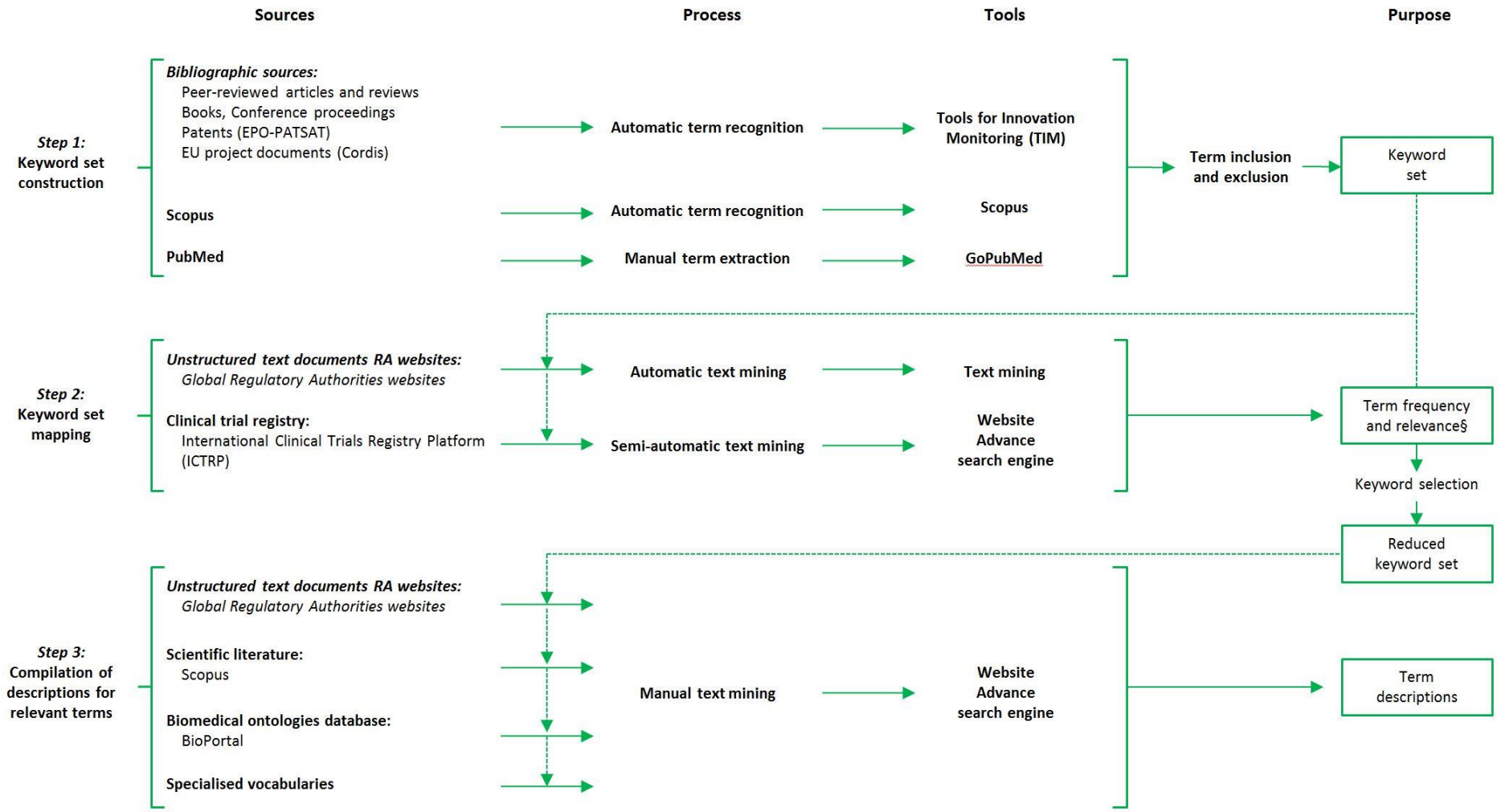
[2] http://www.who.int/ictrp/en/

for regulators and policy makers to improve their national innovation systems, for example investing in new innovation infrastructures or targeting research funding programs [18]. The structure of these technical documents are similar to scientific publications, including an abstract, background information on the technology patented, methodology, and bibliography related with the technology. Patent information on nanomedicine products may include description of the composition, production methods, targeting, or methods of use [19].

EPO-PATSTAT

EPO-PATSTAT, a database that contains bibliographic and legal status data on published European and Euro-PCT (Patent Cooperation Treaty) patent applications launched by the European Patent Office (EPO) in 2016 (https://www.epo.org/searching-for-patents/business/patstat.html). This database was queried using a specific bibliometric program for automatic keyword extraction. This database was queried using a specific bibliometric program for automatic keyword extraction.

Figure 1 Overview of the methodological approach



§Relevance refers not only to the assessment of weight of a given term in the pool of scientific publications but also to terms that are not highly frequent but still considered as relevant for the ongoing discussion. The report refers in particular to terms that are mentioned by specific regulatory agencies but not present in others (e.g. nanosimilars). RA= regulatory authorities and agencies

2.2 Data collection and analysis

The applied methodology consisted of three steps illustrated in **Figure 1**: 1) building a "keyword set" via automatic and manual extraction of keywords relevant to nanomedicine from specialised scientific literature (bibliographic databases and European patents); 2) applying the identified keyword set for mapping and analysis of the nanomedicine keyword set in documents that have relevance in a regulatory landscape, such as those available from regulatory authorities' websites and clinical data registries, and 3) manual selection and compilation of descriptions for a selection of relevant terms from information sources with regulatory relevance.

Due to the nature of the methods and tools used to extract and map the nanomedicine keyword set, the following types of information sources in the different steps have been explored (**Figure 1**). Information on the time period of the data collection and analysis is summarised in **Table 3.**

Table 3. Overview of data collection and analysis timeline by source

Source	Tool	Process	Period
Bibliographic sources: **Scopus database, CORDIS, EPO-PATSTAT**	Tools for Innovation Monitoring (TIM): TIM technology editor	Publication dataset creation Automatic keyword extraction	Year of publication 1996-2016 October 2016
Bibliographic sources: **PubMed database**	GoPubMed	Automatic keyword extraction	October 2016
Bibliographic sources: **Scopus database**	Website advance search engine	Manual keyword extraction from review articles	October 2016
Regulatory authorities websites	Web crawlers	Web crawling and data collection	June 2016- March 2017
	Text mining	Term descriptions collection	November 2015- June 2017
Clinical trials registries	Website advance search engine	Semi-automatic keyword extraction	November 2016

2.2.1 Step 1: Keyword extraction and keyword set construction

The first step in this methodological approach aims to identify a set of keywords related with nanomedicine in an unbiased manner, which is used as a tool to explore the impact of nanomedicine terminology in the various information sources with regulatory relevance. In order to build a reliable keyword set on nanomedicine, a combination of techniques and tools used in the field of bibliometrics have been applied [20, 21].

A specialised dataset of documents has been created by using the *Tools for Monitoring Innovation (TIM) technology* editor and *GoPubMed* as bibliographic search engines. The dataset has taken a 20 years publication period (from 1996 to 2016) into account which included scientific publications, EPO patents and project reports from bibliographic databases containing the keyword *"nanomedicine*"* either in the title, abstract, author keyword list or in the text corpus. The application of automatic term recognition algorithms on the metadata (e.g., title, author keyword list, abstract) and body text of the specialised documents aids to harvest a list of the most relevant and frequent

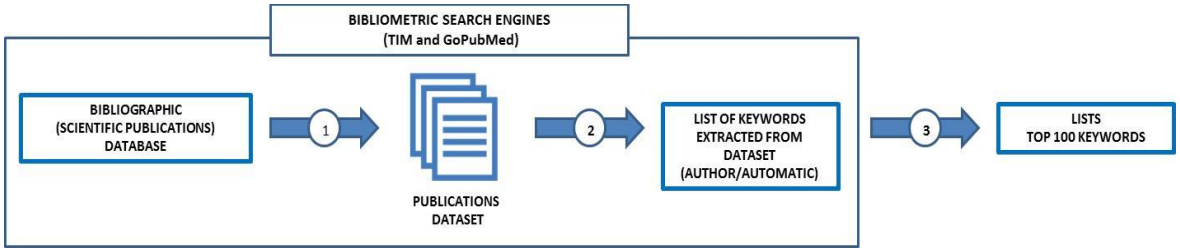
terminology, that allows to profile this field and create an initial nanomedicine-specific keyword set. Ideally, this nanomedicine keyword set should contain specific nano-prefixed terms, specific non nano-prefixed terms and multiword terms describing materials, processes or areas of application of this field.

Then, to complement this initial keyword set, a literature review and manual extraction of keywords from the most cited reviews on the topic (according to the CiteScore[3] function from Scopus) aiming to capture additional terms used to define nanomedicine products or materials has been performed.

2.2.1.1 Automatic keyword extraction

The automatic keyword extraction is defined as the process of identifying sets of keywords (single words or multiword terms) from a document, which can characterise the topic addressed in that document. The process of automatic keyword extraction used in this study is shown in **Figure 2** and is partly based on an *expanded lexical query* methodology as applied in previous works to assess emerging sciences and technologies [22]. Using two bibliographic search engines (see below), several bibliographic databases (section 3.1.1) with a general search string have been queried (i.e., *"nanomedicine*"*, the wildcard "*" was used to capture term variants). By identifying this search string in the bibliographic metadata (i.e., title, abstract, author keyword list) or in the text corpus of the documents, these tools create a specialised (or topic-targeted) dataset of documents (1 in **Figure 2**). On this target document dataset, called in this report "publications dataset", these tools apply automatic term recognition algorithms on the bibliometric metadata resulting in a list of the most frequent and relevant terminology profiling this topic (2 in **Figure 2**). To generate a reasonable representation of the topic terminology, when possible, a cut off of the top 100 keywords was applied resulting from the automatic extraction of keywords present in the publications dataset (3 in **Figure 2**).

Figure 2. Process of automatic keyword extraction



Description of the process for keyword extraction using bibliometric search engines: 1) query of bibliographic databases using specific search strings (e.g. *nanomedicine**) resulting in a number of topic publications that form the publications dataset; 2) application of algorithms to extract topic keywords; 3) manual extraction of top 100 frequent (hit counts) or relevant keywords (see **Annex 1**).

2.2.1.2 Bibliographic search engines

One component of the selected methodology was the identification of appropriate bibliographic search engines to survey the bibliographic databases listed in section 2.1 (i.e. Scopus from Elsevier, PubMed, and CORDIS). The selection criteria were: first, the search engines should be able to explore databases specialised in the field of interest, and second, they should include a tool for automatic extraction of keywords associated to the search results as well as provide quantitative data on keyword occurrence (hit counts: number of documents including a given keyword in its metadata).

As a result, two online search engines have been selected: 1) *Tools for Monitoring Innovation (TIM)* technology editor, an online search engine developed by the JRC for European Commission staff member that allows its users to create and visualise datasets

[3] https://www.elsevier.com/solutions/scopus/features/metrics

about specific technological issues. This tool gathers together datasets such as patents, scientific publications, and EU grants (www.timanalytics.eu); 2) *GoPubMed*, a public web server which allows users to explore information from scientific publications in PubMed [23]. Each search engine provided a means of extracting nanomedicine-related terms in a distinct way and gave useful information for other components used in this study. Both programs combine full text analysis (identification of topic related keywords) and traditional bibliometrics methods (quantitative analysis of publications, citation analysis, or calculation of keyword frequency in the dataset). TIM also facilitates the visualisation of the keyword extraction results through word maps, also called keyword co-occurrence networks (KCO).

The methodology followed to extract keywords was the same for the two search engines (**Figure 2**). The list of keywords is presented either by how frequently they appear in these documents (hit counts) and/or, as in the case of TIM, by their relevance (estimated weight/importance of some keywords within the pool of the documents in the specific dataset).

Using TIM, also relevant terms for the search string *"nano* AND medical devices"* in addition to *"nanomedicine*" were* extracted.

Annex 1 contains supplementary information on these bibliographic search engines and the lists of keywords extracted with TIM and GoPubMed.

2.2.1.3 Manual keyword extraction

A manual keyword extraction was performed to complement the initial keyword set resulting from the use of the search engines TIM and GoPubMed, especially to capture terms that describe nanomaterials or molecular entities used in the field of nanomedicine. The manual extraction of keywords was applied to a number of review publications selected through a dedicated literature search. These types of publications usually summarise the state-of-the-art on a topic and provides lists of terms and descriptions of the type of materials under investigation. They were therefore chosen to extract keywords characterising the investigated nanomaterials or the medicinal products containing nanomaterials that are used, which are not commonly extracted by engines.

In order to select a list of reviews on nanomedicine, the bibliographic database Scopus with the same search string as for the automatic keyword extraction (i.e. *"nanomedicine*"*) was queried and 50 review publications were identified. These review publications met the following three criteria: i) reviews with the highest number of citations; ii) reviews with open access to the full text; iii), publications that provide an explicit list of nanoscale materials or molecular entities in the body of the publication (e.g., tables or figures containing terms that describe materials, such as *dendrimers*, or *liposomes*, or terms to describe material classes, such as *inorganic nanoparticles*, or *polymer based nanocarriers*). The terms of interest were manually extracted from these publications, applying expert judgement, and are listed in **Annex 3** (**Table 18**).

2.2.1.4 Keyword sets construction

To be able to map the information sources, two keyword sets were constructed and applied depending on the type of mapping approach. A comprehensive keyword set was constructed for automatically map the regulatory authorities using text mining tools; a second reduced keyword set was built to explore those information sources where, due to technical limitations, a manual search using search engines had to be performed instead. This reduced keyword set was also used for the compilation of descriptions.

In order to construct the keyword set for automatic mapping, keywords that have been automatically extracted from publications datasets with the search engines TIM and GoPubMed (List of keywords in **Annex 2**) were merged with keywords manually captured from the literature search on reviews in Scopus (**Annex 3**).

The cut off value considered the top 100 most frequently occurring author keywords and relevant keywords (**Annex 2: Table 11** and **Table 12**, respectively) extracted automatically with TIM using *"nanomedicine*"* as search string and complemented with top 100 author and relevant keywords extracted with the search string (*"nano* AND medical devices"*) in a 20 years publication range (from 1996 to 2016) (**Annex 2: Table 13** and **Table 14)**. The selection of the 100 top frequent terms cut off was based on results from previous bibliometric studies for research domain analysis [16]. These lists of terms were merged and complemented with the list of terms extracted from GoPubMed querieng *"nanomedicine*"* as search string (**Annex 2**: **Table 15** and **Table 16**). Then, the terms retrieved from the manual extraction were added (**Annex 3: Table 17**). The merged list was consolidated eliminating duplicates and particular plural forms (for those cases in which the meaning of the terms were not affected by their plural form). Expert judgement was applied to eliminate general terms not specific for nanotechnology and to ensure the inclusion of some specific terms.

Although the use of text-mining tools for mapping of regulatory authorities' websites, in step 2, allowed easily parsing nano-prefixed terms in a text corpus, the keyword set was adjusted including specific nano-prefixed terms to reduce the identification of nano-prefixed terms that are unspecific to the health sector during the mapping exercise. For example, many regulatory agencies surveyed in this study in step 2 also address nanotechnology products for applications other than nanomedicine, such as cosmetics or foods, and a general search for *"nano*"* may retrieve many terms that are not specific to nanomedicine. General nano-prefixed terms referring to metrics, such as *nanometre* or *nanomolar*, were excluded from this final keyword set.

A reduced keyword set, for manual mapping, was built considering the term frequency results from the extraction of publications dataset's keywords and from the analysis of terminology in the regulatory agencies. These terms were either more frequently mentioned in the regulatory authorities' websites analysed in the following Step 2, or relevant because their uniqueness, i.e. terms used by only one specific regulatory authority. As in the comprehensive keyword set, the reduced keyword set includes nano-prefixed and non nano-prefixed terms.

2.2.2 Step 2: Methods for mapping nanomedicine terminology

In the context of this report, *mapping* refers to the process of mining, identification and analysis (term frequency and/or term relevance) of the use of nanomedicine-related terms in various sources of information with regulatory relevance.

In step 2, text mining and bibliometric methods were applied, such as analysis of keyword occurrence frequency and the mapping of selected nanomedicine-related terms in different technical documents with regulatory relevance. Raw texts were extracted from a selection of regulatory authorities' websites using web crawlers creating a websites documents dataset, which was then searched by the keyword set generated in step 1 to produce a list of matching documents for each term of the keyword set. In addition, keywords from the clinical trials registries database were manually extracted by using the advanced search engines offered by the databases, as it was not possible to extract raw data from these two databases. This section details the methodology followed in each approach.

It is important to point out that this report does not aim to show a quantitative mapping of terminology, but a semi-quantitative representation of the type and use of nanomedicine terminology in diverse sources of information.

In order to map the use of nanomedicine terminology in the regulatory landscape, unstructured text were extracted from 14 health-related regulatory authorities' websites participating in the Nanomedicine working group of the IPRF. The criteria to select these websites were: first, these regulatory agencies either regulate medicinal products, medical devices or both, and second, the websites provided information in English. The names and links of these authorities were obtained from the IPRF's website

(https://www.i-p-r-f.org/index.php/en/members/). In addition, the websites of two departments of the European Commission, the Directorate-General for Health and Food Safety (DG SANTE) and the Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW), were considered as they are responsible for EU policies on health products. **Table 1** in section 2.1.2 lists the regulatory authorities' websites surveyed in this study and the type of products that they oversee and regulate.

The described two-step approach for exploring the use of nanomedicine terminology in the regulatory authorities' websites is based on methodologies applied in previous bibliometric studies aimed to understand emerging technologies [24]. First, text-mining tools to extract unstructured information from the websites of interest were used. Second, the data generated in the previous step was queried with the keyword set constructed in step 1 to locate nanomedicine terms as well as calculate their occurrence in the text.

2.2.2.1 Web Crawling and metadata extraction

Using two different web crawlers, WinHTTrack WebSite Copier and Crawler4j, retrieved raw text from several document file formats including HTML, XML, MS Word, MS PowerPoint, MS Excel and PDF, posted in the selected regulatory authorities' websites were retrieved. 13 regulatory authorities' websites were successfully crawled but the crawling tools failed to extract information from the Japan's Pharmaceuticals and Medical Devices Agency (PMDA) due to technical problems with the translated English version. It cannot be excluded that the web crawlers might have failed to extract clear text from other websites in which English was not the official language.

2.2.2.2 Keyword set matching and analysis

Once the metadata from the regulatory authorities' websites was extracted, a series of analyses were undertaken to evaluate the information on nanomedicine provided by these platforms. For the data analysis, the number of documents (referred in this report as term frequency or hit counts) were calculated for a given keyword in the keyword set for each regulatory authority website as well as the frequency of the term within the total number of documents per regulatory authority website. The current report aims to describe the amount and the type of information provided on nanomedicine by each regulatory authority, capture the most frequently used nanomedicine-related terms, and identify those terms that were uniquely used by a particular regulatory authority. To assess the quality of the results and the type of information provided, manual text-mining was performed for relevant terms. This validation was especially appropriate for terms that were unique to certain authorities.

2.2.2.3 Mapping in clinical trials registries

Due to the technical challenges to crawl the data available from the International Clinical Trials Registry Platform (ICTRP) (see section 3.1.1), the ICTRP website's advanced search engine was used to explore the use of nanomedicine terminology in the ICTRP. Since it was clear that materials, products, or research procedures described in the ICTRP would correspond exclusively to the health sector to identify nano-prefixed terms the advance search engine was queried with the string *nano**. In order to map the use of non nano-prefixed terms, a reduced keyword set similar as performed in [25] (see **Table 5**) was manually introduced into the advance search engine. In this case, the number of trials found for each term is regarded as hit counts.

Figure 3 shows an example of the mapping approach used for the term *liposome*.

Figure 3. Screenshot of the ICTRP Search Portal results webpage using "liposome" as search string

World Health Organization

International Clinical Trials Registry Platform Search Portal

Home | Advanced Search | List By | Search Tips | UTN | ICTRP website | Contact us

Back to Search | Export to CSV | Export results to XML

1305 records for 972 trials found for: LIPOSOME (What is this?)

Show 10 records per page

1 2 3 4 5 6 7 8 9 10 ... >>

Recruitment status	Prospective Registration	Main ID	Public Title	Date of Registration	Results available
Not Recruiting	Yes	CTRI/2018/01/011550	A comparative study of Doxorubicin Hydrochloride Liposome Injection 20 mg/10 mL (2 mg/mL) in patients with a cancer of female organs that produce eggs	24-01-2018	Yes
Not Recruiting	Yes	CTRI/2018/01/011498	A comparative study of Doxorubicin Hydrochloride (Pegylated Liposomal) in patients with a cancer of female organs that produce eggs	23-01-2018	Yes
Not Recruiting	Yes	RBR-5r93wn	Comparison of the effect and toxicity between two options for the treatment of Mucosal Leishmaniasis: Miltefosin and Liposomal Anfotericin B	15/01/2018	
Not recruiting	Yes	NCT03393117	Bupivacaine Versus Liposomal Bupivacaine For Breast Pain Management After Breast Recontruction	26/12/2017	
Not recruiting	Yes	NCT03388749	Study of Liposomal Annamycin for the Treatment of Subjects With Acute Myeloid Leukemia (AML)	25/12/2017	
Recruiting	Yes	CTRI/2017/12/010926	Clinical Bioequivalence Study of Doxorubicin Hydrochloride Liposome Injection (IV) 2 mg/ml (50mg/m2) in Ovarian Cancer Patients whose disease has progressed or recurred after platinum-based chemotherapy under fasting conditions	20-12-2017	Yes
Recruiting	Yes	NCT03383198	Pectoralis (II) Block With Liposomal Bupivacaine vs Bupivacaine for Breast Surgery	19/12/2017	
Recruiting	Yes	ChiCTR-INR-17013961	A pilot randomized controlled trial for comparing decitabine in Combination With DT-PDCE versus DT-PDCE Alone in Subjects with Relapsed or Refractory Multiple Myeloma	2017-12-15	
Recruiting	Yes	NCT03387943	PLD Combined With Cisplatin in the Treatment of Advanced Poorly Differentiated Thyroid Carcinoma	11/12/2017	
Not recruiting	Yes	NCT03373591	Liposomal Bupivacaine in Bariatric Surgery	09/12/2017	

1 2 3 4 5 6 7 8 9 10 ... >>

Disclaimer: Trials posted on this search portal are not endorsed by WHO, but are provided as a service to our users. In no event shall the World Health Organization be liable for any damages arising from the use of the information linked to in this section. None of the information obtained through use of the search portal should in any way be used in clinical care without consulting a physician or licensed health professional. WHO is not responsible for the accuracy, completeness and/or use made of the content displayed for any trial record.

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Source: http://apps.who.int/trialsearch/Default.aspx (screenshot taken on February 2018)

To identify nano-prefixed terms, the database was queried to find terms in the clinical trial summaries matching *"nano*"*. The extensive search resulted in many unspecific terms, including terms indicating metrics (e.g. nanometre, nanomole, nanogram or nanosecond), product names (e.g. NanoKnife®, Nanotube®, NanOss Bioactive, or Nanette™), companies' names (e.g. Nanotherapeutics, Inc., Nanos Tim, Inc., Nano Bio Corporation, or NanoString Technologies, Inc.) and terms describing methodologies or techniques (e.g. Nanofiltration, or Nano-scintillator). These unspecific terms were excluded from this analysis. The remaining terms found in this search were analysed and the number of clinical trial registrations matching each reported term were calculated. As in the analysis of the publications dataset performed in step 1, each clinical trial document/registration extracted was considered as a hit count to estimate the term occurrence. Particle size description of the material under research is unavailable in most of the clinical trials registered; therefore, this analysis was based on the assumption that the materials described with a nano-prefixed term were at least smaller than 1,000 nm, based on the working definition of *nanomedicine* used at the European Medicines Agency (**Annex 5**: **Table 20**), the working definition of *nanomaterial* suggested by the U.S. Food and Drug Administration (**Annex 5: Table 22**), and the definition of *synthetic nanoparticles* present in medicinal products suggested by Swissmedic (**Annex 5: Table 26**).

2.2.2.4 Mapping in patent databases

The publications dataset extracted with the TIM tool includes also patents from EPO-PATSTAT which contain the keyword *nanomedicine* in their information. The analysis with TIM also reported the term frequency of the automatically retrieved keywords in these specific documents (see section 3.1.1) through language processing algorithms (step 1, section 3.2). See results in section 3.2.4.

2.2.3 Step 3: Methodology for collection of term descriptions

The compilation of term descriptions or definitions was performed by manually searching terms from the reduced keyword set (**Table 5**) in the regulatory authorities' websites, previously mapped, and other relevant sources including specialised glossaries or scientific publications.

As previously proposed in other glossaries or terminologies[4], this report classifies terms in two categories: *general terms* referring to terms that describe the field of nanomedicine and *specific terms* to describe molecular entities, structural entities or methodologies used in the application of nanotechnology in medicine.

2.2.3.1 Manual collection of descriptions from regulatory authorities' websites

Regulatory authorities' websites are an important source of information to identify terms and descriptions within a regulatory context. In addition to mapping the nanomedicine-related keyword set automatically, descriptions of the selected terms were also manually retrieved by using the search function at the same webpages.

Many regulatory authorities assess and monitor activities related to products other than health care products, such as food, cosmetics, or tobacco that also benefit from the application of nanotechnology. In this report only those descriptions or definitions that apply to the regulation of health products were selected. Care was taken to exclude documents and terminology exclusively related to such other topics during the mapping and descriptions collection, and, when available, an advanced search engine to refine the search was used. Also, when information from English language websites was scarce, a search in Google or/and Google Scholar was performed, indicating the regulatory authority's name/abbreviation and the term of interest (e.g. search string: *"FDA Taiwan AND nanomedicine*"*).

2.2.3.2 Manual collection of descriptions from other sources

Terms describing materials or formulations within the regulatory authorities' websites generally lacked descriptive information. To fill this gap, descriptions from existing health-related terminologies, vocabularies, glossaries, and scientific ontologies, both standardised and not standardised were extracted. **Table 4** summarises the information about the sources referred in this section.

2.3 Internationally activities contributing to a standardised terminology

Several national and international organisations are developing terminology and standards for the application of nanotechnology in the health care sector. In 2007, the British Standards Institution (BSI) published a Publicly Available Specification (PAS) on terminology for medical, health and personal care applications of nanotechnology (PAS 131). A PAS is published to respond to an urgent market need, representing either the consensus of the experts within a working group, or a consensus in an organization external to ISO. PASs are published for immediate use and also serve as a means to obtain feedback for an eventual transformation into an International Standard. PASs have a maximum life of six years, after which they can be transformed into an International Standard or withdrawn[5].

In 2011, ISO published a new document entitled *Nanotechnologies -- Vocabulary -- Part 7: Medical, health and personal care applications* (ISO/TS 80004-7:2011) as part of a series of documents on nanotechnology-related vocabulary. This document refers to the use of nanotechnologies in medical diagnostics and therapeutics, terms related to the exploitation of material features for diagnostic or therapeutic purposes in relation to human disease. Aware of the need of a standard terminology in the field of nanomedicine, ISO also drafted a technical report on *Nanotechnologies-Framework for identifying vocabulary development for nanotechnology applications in human healthcare* that pursued to provide a taxonomic framework for the development of vocabulary for clinical applications in human healthcare (ISO/TR 17302, 2015).

[4] http://www.who.int/ipcs/methods/harmonization/areas/terminology/en/
[5] https://www.iso.org/deliverables-all.html#PAS

2.3.1 Glossaries and non-standardised terminologies

In recent years, much effort has been undertaken to develop controlled vocabularies[6] and scientific ontologies in biomedical fields. Terminology standardisation and data handling are both included as informatics components, which are essential to nanotechnology data-sharing and interdisciplinary communication. They enable easier data and protocol storage, information retrieval and modelling of data output.

In nanoinformatics, ontologies can be considered as a semantic framework representing also the nanomedical domain. The National Center for Biomedical Ontology has created BioPortal (http://BioPortal.bioontology.org), which is an open repository of biomedical ontologies that provides web-access to ontologies developed in different computer languages (e.g. OWL, RDF, OBO format and Protege frames). As the number of biomedical ontologies increases, so does the number of repositories that index and organize ontologies. BioPortal has indexed biomedical data sets available online such as ClinicalTrial.gov with ontologies in BioPortal. Considering BioPortal's wealth of information on descriptions for nanomedicine-related terms and aiming to complement the compilation of descriptions captured in documents relevant for regulatory purposes, BioPortal was used to extract descriptions of selected terms.

Table 4. List of terminologies, scientific ontologies and vocabularies used in Step 3 to manually collect term descriptions from other sources than regulatory authorities' websites

Source terminology /ontology	Acronym	Website	Description
International Organization for Standardization	ISO	www.iso.org	ISO is developing standards for terminology and nomenclature in the field of nanotechnologies under the technical committee ISO/TC 229 (Nanotechnologies). This TC is developing a series of vocabulary documents on nanotechnology, the ISO/IEC 80004 series: Nanotechnologies — Vocabulary. This series includes ISO/TS 80004-7:2015, Nanotechnologies — Vocabulary — Part 7: Medical, health and personal care applications, currently under preparation.
British Standards Institution	BSI	www.bsigroup.com	A Publicly Available Specification (PAS) is published to respond to an urgent market need, representing either the consensus of the experts within a working group or a consensus in an organization external to ISO. As with Technical Specifications, PASs are published for immediate use and also serve as a means to obtain feedback for an eventual transformation into an International Standard. PASs have a maximum life of six years, after which they can be transformed into an International Standard or withdrawn.
NanoParticle Ontology	NPO	purl.bioontology.org/ ontology/NPO	An ontology that represents the basic knowledge of physical, chemical, and functional characteristics of nanotechnology as used in cancer diagnosis and therapy (description in BioPortal).

[6] Controlled vocabularies are list of terms created to facilitate knowledge organisation (indexing) and information retrieval, e.g. MeSH (Medical Subject Headings in the U.S. National Library of Medicine: https://www.nlm.nih.gov/mesh/)

Table 4 (cont.)

Source terminology /ontology	Acronym	Website	Description
U.S. National Cancer Institute Metathesaurus	NCIm	ncim.nci.nih.gov/ncimbrowser/	Biomedical terminology database that covers most terminologies used by NCI for clinical care, translational and basic research, and public information and administrative activities (NCIm webpage).
National Cancer Institute Thesaurus	NCIt	ncit.nci.nih.gov/ncitbrowser/	Reference terminology for many NCI and other systems. It covers vocabulary for clinical care, translational and basic research, and public information and administrative activities (NCIt website).
Computer Retrieval of Information on Scientific Projects Thesaurus	CRISP	www.nlm.nih.gov/research/umls/sourcereleasedocs/current/CSP/	A terminology used for indexing biomedical information. It was developed by the National Institutes of Health for use in the CRISP database of research projects funded by the U.S. Public Health Service (PHS) (Source: CRISP website).
Medical Subject Headings	MeSH	www.nlm.nih.gov/mesh/	Hierarchically-organized terminology for indexing and cataloguing of biomedical information from various databases including MEDLINE/PubMed, other NLM databases as well as RxNorm database, and managing the curation of the UMLS and Snomed CT database (Source: MeSH website).
Chemical Entities of Biological Interest Ontology	CHEBI	www.ebi.ac.uk/chebi	A freely available dictionary of molecular entities focused on 'small' chemical compounds (Source: CHEBI webpage).
Neuroscience Information Framework (NIF) Standard Ontology	NIFSTD	purl.bioontology.org/ontology/NIFSTD	A set of modular ontologies that provide a comprehensive collection of terminologies to describe neuroscience data and resources (Source: NIFSTD website).
Physician Data Query Terminology	PDQ	www.cancer.gov/publications/pdq	Online source of cancer information that is developed and maintained by the National Cancer Institute (NCI). It contains cancer information summaries on a wide range of cancer topics; drug information summaries on many cancer-related drugs and drug combinations; and dictionaries of general cancer terms, drug terms, and genetics terms (Source: PDQ website).

In this report, the Medical Dictionary for Regulatory Activities (MEDDRA*), a medical terminology developed by the ICH* [International Conference on Harmonisation] *to facilitate sharing of regulatory information internationally for medical products used by humans*[7] *was consulted*; however, this dictionary does not include any of the selected terms. Using the MEDDRA search engine from its website, no nano-prefixed terms indicating the application of nanotechnology could be identified even if cross-checked by querying the MEDDRA ontology displayed in *bioportal.org*.

[7] http://www.ich.org/products/meddra.html

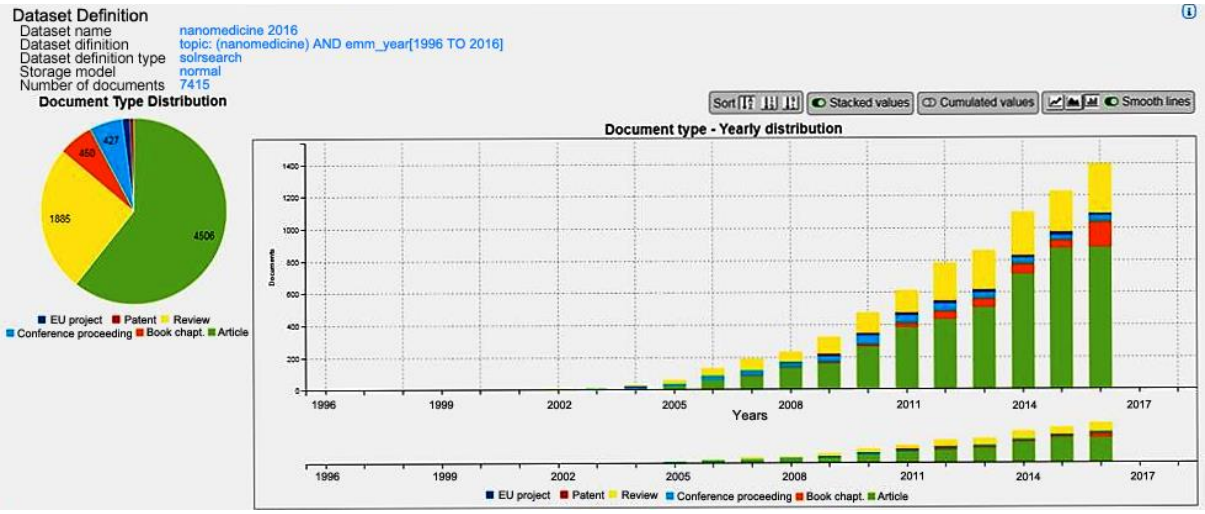
3 Results

3.1 Step 1: Construction of a nanomedicine keyword sets

3.1.1 Bibliometric analysis: capturing keywords in bibliographic sources

Querying TIM datasets using the search string *"nanomedicine*"* yielded a publications dataset of more than 7000 documents (data from 1996 to 2016), in which 98% were scientific publications from Scopus, and the remaining 2% were documents retrieved from the EU research projects platform (CORDIS) and patents (EPO-PATSTAT) (**Figure 4**). When applying algorithms for automatic keyword recognition to this dataset, TIM automatically extracted keywords from different sections in these publications (title, abstract, author keywords, and full text) resulting in a large pool of emerging terminology referring to the field of nanomedicine.

Figure 4. Screenshot of TIM describing the publications dataset for nanomedicine

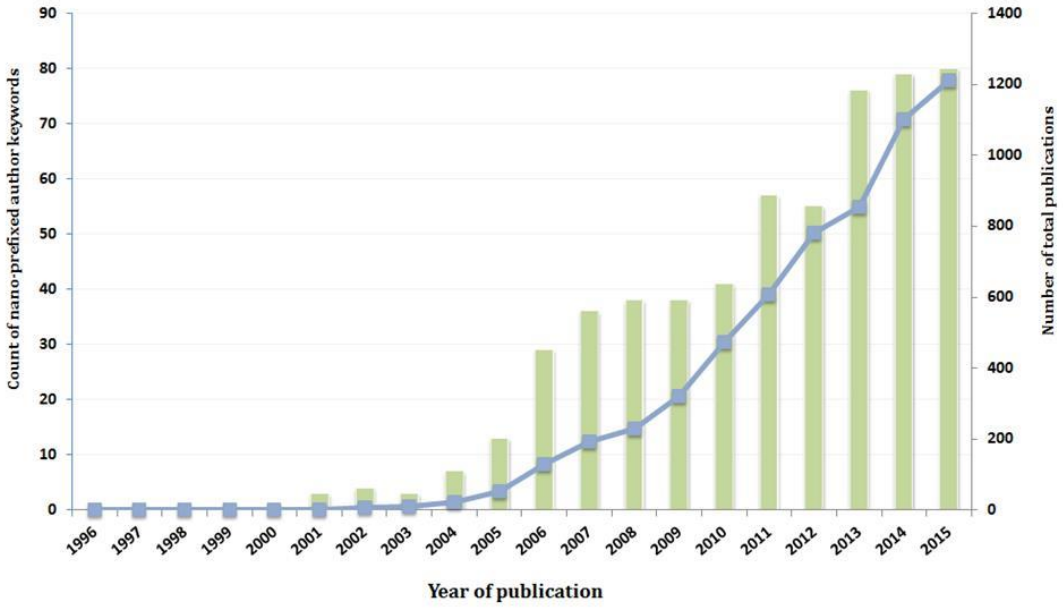


The bars represent the yearly distribution of publication records matching the search string "nanomedicine*" for the period of 1996 to 2016. The different colours identify the type of documents: scientific articles (green), book chapters (orange), conference proceedings (light blue), European granted projects (dark blue) and EPO patents (red). The pie chart on the left shows the type of document distribution in the publications dataset.
Source: http://tech.timanalytics.eu

3.1.1.1 Terminology expansion

From the publications dataset, 13084 author keywords were identified. These author keywords included spelling variants for each term, for example plurals (e.g., *nanomedicines*), use of capital letters (e.g., *Nanomedicine*), and use of hyphenation (e.g., Nano-medicine), therefore the list of genuinely different keywords would be significantly shorter. A general analysis of the use of nano-prefixed author keywords in the period 1996 to 2016 in the publications dataset showed that the number of scientific articles on nanomedicine increased as did the specialised terminology (**Figure 5**, blue line). This growth of nanomedicine records has been noted in many bibliometric studies when studying the evolution of terminology in nanotechnology [17].

Figure 5. Number of total scientific articles on nanomedicine and number of nano-prefixed author keywords by year of publication



In this period the number of scientific articles records mentioning the term nanomedicine continuously increased (blue line). The use of nano-prefixed terms showed a pronounced increase in the years 2006, 2011 and 2014, growing year by year and contributing to the expansion of a specialised terminology (green bars). Source: TIM (search string: "nanomedicine*" information source: Scopus)

This emergence of specialised terminology in the field was also confirmed through the term frequency analysis (number of documents with a given term), in which a few terms seemed to consolidate across the scientific articles although there was still a consistent generation of new terms (**Annex 2**).

This expansion of terminology in an innovation field can be visualised in the keyword co-occurrence network (KCO) (**Figure 6**). This network represents the 13084 author keywords (nodes) and 6297 co-occurrences or connections (edges) extracted from the publications dataset. Only few keywords, usually well established, general terms (*nanomedicine*, *nanotechnology*, *nanoparticle*, or *drug delivery*, *theranostics* or *nanobiotechnology*), are highly connected within the network.

Result 1: Frequency of author keywords used in the scientific literature

From more than 7000 scientific documents containing 13084 author keywords:

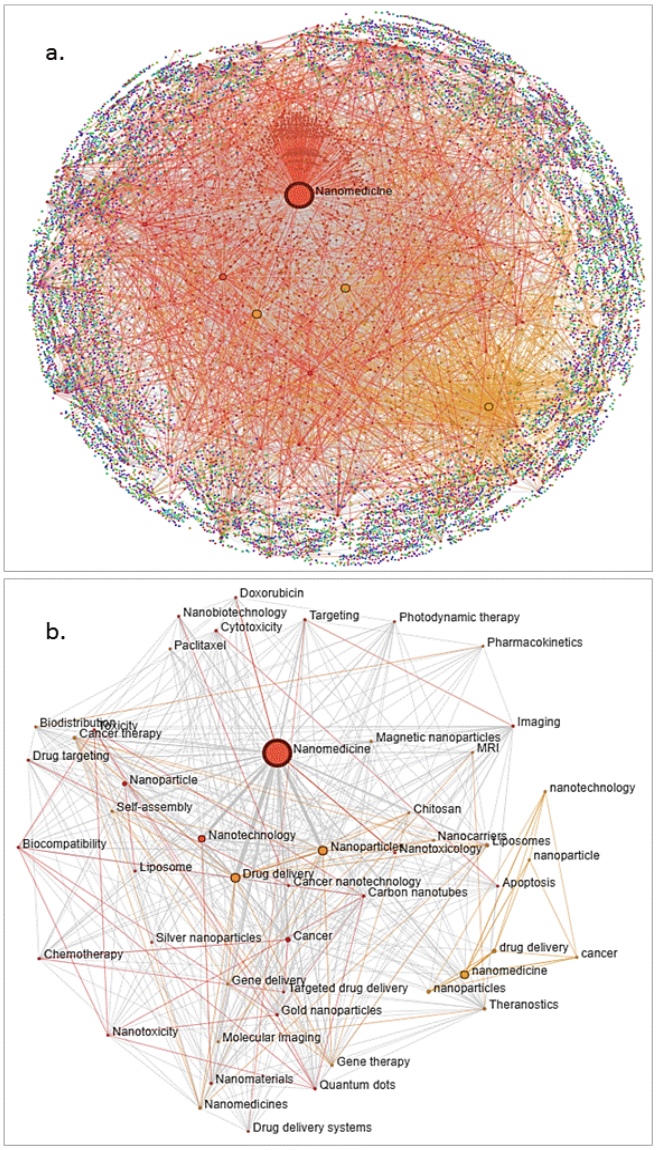
— More than 90% were mentioned in less than 5 scientific documents,

— Approximately 78% of these terms were used only in one scientific article,

— 2% were present in more than 10 documents, and out of these 20% were nano-prefixed terms,

— Only a few terms were used as author keywords in more than 100 scientific articles (i.e., *drug delivery*, *nanoparticle*, *nanotechnology*, *cancer*, and *liposomes*) (see **Annex 2**)

Figure 6. Term map related to the topic of nanomedicine. A. Network representing all author keywords extracted with TIM; B. Network of author keywords present in more than 50 scientific articles.



Each node represents a different keyword in the publications dataset, and the size of the nodes size is proportional to the respective keyword's frequency (number of documents mentioning a given author keyword); the edges represent the connection among keywords that are mentioned in the same documents, and the thickness of the edges represents the co-occurrence of the linked nodes (number of documents sharing keywords). In this case the different colours of the nodes do not reflect clear subtopics. Orange and red nodes are keywords that have been listed in at least 2 papers as author keyword; nodes of other colours, and placed in the network's outside, are keywords mentioned only in 1 paper. The network on the top (Figure 6, A) represents the KCO of all the author keywords extracted from the publications dataset. Keywords present in less than 5 documents correspond to the 86% of the total number of connections, which points out the expansion of the terminology in this field. *Source*: TIM (http://tech.timanalytics.eu; search string: "*nanomedicine**")

The list of the most frequently occurring author keywords (source: TIM) indicates the direction of the current research activities and can provide some foresight information on the nanomedicine field (**Annex 2**).

The top 50 most frequent author keywords in the publications dataset (**Figure 6**, B) included general terminology (*nanomedicine*, *nanotechnology*, or *nanoscale*) and specific terms describing the main applications of nanomedicine, potential targeted diseases, types of nanomaterials and nanotechnology-based products. For example, the term *drug delivery* was the most frequent author keyword mentioned in approximately 10% of the scientific publications; the terms *cancer* and *cancer therapy* were referenced in 5% of scientific articles in the dataset. This list also includes keywords related to the type of materials already in use or under research such as *liposomes*, *carbon nanotubes*, *gold nanoparticles*, *silver nanoparticles*, *quantum dots*, *magnetic nanoparticles*, *dendrimers* or *nanocarriers*. Other applications of nanomedicine identified in this list were for example *theranostics, imaging, gene therapy, tissue engineering* or *regenerative medicine*.

In addition, the 'discrimination' of terms was analysed, i.e. to what degree a set of terms can aid to distinguish one scientific domain from others [16]. Discrimination of terms identifies words that may have low frequency but still are important to reflect the field's innovation. Using Natural Language Processing (NLP) algorithms, "TIM" captured a set of automatic keywords present in distinct parts of the documents within the dataset. The occurrence-frequency of automatic keywords (see **Annex 1** for description) in the publications dataset was the basis for the calculation of *relevant keywords*. These refer to a group of concepts in this dataset identified by combining and ranking term frequency and discrimination.

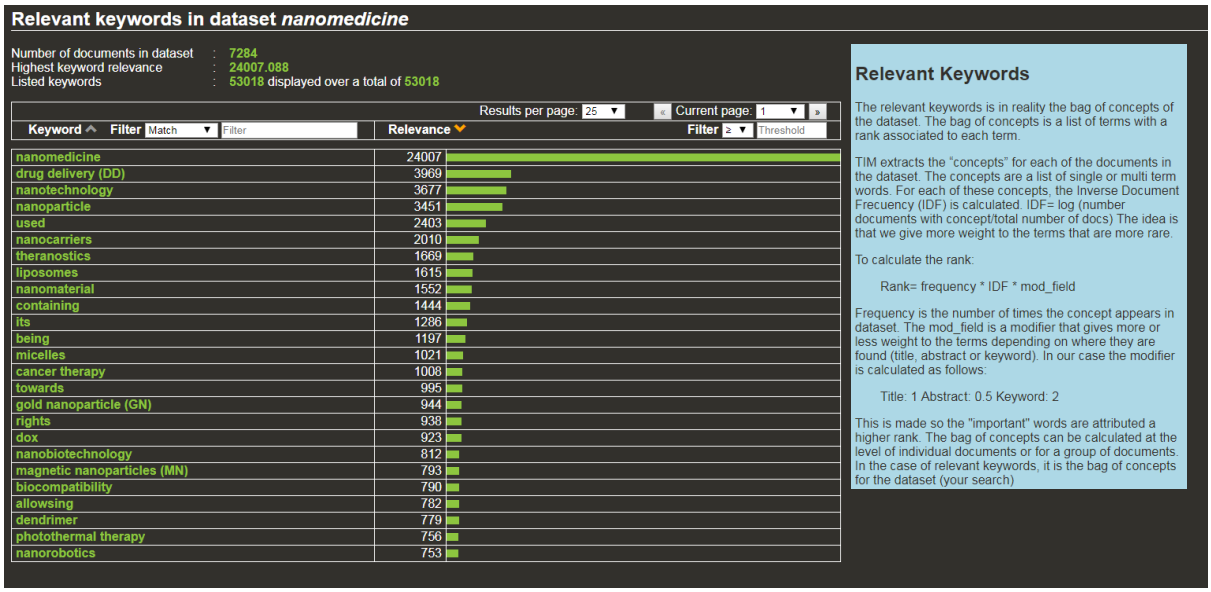
Figure 7 shows the list of the 25 most relevant keywords extracted from the metadata of this study; **Annex 1** shows the extended list of the top 100 relevant keywords. The top relevant keywords retrieved from the studie's publications dataset included several general terms such as *nanomedicine*, *nanotechnology, nanoparticle*, *theranostics*, or *nanomaterial*, and specific terms such as *nanocarriers, liposomes, quantum dots o*r *micelles*. Other terms listed as relevant were related to biological properties of nanomaterials, such as *biocompatibility*, *conjugation*, *protein corona, self-assembly,* or *EPR effect* (Enhanced Permeability Retention).

The evaluation of the resulting most frequent and relevant terms demonstrated the ability of TIM to identify specialised terminology in the field of nanomedicine. Following a similar reasoning for calculation as described in van Eck et al. [26] to evaluate emerging fields, the retrieval precision[8] was calculated in the two sets of the 100 most frequent and relevant keywords, resulting in a precision of 90% and 100%, respectively. The retrieval recall[9] could be not calculated because not every expected list of terms to be compared with TIM's results was available.

[8] *Precision* is the fraction of retrieved documents that are relevant. It is the number of correctly identified terms divided by the total number of identified terms (in a set of 100 terms).

[9] *Recall* is the fraction of relevant documents that are retrieved. Recall is the number of correctly identified terms divided by the total number of correct terms.

Figure 7. List of the 25 most relevant keywords in the nanomedicine field



Relevant keywords have been considered to build the keyword sets used for mapping and compilation of descriptions. *Source*: TIM (search string: "nanomedicine*")

Beside the use of nanotechnology for medicinal products, the application of nanotechnology will be crucial for innovative medical devices. The new medical device regulation is in particular referring to classification needs if a medical device has incorporated or consist of nanomaterial and an internal exposure is expected (refer to rule 19 L117/145). In order to check whether the initial keyword set of this study covered the application of nanotechnology in medical devices an alternative publications dataset (source: TIM) using the search string *"nano* AND medical device"* from year 1996-2016 was created and identified a total of 1548 documents on this topic. The TIM tool automatically extracted a list of relevant keywords. Besides specific types of nanomaterials with a broad range of applications in nanomedicine, this refined search for medical devices showed an enrichment of synonyms given for silver nanoparticles (*silver nanoparticle*, *nanosilver*, *silver*, *silver ions, AgNPs*, and *AgNO*) and an increased relevance score for some terms such as *nanocomposites*, *nanofiber*, *nanostructure,* or *nanostructured surface nanotube*, *nanocoating*, *hydrogel*, and *block polymer*. Although these terms were not present in the top 100 relevant keywords using the search string *"nanomedicine*"*, they did appear in the complete list of keywords retrieved with TIM from the search *nanomedicine*. The top 100 relevant and author keywords for the specific search in the publications dataset for medical devices are also listed in **Annex 2**. Only few keywords (11) from this list were used to complement the nanomedicine keyword set based on expert judgement.

Finally, the literature review (see section 3.2.1.2) revealed a variety of individual terms (268) used to describe nanomaterials or nanotechnology-based materials used in nanomedicine research and application, expanding significantly the initial set with 111 keywords, most of them being variants of the keywords extracted using the automatic extraction (for example *dendrimeric*, *polymer based nanocarrier*, and *polymeric micelle*). **Annex 3** presents a summary of the terms and categories suggested by several authors for nanomaterials and products in the field of nanomedicine.

The literature review also revealed a variety of general terms used to describe these nanomaterials such as *nanomedicine*, *nanomedicines*, *nanoparticles* and *nanocarriers*. In some cases, these terms appeared in combination with others such as *polymer-based nanomedicine*, *nanomedicinal products* and *drug nanoparticles.* Other terms identified

were *nanoplatforms*, *nanodrugs, nanoformulations, nanopharmaceuticals, nanoscale therapies* and *carrier systems*.

A few reviews provided sub-categories for these formulations or materials, which ranged from general categories such as *organic nanoparticles*, *inorganic nanoparticles*, *carbon nanotubes* [27], and *lipids* and *polymers* [28], to more specific ones such as *lipid-based nanocarriers*, *drug-conjugates*, *polymer-based nanocarriers*, *inorganic nanoparticles* and *viral nanoparticles* [29]. In some reviews, the type of polymer used was also considered to derive a different classification such as *polymer-based nanomedicin*e (e.g., polyetherimide (PEI), poly(L-lysine) (PLL), and chitosan), *polymeric micelles* (e.g., poly(ethylene glycol (PEG)–poly(amino acid), PEG–polyester and PEG–lipid), *polymer–drug conjugates* and others [30]. Other general categories identified were *protein nanoparticles*, *base nanoparticles*, *lipid base nanocarriers*, *metal based nanocarriers*, and *nanostructured materials*.

This terminology variation was also evident from the number of distinct keywords within the categories. The most frequent keywords identified in this review were *liposome* that appears in 82% of the reviews, followed by *micelle* (37%), *polymeric nanoparticle* (27%), *nanoparticle* (22%), *carbon nanotube* (20%), *polymeric micelle* (20%) and *solid lipid nanoparticle* (18%). Other terms and term variants were mentioned in less than 10% of the documents, and 162 term variants were mentioned only in 1 review. The list of terms contains 25 types of nanoparticles (e.g., *albumin bound nanoparticle*, *carbon nanoparticle*, *gold nanoparticle*, and *crystalline nanoparticle*), 4 types of micelles (*polymeric micelles*, *block copolymer micelles*, *lipid-based micelles* and *micelleplexes*), and 21 terms to describe polymer-based nanomedicines (e.g., *polymeric nanogels*, *polymeric conjugates*, and *star block copolymers*).

Result 2: Division of final keyword set of 383 terms[10] into four categories

- n=79 General terms defining general concepts including *nanotechnology*, *nanomedicine*, *nanomaterial*, *theranostics* and *nanosimilars*;

- n=235 Structural entities terms: terms covering nanoscale materials and nanotechnology platforms used in the field of nanomedicine including *dendrimers*, *liposomes*, *quantum dots* and *nanocomposites*;

- n=29 Terms to define chemical processing such as coating, emulsion, functionalization, and nanoformulation;

- n= 41 Terms indicating methodologies, techniques or properties applied to material characterisation and relevant to nanotechnology such as particle size, surface morphology, dynamic light scattering and dustiness.

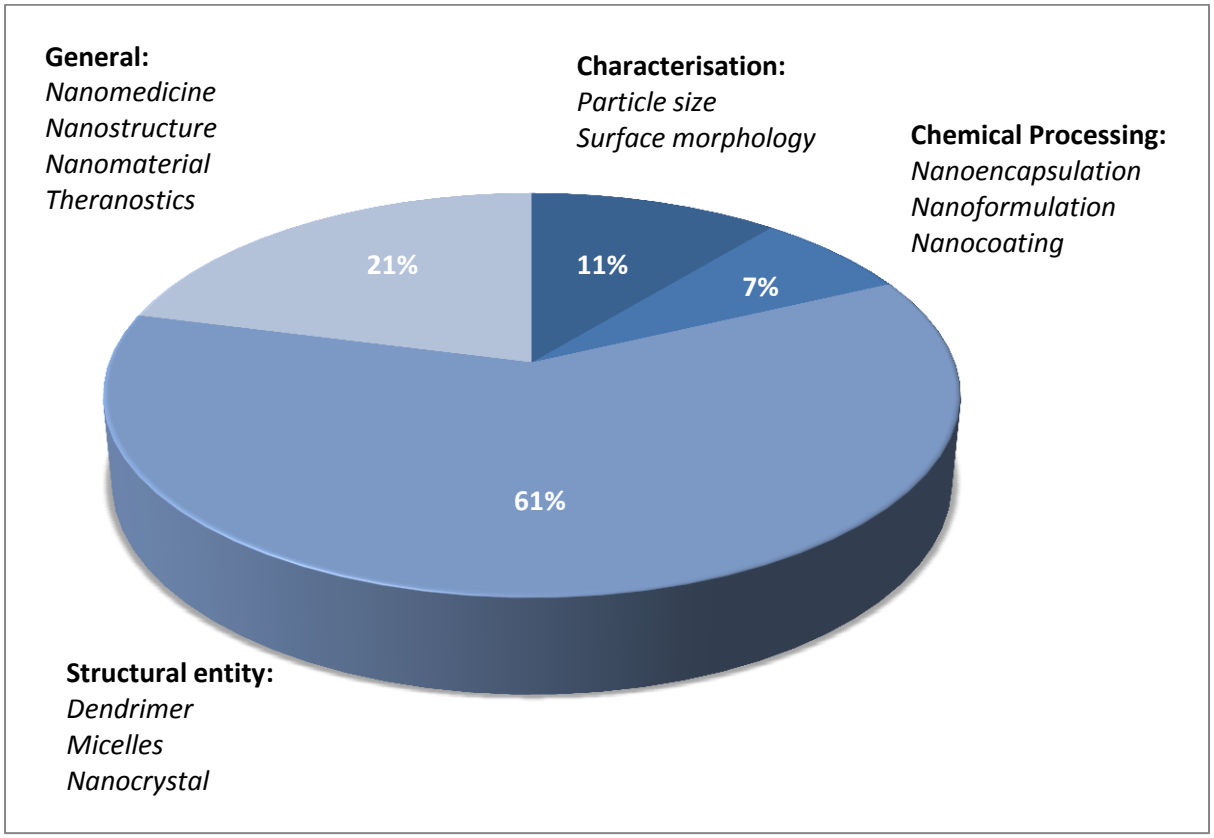
3.1.2 Description of the final keyword set for nanomedicine

By merging the resulting lists extracted in Step 1 (section 2.2.1), a final keyword set was built that contained 383 terms including plurals and variants (290 when excluding these). This keyword set is composed of nano-prefixed terms and non nano-prefixed terms that are relevant to the topic and includes terms describing nanoscale materials (e.g., *dendrimers*, *liposome*), chemical processes (e.g., *conjugation, emulsion and functionalization*), and various aspects of nanomaterial physicochemical characterisation including results and techniques (e.g. *aggregation, chemical composition,* and *dynamic light scattering*). The keyword set of this study contains single keywords, combined keywords (e.g., *polymeric nanoparticles*, *protein polymer conjugate* and *lipid based*

[10] This list includes term variations such as plurals, or hyphenated variations.

micelles) as well as plurals and adjective variants when appropriate (e.g. *micellar*, *colloidal*, *nanosized*, and constructions such as *nanotechnology-based* and *nanoparticle-based*). Similarly, as proposed by the BSI terminology[11], selected terms were divided in four categories to describe the keyword set (see textbox). **Figure 8** indicates the percentage of terms included in the keyword set for each category.

Figure 8. Distribution of terms from the nanomedicine final keyword set



Finally, the publications set was queried with both search engines TIM and GoPubMed in order to validate the simple string search strategy by using a series of alternative search strings: *"nano* AND medicine"*, *"nanotechnol* AND drug*"*, *"nanomed* AND medical device*"*, and *"nanomedicine AND regulatory"*. The relevant keywords and top terms extracted with these searches were already present in the keyword set and therefore this search did not contribute to its enlargement. **Figure 9** shows the final keyword set selected for the mapping of terminology in regulatory authorities' websites in Step 3. A reduced keyword set, based on this one, was selected to map the other sources: clinical trial registry database (see **Figure 5**).

[11] British Standards Institution (2007) PAS 131 Terminology for medical, health and personal care applications of nanotechnologies

Figure 9. List of terms in the nanomedicine final keyword set

3.1.3 Selection of a reduced keyword set for manually mapping identified sources

Only the previously described scientific publications lend themselves to a fully automatic extraction of keywords and associated frequency of occurrence, and the mapping of the regulatory agencies can be done in a semi-automatic way using the terms listed in **Figure 9**. The exercise of mapping of the scientific publications and regulatory agencies provided the basis for a refined keyword set that allows easily manual mapping information from other sources, such as the clinical trial registry, which did not permit to automatically retrieve information. In fact, keywords from these databases were manually extracted by querying their website's advanced search engine with the reduced keyword set described below.

For the manual mapping exercise, some of the keywords relating to general terms were chosen based on their frequent occurrence and relevance, in text by the regulatory authorities on the application of nanotechnology in the health sector. Other general terms were selected due to their distinctive use, e.g. by one regulatory authority, and therefore their potential implications in global communication among authorities.

Table 5. Selected terms (in random order) for manual extraction

General terms	Specific terms		
Nanotechnology	Nanoparticle	Dendrimer	Nanosuspension
Nanoscale	Metal nanoparticles	Carbon nanotube	Nanocomposite
Nanostructure	Magnetic nanoparticles (SPIO, SPION, USPION)	Micelle	Nanoaerosol
Nanomaterial	Polymer therapeutics	Quantum dot	Nanobody
Nanomedicine	Polymeric nanoparticles	Colloid	Virosome
Nanomedicines	polymeric nanoparticle	Fullerene	
Nanodevice	polymeric micelles	Nanocrystal	
Theranostic products	Solid lipid nanoparticles	Nanocarrier	
Combination products	Albumin-bound nanoparticles	Nanocapsule	
Borderline products	Liposome	Nanoemulsion	

3.2 Step 2: Mapping nanomedicine terminology in information sources

3.2.1 Summary of terminology mapping

Table 6 summarises the term frequency of all sources explored in this report. The term frequency for the scientific literature represents the number of publications, within the publications dataset extracted with the search string *nanomedicine**, containing each term either in the title, abstract, author keywords or in the text corpus. For the regulatory authorities' websites, term frequency refers to the number of extracted pages containing each term, whereas for the clinical trial registries database the term frequency correspond to number of entries with each term listed in the table.

Detail mapping results and discussion for each is provided in the following subsections.

Table 6. Summary of term frequency (number of documents) of keyword set in various information sources.

keyword set	N° of documents from scientific	N° of documents from regulatory authorities												N° of clinical trials
		TGA	Swissmedic	Health Canada	FDA	TFDA	EMA	MHLW	MFDS	HSA	DG SANTE	DG GROW	Occurrence**	
Drug delivery system	1815	58	632	229	**1087**	13	1	9	-	2	3	5	10	121
Nanoscience	104	-	-	4	**5**	2	-	-	-	-	4	2	5	-
Nanotechnology	1459	37	235	236	**1230**	25	730	-	-	-	121	371	8	14
Nanomedicine	5958	4	29	5	**38**	7	10	-	-	-	1	3	8	-
Nanomedicines	116[§]	1	12	1	2	-	**785***	-	-	-	-	-	5	-
Nanosimilar	2[§]	-	-	-	-	-	**8**	-	-	-	-	-	1	-
Nanoparticle	2763	107	112	118	**309**	74	10	-	-	1	39	31	9	239
Aerosol	22	101	288	91	**712**	1	6	2	-	-	7	49	9	300
Nanomaterial	757	17	4	**584**	498	43	2		1		123	373	9	2
Colloid	98	67	62	98	**291**	-	18	-	-	1	1	1	8	173
Nanocolloid	4	-	-	-	1	-	14	-	-	-	-	-	2	7
Emulsions	-	91	**3651**	47	260	22	33	-	-	-	-	21	7	547
Nanoemulsion	-	-	-	-	1	-	-	-	-	-	-	1	2	10
Micelle	326	5	1	6	7	**37**	3	-	-	-	-	1	7	30
Nanomicelle	28	-	-	-	-	-	-	-	-	-	-	-	-	2
Liposome	494	4	-	16	**290**	8	52	-	-	-	-	-	5	886
Nanoliposome	14	-	-	-	3	-	-	-	-	-	-	-	1	10
Nanostructured Materials	98	1	-	2	20	**24**	-	-	-	-	-	7	5	4
Quantum dot	267	3	-	**21**	12	6	-	-	-	-	-	1	5	-
Nanotubes	448	-	-	8	**52**	4	-	-	-	-	-	1	4	3
Hydrogel	50	13	**189**	30	81		-	-	-	-	-		4	230
Nanocapsule	71	-	2	-	-	**6**	-	-	-	-	-	1	3	-
Dendrimer	227	-	-	-	**11**	-	-	-	-	-	-	1	2	1
Fullerene	77	-	-	-	**14**	7	-	-	-	-	-	-	2	-
Nanowire	37	-	-	-	**5**	-	-	-	-	-	1	-	2	-
Nanocomposite	89	-	-	-	3	-	-	-	-	-	-	3	2	1
Nanocrystals	82	-	-	2	**3**	-	-	-	-	-	-	-	2	21
Virosome	2	-	**25**	-	-	-	3	-	-	-	-	-	2	37
Nanoporous materials	3	-	-	-	1	-	-	-	-	-	-	-	1	1
Nanocarrier	557	-	-	-	-	1	-	-	-	-	-	-	1	5
Nanorods	44	-	-	-	2	-	-	-	-	-	-	-	1	-
Nanosheets	11	-	-	-	1	-	-	-	-	-	-	-	1	-
Nanoshells	38	-	-	-	1	-	-	-	-	-	-	-	1	-

Table 6 (cont.)

keyword set	N° of documents from scientific	N° of documents from regulatory authorities												N° of clinical trials
		TGA	Swissmedic	Health Canada	FDA	TFDA	EMA	MHLW	MFDS	HSA	DG SANTE	DG GROW	Occurrence**	
Nanospheres	-	-	-	-	**22**	-	-	-	-	-	-	-	1	1
Polymeric nanoparticle	34§	-	-	-	-	-	-	-	-	-	-	-	-	1
Polymeric micelle	24§	-	-	-	-	-	-	-	-	-	-	-	-	7
Solid lipid nanoparticle	73	-	-	-	-	-	-	-	-	-	-	-	-	-
Nanopharmaceutical	57	-	-	-	-	-	-	-	-	-	-	-	-	-
Nanotherapeutics	140	-	-	-	5	-	6	-	-	-	-	-	2	-
Polymer-drug conjugate	13	-	-	-	-	-	-	-	-	-	-	-	-	-
Nanoconjugate	40§	-	-	-	-	-	-	-	-	-	-	-	-	-
Block copolymer	102	-	-	-	-	-	-	-	-	-	-	-	-	2

*search string: "*nanomedicine**" (extracted automatic keywords hit counts); §author keyword; **calculated by number of authorities including a given term; number between brackets indicate results from an advance search string ("a given term AND nanotechnology"). Numbers in bold indicate regulatory agencies with highest hit for each keyword. Sources: scientific publications (TIM), regulatory authorities' websites, clinical trials (ICTRP)

3.2.2 Mapping of keywords in regulatory authorities' websites

The number of documents extracted from 13 websites (**Table 7**) mentioning the keywords (hit counts) were quantified. **Annex 4** contains a summary table of the results of this mapping exercise.

Table 7. Number of webpages crawled for this study per regulatory authority

Regulatory authority	URL (English version)	#documents retrieved
Australian Government Department of Health	www.tga.gov.au	6128
Agência Nacional de Vigilância Sanitária, Brasil	portal.anvisa.gov.br	472
Health Canada	www.hc-sc.gc.ca	15197
Ministry of Health Labour and Welfare, Japan	www.mhlw.go.jp/english/	2248
Ministry of Food and Drug Safety, Korea	www.mfds.go.kr/eng/	87
Russian Federal Service for Surveillance in Health Care	www.roszdravnadzor.ru/en	70
Health Sciences Authority, Singapore	www.hsa.gov.sg/content/hsa/en.html	487
Swiss Agency for Therapeutic Products	www.swissmedic.ch/index.html?lang=en	35368
U.S. Food and Drug Administration	www.fda.gov	76754
Food and Drug Administration, Taiwan	www.fda.gov.tw/EN/	4052
European Medicines Agency	www.ema.europa.eu	4704
European Commission, DG Grow	ec.europa.eu/growth/index_en.htm	71783
European Commission , DG Santé	http://ec.europa.eu/health/index_en.htm	3383

This table shows the variation in the amount of information (in number of text documents), in English, extracted from the different bodies.

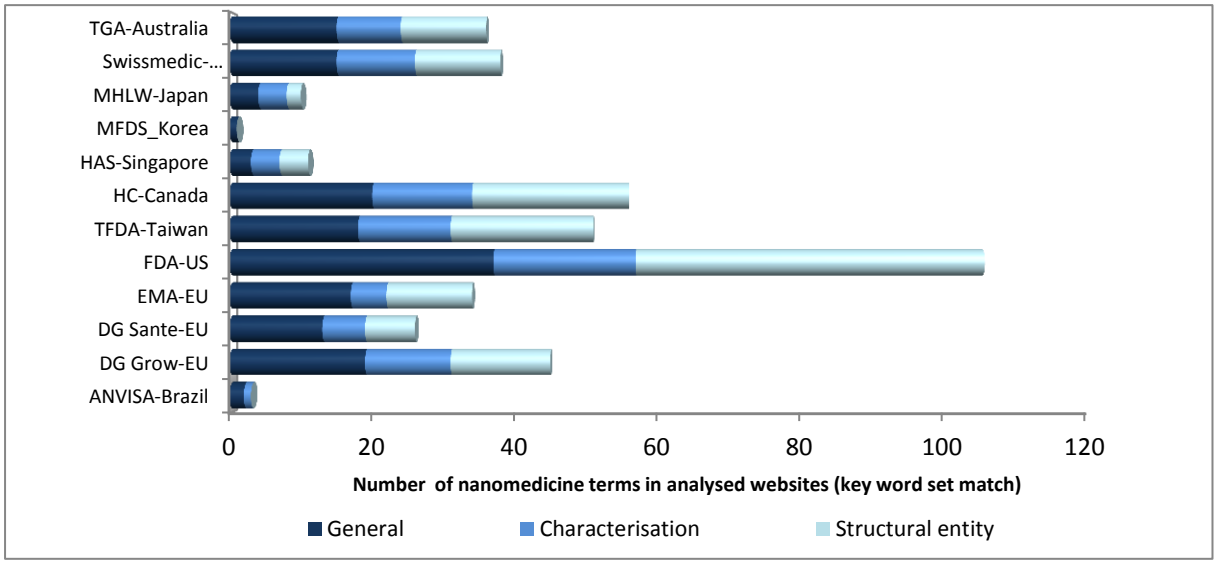
3.2.2.1 Information on nanomedicine in the websites of regulatory agencies

The first set of findings concerned the variability of the total information amount retrieved from each regulatory authority's English language version website. Using the metadata extracted from all crawled websites, a database comprising 220 733 unstructured text documents was built. The number of documents extracted from each website using the WebCrawler software showed the variability of the information provided, ranging from thousands of text documents published by the FDA (76754) to a few dozen published by the Russian regulatory authority website (70). As the search was restricted to publications in English and there are significant differences between the types of products regulated by each authority, a quantitative comparison of the search results from the regulatory authorities' websites was not meaningful and this fact needs to be taken into consideration when interpreting the outcomes of this mapping. The translated websites tend to provide fewer documents such as the Russian Federal Service for Surveillance in Healthcare's (Roszdravnadzor) and the Korean Ministry of Food and Drug Safety's websites only 70 and 84 texts were extracted, respectively. In addition, some regulatory authorities are regulating different types of products which had an impact on the level of information provided in the website. Due to technical limitations the crawling could not filter only by the type of products (e.g. medicinal products and medical devices) resulting in an increase of documents providing

information about product types that are outside the scope of this report. For example, the FDA not only regulates drugs and medical devices but also regulates e.g. food products, cosmetics, and tobacco; the FDA had the highest number of documents retrieved as it is English mother tongue and regulates several different fields (76754). Other agencies that use English intensively, for example EMA, cover mainly one regulatory field, medicinal products, and therefore the total number of text documents extracted was significantly smaller (4704). Finally, the information architecture in the website could also explain the variation in number of documents retrieved from some regulatory authorities' websites. An example of this is Swissmedic, the Swiss Agency for Therapeutic Products, which is involved in the authorisation and monitoring of medicinal products and medical devices; even though English is not a primary language, the crawling exercise extracted 35368 text documents, almost tenfold difference compared to the number of documents provided by the EMA's website. This high number is attributed to the publishing of documents in several official languages (German, French and Italian), which were included in the English language webpage. Documents in languages other than English were also extracted from Health Canada's website, which also has French as an official language and from the Brazilian ANVISA (Agência Nacional de Vigilância Sanitária).

Inter-agency variations in the number of terms matching the keyword set (**Figure 10**) were observed. All websites, except the Russian Roszdravnadzor English version, showed at least one term matching the nanomedicine keyword set. For example, the websites of the FDA, Health Canada (HC) and TFDA had a higher number of terms matching the keyword set, while the Brazilian ANVISA and the Korean MFDS had less than 5 terms matching the keyword set. The number of documents extracted from each regulatory authority website for each term of the keyword set was counted. After data consolidation, i.e. grouping counts of the singular and plural forms (when appropriate), this approach returned a total of 141 terms matching the keyword set (**Annex 4**). In general, approximately 80% of the terms from the keyword set were used by less than half of the regulatory agencies, and more than 40% of the terms were present only in 1 of the webpages surveyed.

Figure 10. Total number of terms matching the nanomedicine keyword set in documents extracted from regulatory authorities' (RAs) websites.



According to the text mining results, the FDA's website showed the highest number of terms (115) matching the keyword set. Since English is the main language used by the

FDA and this agency addresses many regulatory fields, this might be a reason for the higher number of informative documents at the website.

This list included general terms such as *nanohealth, nanopharmaceutical and nanodrug.* General terms such as *nanotechnology*, *nanomaterial* and *nanoparticle* were the most frequently nano-prefixed terms matching the keyword set within this website. Regarding nanomedicine-specific terms, the FDA has the website using the highest number of terms to describe structural entities compared to other agencies. The list includes terms such as *liposomes* (in 150 documents), *hydrogel* (48), *nanospheres* (10), *micelles* (6) and *dendrimers* (5). A closer look to the type of documents mentioning these terms revealed the enrichment on information on science and research projects in the webpage from external sources (universities or research centres). This is also the case of the term *nanomedicine* that appeared only in 16 documents and it was also used mainly to describe names of academic departments or titles of research projects and publications from external sources. The FDA does not recognise the term *nanomedicine* to describe any type of medicinal or medical product; instead, the agency uses the general terms *nanotechnology products*, *drug products that contain nanomaterials* or *products that involve the application of nanotechnology* [31].

Health Canada is the second regulatory authority website matching a high number of nanomedicine-related terms (64) from the applied keyword set. Besides the term *delivery system,* words such as *nanotechnology, nanomaterial* and *nanoscale* were the most mentioned from the keyword set. Almost 43% of these terms described structural entities such as *iron oxide*, *colloid*, *aerosol and hydrosol* and these were the top 20 most frequent terms in this analysis of the data from Health Canada; the list also included terms such as *quantum dot*, *liposome*, *SPIO* (superparamagnetic iron oxide) and *nanocarrier*. The general terms *nanomedicine* and *nanomedicines* were also found in the matching list. Neither term was frequently used in the information extracted from the website; however, these terms were included in the informative webpage for *Frequently Asked Questions Related to the Policy Statement on Health Canada's Working Definition for Nanomaterial*. In this context, *nanomedicine* describes the *application of nanotechnology to treat diseases or restore functions*, and the term *nanomedicine* defines the resultant product of this application. The term *nanomedicines* in this text also denotes the application of nanotechnology for both pharmaceutical drugs and medical devices.

Taiwan FDA (TFDA) returned a total of 59 terms matching the keyword set, and this was the third best terminology match for nanomedicine for regulatory authorities. General terms such as *nanoparticle*, *nanomaterial*, *nanotechnology*, *nanoscale and nanostructure* were the most frequently mentioned ones in the information extracted from this agency. The terms *nanomedicine* and *theranostic* were also found among TFDA website's metadata. Comparable to Health Canada, structural entities contribute to a significant percentage of the matching terms captured. The most frequent categories were *nanoparticle*, *micelles*, *liposomes and quantum dots.* Among the unique terms, the following were found: *nanocarrier*, *metal nanoparticle and mesoporous silica*. A closer look at the type of documents, however, indicated that these terms were used in citations from articles published in English. None of the terms mentioned in the English version of the TFDA's website had an associated definition.

EMA's information texts matched 40 terms of the keyword set, from which the most frequent general terms were: *nanomedicine,* the plural form *nanomedicines*, *tissue engineering*, *nanotechnology*, and *personalised medicine*. The list of specific terms included keywords to identify structural entities such as *nanocolloidal,* or *colloid, liposome* or *liposomal, micelle* and *virosome*. A specific term extracted from EMA's website is *nanosimilars* used to describe the concept of *nanomedicines that are claimed to be similar to a reference nanomedicine*[12]. Another relevant term found, although not

[12] http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp& (retrieved 31/08/2017)

exclusively for nanomedicine, is *borderline product*. This term is mainly used in a European context (by EMA, DG GROW, DG SANTE and Swissmedic).

This mapping approach also revealed that certain terms were uniquely used by certain regulatory authorities. Two issues should be considered for a further discussion on terminology harmonisation: 1) the uniqueness of certain terms in this analysis, e.g. terms may be found in only one source illustrated by EMA being the only source using *nanomedicines*, and 2) the frequency of occurrence of texts mentioning a term in each regulatory authority. The first issue contributes to the extension of the vocabulary; the second may indicate the establishment of a term in the field and it might motivate the discussion on harmonisation of a specialised terminology. To detect those terms specific to an agency or regulatory body, the contribution of such terms was included in the analysis of the total dataset of extracted texts from the different websites. This approach allowed identifying those agencies that were the main contributors to the frequency of a specific term. This approach is relevant to understand the emerging nanomedicine terms that are regionally accepted but are not accepted by other regulatory bodies.

A clear example of agency-related preference for terminology is the use of general key terms such as *nanomedicines*−in the plural form− and *nanomaterial* in the healthcare sector context. The plural form of the term *nanomedicine* is almost exclusively used by EMA (*nanomedicines* term frequency: 731 hits) to describe the application of nanotechnology to medicinal products. This use of the term *nanomedicine* may also explain the low number of documents retrieved from EMA with the term *nanomaterial* compared to the other regulatory bodies, in which the term *nanomaterial* is used to describe medicinal products, such as *drug products containing nanomaterials,* as in the FDA.

Also Swissmedic rarely uses the term *nanomedicines* (4 hits) in the information provided, and shows a pattern similar to EMA's for the term *nanomaterial*. The term *nanomedicine* is not adopted by Swissmedic for the description of drugs and devices; instead, the agency describes *human medicines* as *products containing nanoparticles,* where *the particles have at least one nanoscale dimension (1-1000 nm) plus a function and/ or mode of action based on nanotechnology characteristics* (in the form entitled *Application for Authorisation/ Variation of human medicines* [32]).

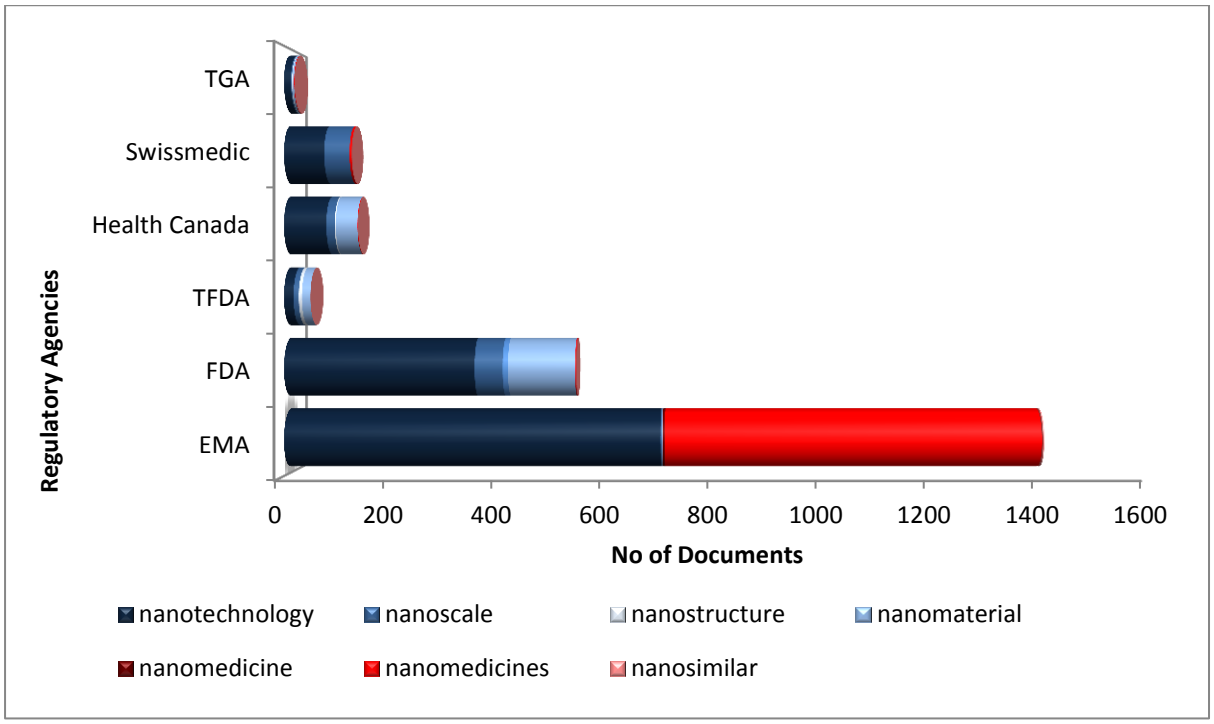
RESULT 3: Mapping of keywords (n=383) in regulatory authorities' websites

- Establishment of a database of 220733 unstructured text documents derived from 13 websites of regulatory/legislative bodies
- Variations between agencies matching the keyword set i.e. FDA=115 keywords
- Nanotechnology, nanomaterial, nanoscale, and nanomedicine used by nearly every agency
- The term *nanomedicines* is mainly used in European websites

An analysis of the term frequency of these selected keywords (**Table 5**) offers an initial assessment of the type and amount of information provided by the different regulatory sources on the topic of nanomedicine as well as the compilation of descriptions for future discussion of harmonising the terminology.

Figure 11 represents the frequency of the same nano-terms in the six websites of the regulatory agencies that had the most information in English on nanomedicine. The presented results showed that general terms such as *nanotechnology*, *nanomaterial*, *nanoscale,* and *nanomedicine* were mentioned in almost every website suggesting that information on the application of nanotechnology in the healthcare sector was being provided by the selected websites, whereas other terms were used almost distinctively in some regulatory agencies, as in the case of the above discussed term *nanomedicines*.

Figure 11. Frequency of general terms in selected regulatory authorities' websites

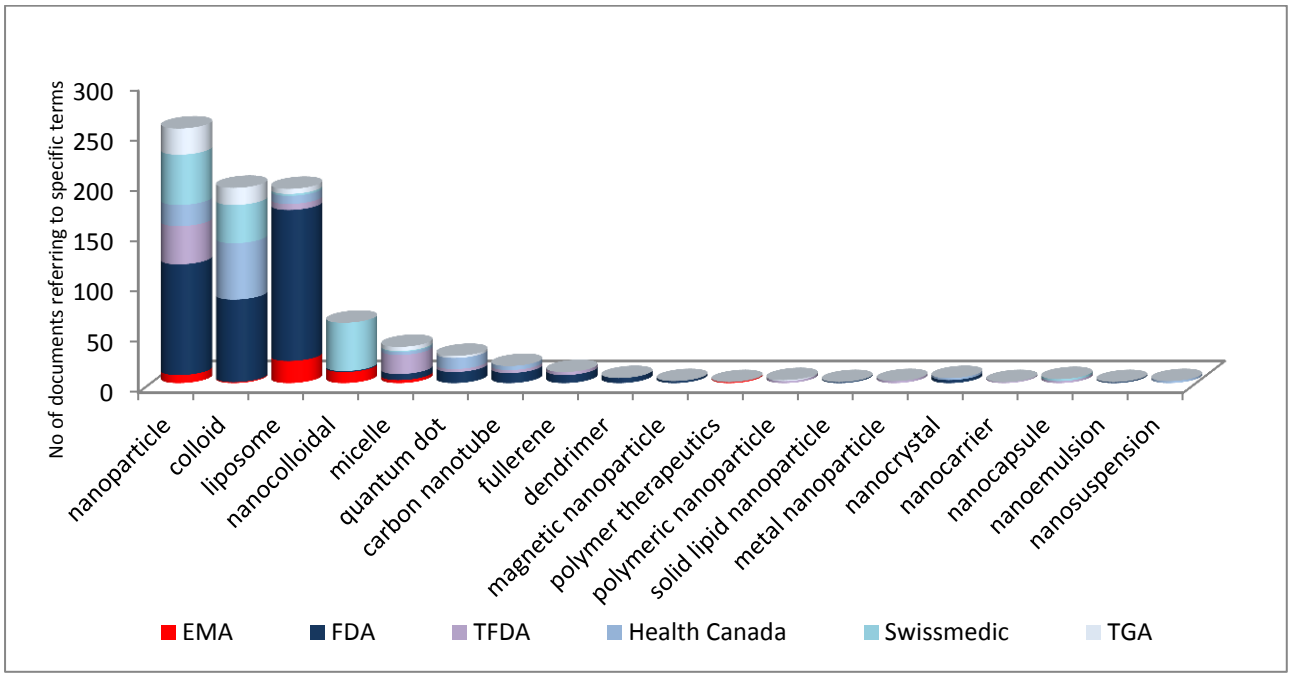


Analysis of most frequently used general terms in six of the most active regulatory agencies providing information on nanomedicine, analysed in this report.

Specific terms, such as terms to define nanotechnology platforms used in nanomedicine, were selected by their frequency in the scientific publication review as well as by their presence in the mapping analysis of regulatory authorities' websites. The results of the matching documents with these terms (**Figure 12**) may provide an initial indication of the categories of nanomedicine products upcoming in the regulatory domain.

There were significant differences in the use of the selected terms among the regulatory authorities. The results from term frequency analysis showed that *nanoparticles* and *liposomes* were the only specific terms mentioned in almost all the websites analysed followed by the terms *micelle* and *colloid*. The FDA agency showed the highest number of specific terms to describe nanoscale materials and formulations. A closer look at the type of documents including these terms revealed that many of these documents were related to information regarding research programmes.

Figure 12. Frequency of specific terms in selected regulatory authorities' websites



Analysis of most frequently used specific terms in six of the most active regulatory agencies providing information on nanomedicine, analysed in this report.

3.2.3 Mapping in clinical trial registries

In 2013, Etheridge et al. [25] reviewed existing commercial and investigational nanomedicine products in order to describe the type of nanotechnology-based products currently in clinical development. The authors selected a number of representative terms (see **Annex 4**) and identified 247 nanomedicine products approved or under clinical investigation. Also, De La Iglesia et al. [33] presented the first attempt to automatically identify information on nanodrugs and nanodevices in clinical trials using text-mining tools and aiming to distinguish clinical trials of nanotechnology-based products from clinical trials of conventional drugs. By applying a different keyword set, these authors identified 414 clinical trials involving nanotechnology products; however, a complete description of the terms and the products was not provided in the publication. Their results were valuable background information for this research, and terms proposed in these studies were also introduced in this keyword set. However, these papers had the objective to describe the type of nanotechnology-based products as well as the products themselves as reported in clinical registries, not the terminology.

This study explored the variety of nanomedicine related terms in the clinical trials (CT) that were registered in the WHO clinical registry. The term frequency refers to the number of clinical trial summaries containing the term and provided in this database.

In total 1230 CTs potentially related to the application of nanotechnology in medicinal products (drugs) and medical devices were captured. Terms defining product brands, company names, methodologies and metric variables that are unspecific in the field of nanomedicine were excluded resulting in total number of 722 CTs. The results were perfectly matching the list of clinical trials reported by De La Iglesia et al. [33].

3.2.3.1 Increase of nanomedicine terminology in clinical registries

The increase of specific terms in the text of the summaries allowed monitoring the emergence of nanomedicines in CTs. The analysis indicated an increase of nanomedicine products in clinical trials as well as an increase of nano-prefixed terms describing these

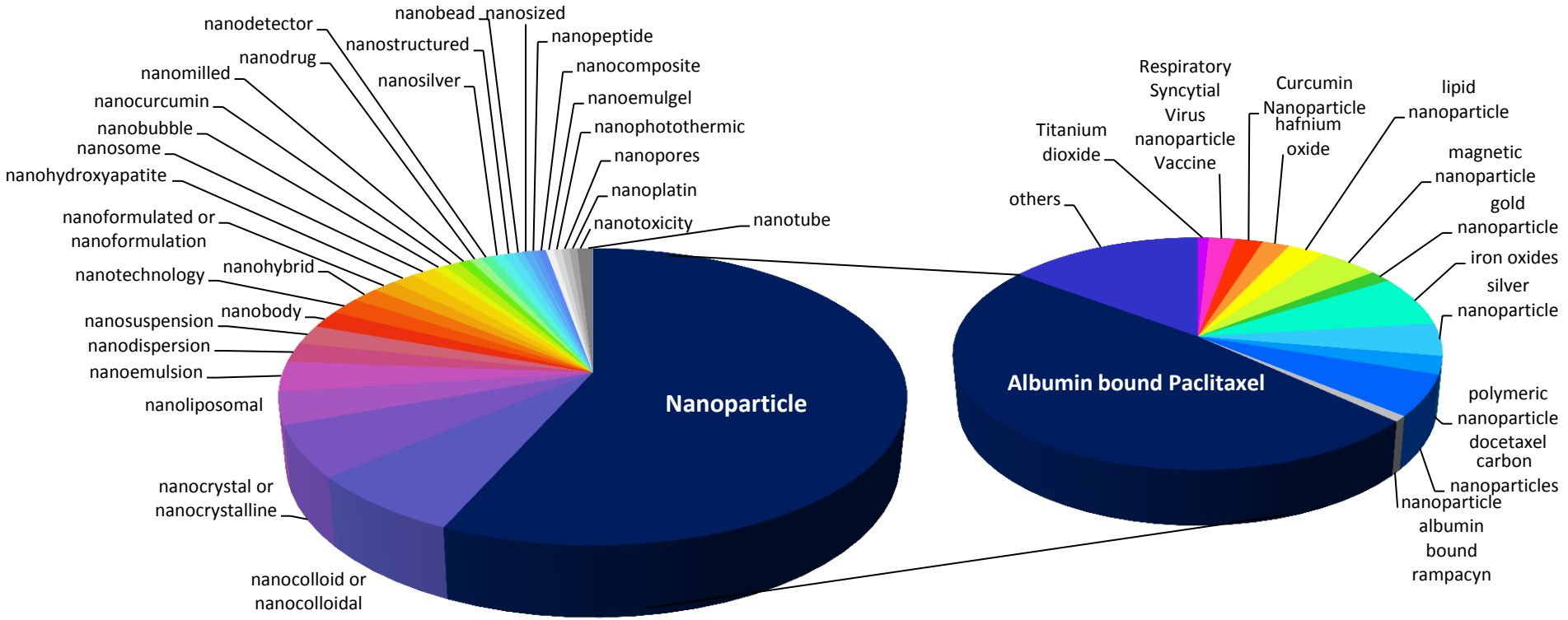
products. Even if this study is not an exhaustive analysis of nanomedicine products currently in clinical development, the analysis demonstrates the expanding terminology in the field of nanomedicine.

From 2004 to 2016 54% more nano-prefixed terms were used in the title of the retrieved CT summaries.

The analysis of nanomedicine terms used in CT summaries revealed that the most retrieved CTs (53%) describe investigational health products are using the term *nanoparticle* (**Figure 13**). The majority of this use of the term nanoparticle were referring to CTs (n=117) related to the nanoparticle albumin-bound paclitaxel (nab-paclitaxel) [34]. This subset represented however less than 50% of the CTs registered for nab-paclitaxel, and when searching by using the term *nab-paclitaxel* or the brand name *Abraxane* 630 CTs were identified.

The selected terms listed in **Table 5** were searched using the advance search engine of the WHO-ICTRP website. In comparison to the number of specific terms related to nanomedicine, the number of CTs mentioning general terms was rather low, and terms such as *nanomedicine* and *nanomedicines* were not mentioned in any of the CTs to describe the scientific field or formulations, neither other variants such as *nanopharmaceutics* or *nanotherapeutics*. Only few new terms and variants such as *nanodiamond*, *nanomicellar*, or *nanofibrous* were identified in this dataset.

Figure 13. Term frequency of nano-prefixed terms selected to describe the use of nanotechnology in clinical trials registries



3.2.4 Mapping in patents

Patent databases are a valuable tool to understand the innovative potential of new technologies. As already described by Daim, 2006 [35], the analysis of patents can help with forecasting the impact and upcoming needs of products derived from emerging technologies. However, due to legal issues with patents, a clear understanding of the terminology among stakeholders is essential. Queries in the patent data base "*EPO-PATSTAT*" using the search string *"nanomedicine*"* with TIM resulted in the identification of 40 patents. The number of patents increased to 116 and 255 when other keyword combinations such as (*nanotech* AND medicine*) and (*nano* AND "medical device"*) have been used. The top 10 keywords extracted from these 40 patents included mostly general terms, applicable to other biomedical areas, such as *invention*, *medicine*, *preparation methods, diagnostics, biocompatibility* and *therapeutic effects,* and only few specific terms for nanomedicine such as *nanoparticle* and *quantum dot*.

Patent officers examine and classify patents into the technology classes of the Cooperative Patent Classification (CPC) system (see examples in **Table 8**). The CPC is a common, internationally compatible classification system for technical documents, in particular patent publications; depending on the foresee applications of a patent, one patent can be classified in more than one class or subclass. TIM offers the possibility to extract information on CPC classification from the dataset, and map the co-occurrence of classifications in a network (**Figure 14**). The analysis of these data provided further information on the type of products and applications in the field of nanomedicine. The identified 40 patents belong to two major classes according to the cooperative patent classification system (CPC): A61K and B82Y.

Table 8. Main Cooperative Patent Classification (CPC) subclasses found in the patents from the publications dataset.

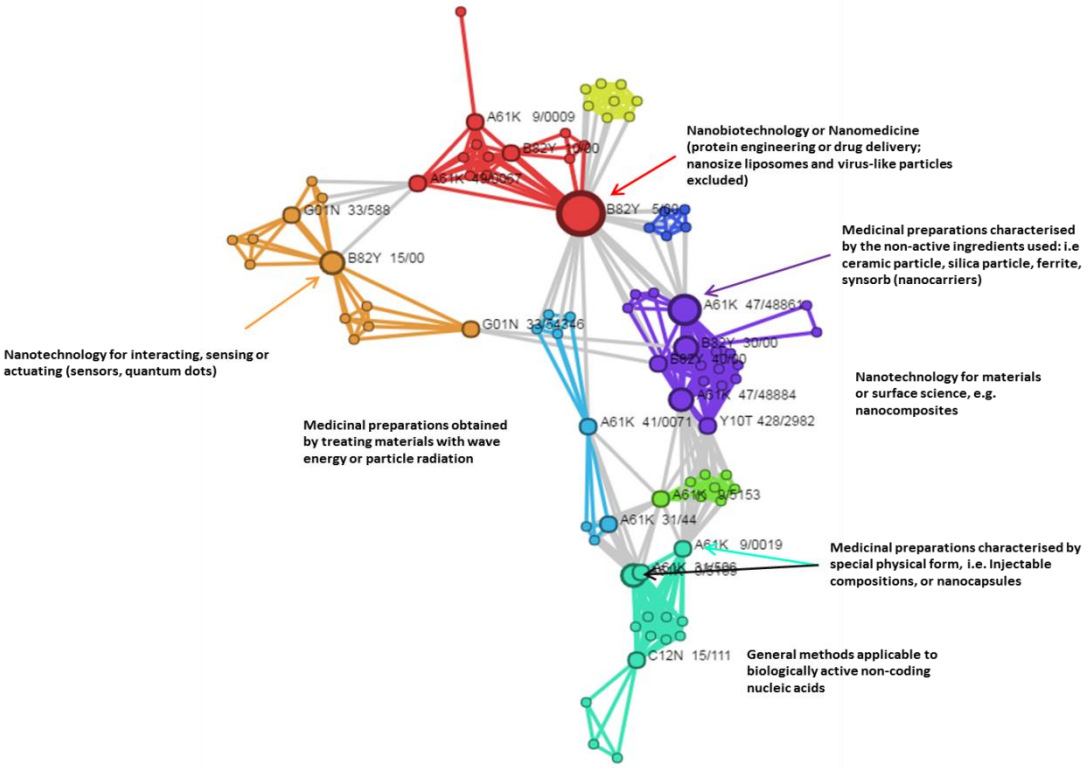
CPC_Class	CPC_Subclass	Title	Definition statement
B82Y		Specific uses or applications of nanostructures; measurement or analysis of nanostructures; manufacture or treatment of nanostructures	Applications and aspects of nanostructures which are produced by any method, and is not restricted to those that are formed by manipulation of individual atoms or molecules.
	B82Y 5/00	Nanobiotechnology or nanomedicine, e.g. protein engineering or drug delivery	Artificial structures, particles, etc. Although they may be of nanosize, liposomes and virus-like particles (VLPs) are not considered to be nanotechnology.
	B82Y 15/00	Nanotechnology for interacting, sensing or actuating, e.g. quantum dots as markers in protein assays or molecular motors	Nanostructures used for sensing or actuating, wherein the nanostructure itself (e.g. quantum dot, nanotube) is at least part of the sensor or actuator.
	B82Y 30/00	Nanotechnology for materials or surface science, e.g. nanocomposites	NA
A61K		Preparations for medical, dental, or toilet purposes	Preparations for dentistry; Cosmetic or similar toilet preparations; Medicinal preparations; Preparations for testing in vivo; Preparations containing radioactive substances for use in therapy or testing in vivo

Table 8 (cont.)

CPC_Class	CPC_Subclass	Title	Definition statement
	A61K 47/00	Medicinal preparations characterised by the non-active ingredients used, e.g. carriers or inert additives; Targeting or modifying agents chemically bound to the active ingredient	Pharmaceutical compositions characterised by the excipients, i.e. the non-active ingredients; New excipients per se.

24 patents also covered applications such as medicinal preparations characterised by the non-active ingredients, classified as A61K 47/00. This categorisation included non-active ingredients being chemically bound to the active ingredients, e.g. *polymer drug conjugates*, and medicinal preparations containing organic active ingredients. Specific terms to describe the materials covered in this group were *nanotubes*, *nano spheres*, *polymerosomes*, *liposomes, drug nanoparticles, nanocapsules, polymeric micelles* or *drug-nanoparticles conjugates.* Also, three subcategories of B82Y were found in the dataset: 6 patents classified as B82Y 5/00 that includes patents describing technology such as *nanocapsules* for drug delivery, therapeutics, or radioactive pharmaceutical preparations, followed by 3 patents classified as B82Y 15/00 that includes patents of tools for measurement of physical, chemical and biological properties at surface with nm-resolution. Finally, 3 patents classified as B82Y 30/00, included materials such as *nanoparticles*, *nanocomposites*, *dendrimers*, *nanotubes* and *fullerenes*.

Figure 14. Visualization of the CPC classification of the patents in this dataset.



The network represents the classification numbers identified in the patents present in the publication dataset (40 patents), using *nanomedicine** as string search. The size of the node reflects the number of patents identify within a class. The map shows a clear enrichment of patents classified as B82Y and A61K. *Source:* TIM

3.3 Step 3: Compilation of information and term descriptions

3.3.1 Compilation of relevant documentation from regulatory sources

Table 9 shows a compilation of documents with regulatory relevance retrieved in this study. The type of relevant documents includes e.g. simple consumer information, reflection papers to help industry and regulators to assess products, and various guidance documents aimed at industry, the general public or agencies' staff. The type of information in these documents included:

- Working definitions or glossaries for relevant nanomedicine terms.
- Information about the characteristics, uses, safety, and benefits of the application of nanotechnology in health products [36, 37].
- Information requirements to enable evaluation of health products in applications, e.g. declaration of ingredients considered nanomaterials, in drug products or veterinary medicines (Health Canada [38]; Swissmedic [32, 39]; EMA [40]); provision of description of nanomaterial quality attributes and structural characterization (e.g. size, charge, morphology, composition, and complexation)[31], provision of additional supporting data [41, 42]; and special requirements for labelling [41].
- Reflection papers on nanomedicines providing guidance for industry and regulators on developing and evaluating nanomedicines [43].

Further text-mining of the dataset that was extracted from the regulatory authorities' websites allowed exploring the existing documentation to obtain information on the application of nanotechnology in the health sector and identify the type of terminology used and information provided. For example, since 2012 Swissmedic requires that nanoparticles are declared using the form entitled *Application for Authorisation/ Variation of human medicines* (VO Form) [32]. This form has a section for pharmaceuticals to provide other information, including if the drug contain synthetic nanoparticles, and to specify which components of the medicinal product contains nanoparticles. According to this document, particles that have at least one dimension in the nanoscale (1- 1000 nm) plus a function and/ or mode of action based on nanotechnology characteristics are nanoparticles. The webpage also highlights that this information must be provided for medicinal products containing innovative nanoparticles (for example, Aerosil, a silicon dioxide, is not considered to be innovative). Another example is EMA's *pre-submission meeting request form*, which aims to provide an *overview of the most relevant topics that an applicant is advised to consider when preparing their upcoming application for initial marketing authorisation, and which can be discussed at a MAA* (marketing authorisation application) *pre-submission meeting*. This document asks for information on whether *the active substance applies nanotechnology*.

The FDA has recently released a *Draft Guidance for Industry – Drug Products, Including Biological Products, that Contain Nanomaterials* to share FDA's current thinking for the development of human drug products, including those that are biological products, in which a nanomaterial is present in a finished dosage form. This FDA draft guidance lists a set of recommendations without a legal enforcement that discusses both general principles and specific considerations for the development of drug products containing nanomaterials, including considerations for establishing the equivalence of such products with other drugs. Considerations for quality, nonclinical, and clinical studies are discussed as they relate to drug products containing nanomaterials throughout product development and production. This guidance applies to drug products, including biological

products, in which nanomaterials may serve as active ingredients, carriers loaded with an active ingredient or inactive ingredients [31]. For medical devices, the FDA does not provide any specific document requiring information on the application of nanotechnology; however the agency has issued a final guidance document entitled Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology that describes FDA's general approach to regulating products that utilize nanotechnology or contain nanomaterials and is applicable to all FDA-regulated products. FDA also accepts information provided in the *Auditor and Technical Expert Competency Summary* form developed by the Medical Device Single Audit Program (MDSAP) in which the expert should express whether medical devices are utilising *nanomaterials* [13].

[13] http://www.fda.gov/downloads/medicaldevices/internationalprograms/mdsappilot/ucm380005.doc.

Table 9. Summary of documents in English language on nanomedicine compiled from regulatory authorities' websites.

Country	Regulatory authorities	Regulate or support regulation	Primary legislation for medical products	Regulatory and guidance documents related to application of nanotechnology in medical products
Australia	Therapeutic Goods Administration (TGA)	**Medicines** **Medical devices**	- Therapeutic Goods Act 1989 - Therapeutic Goods Regulations 1990 - Therapeutic Goods (Medical Devices) Regulations 2002	- Under revision: Australian regulatory guidelines for medical devices (ARGMD) (2011) [44] - TGA webpage for consumer information [36]
Brazil	Brazilian Health Surveillance Agency (Anvisa)	**Drugs**	- Synthetic and semi-synthetic drugs (new, generics and similars); RDC 60/2014 - Classification and Registration Requirements of Medical Products; RDC 185/2001 (Medical devices)	No specific information available
Canada	Health Canada, Health Products and Food Branch (HC)	**Drugs** **Health Products**	- Food and Drugs Act - Natural Health Product Regulations	- Health Canada 3011: Drug Submission Application Form for Human, Veterinary or Disinfectant Drugs and Clinical Trial Application/Attestation - Guidance Document on Topical Anaesthetic, Analgesic or Antipruritic Labelling Standard [25] - Guidance for Completing the Drug Submission Application Form (Part 2- Drug Product Formulation Information) - Guidance Document: How to Complete the Application for a New Medical Device Licence [45] - Future revision of information requirements in Medical Devices Licence Application

Table 9 (cont.)

Country	Regulatory authorities	Regulate or support regulation	Primary legislation for medical products	Regulatory and guidance documents related to application of nanotechnology in medical products
Japan	Ministry of Health, Labour and Welfare (MHLW) Pharmaceuticals and Medical Devices Agency (PMDA)	**Pharmaceuticals** **Medical devices**	- The Pharmaceutical Affairs Law	Two guidance documents on Management Guidance on Clinical Trial Notification: points to consider in the case of some nanotechnology-based medicines (Japanese only) - PFSB/ELD Notification No.05314 (2013) - PFSB/ELD Notification No.05318 (2013) - Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products14 - Guideline for the Development of Liposome Drug Products (2016)15 - Reflection paper on nucleic acids (siRNA)-loaded nanotechnology-based drug products (2016)16
Republic of Korea	Ministry of Food and Drug Safety (MFDS)	**Drugs** **Medical devices**	- Pharmaceutical Affairs Act [Amended by Act No.14170, May 29, 2016] - Medical Device Act 2003	No specific information available
Russian Federation	Roszdravnadzor (Federal Service for Control over Healthcare and Social Development)	**Medicines** **Medical devices**	Federal Law of 12 April, 2010	No specific information available

[14] Japan PMDA Nanomedicine Initiative WG (http://www.pmda.go.jp/english/rs-sb-std/standards-development/cross-sectional-project/0008.html; accessed April 2017)
[15] National Institute of Health Sciences. www.nihs.go.jp/drug/section4/160328_MHLW_liposome_guideline.pdf
[16] National Institute of Health Sciences. www.nihs.go.jp/drug/section4/160328_MHLW_siRNA_RP.pdf

Table 9 (cont.)

Country	Regulatory authorities	Regulate or support regulation	Primary legislation for medical products	Regulatory and guidance documents related to application of nanotechnology in medical products
Singapore	Health Sciences Authority (HSA)	**Western medicine** **Medical devices**	Health Products Act 2007	Draft GN-17: Guidance on Preparation of a Product Registration submission for General Medical Devices using the ASEAN CSDT (HSA, 2014): request information on novel feature due to e.g. nanotechnology in product [46]
Switzerland	Swiss Institute of Therapeutic Products (Swissmedic)	**Medicinal products** **Medical devices**	Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA; SR 812.21)	- Application for Authorisation/ Variation of human medicines" (VO Form) (Swissmedic): Information request on drugs containing nanoparticles [32] - Informational sheet on First-in-Man clinical trials with nanomedicines [47]
United States of America	U.S. Food and Drug Administration (FDA)	**Drugs** **Medical devices**	- Federal Food, Drug, and Cosmetic Act - Public Health Service Act	- Draft Guidance for Industry – Drug Products, Including Biological Products, that Contain Nanomaterials (2017)[31] - Final Guidance for Industry - Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (2014) [48]
European Union	The European Medicines Agency (EMA) European Commission, DG SANTE	**Medicinal products**		Scientific Guidelines for nanomedicines (EMA): - Reflection Paper on Data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product (2015) - Reflection Paper on Data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (2013) - Reflection Paper on Development of block-copolymer-micelle medicinal products (2014) - Reflection Paper on Surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products (2013) - Marketing Authorisation Application (MAA) Pre-submission meeting request form: Request information on topic for consultation

Table 9 (cont.)

Country	Regulatory authorities	Regulate or support regulation	Primary legislation for medical products	Regulatory and guidance documents related to application of nanotechnology in medical products
European Union	Directorate General for Internal Market, Industry, Entrepreneurship and SMEs (DG Grow)	**Medical devices**	- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices - Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices	New regulation of medical devices: - Introduces of a definition for nanomaterials (based on EC Recommendation) - Special requirements for labelling - Direct classification for MDs incorporating nanomaterials (except when encapsulated or bound n such a manner that it cannot be released into the patient's or user's body) - Opinion on the Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices (SCENIHR)[42]
Taiwan	Taiwan Food and Drugs Administration (TFDA)	**Human drugs** **Medical devices** Cosmetics Food	Organization Act of the Food and Drug Administration, Ministry of Health and Welfare (2013)	- Reference guide for nano-medical devices identification (2014) - Draft template of EP/STED17 for dental composites with specifications for nanotechnology application - Draft guidance for technical review of CMC18:with adapted review checklist for nanotechnology-related pharmaceuticals **[49, 50]** - Draft Guidance for technical review of CMC screening standards for liposome drugs

[17] Essential Principles/Summary Technical Documentation
[18] Chemistry, Manufacturing, and Controls

3.3.2 Compilation of descriptions of relevant terms

The reduced set of terms described in section 3.1.3 was used to compile descriptions in sources with regulatory relevance. Most of the descriptions collected were not legally binding or established regulatory definitions but recommendations, working definitions or definitions provided in a specific context.

Table 10 indicates the regulatory authorities that provide a description of the general terms related to nanomedicine on their website. For specific terms for different types of nanomaterials the search failed to find descriptions in most of the regulatory sources explored and as alternative sources to direct regulatory documents, descriptions from international standards were retrieved; biomedical and nanotechnology-specialised ontologies and glossaries; peer-reviewed articles, selected according their relevance in the research field, and other documents with regulatory influence. Descriptions for general and specific terms are listed in **Annex 5**.

Table 10 Authorities providing descriptions in English of selected general terms on their website.

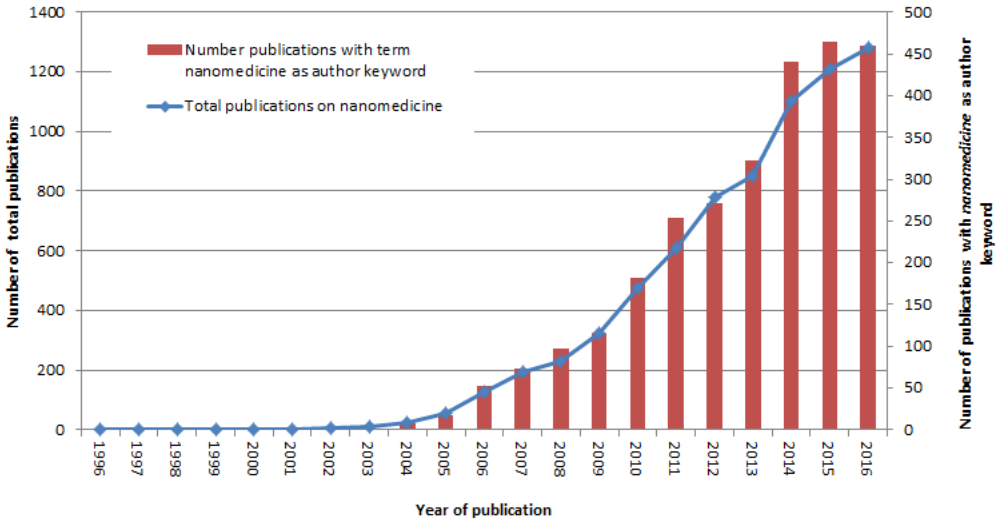
General Terms	European Commission (DG SANTE & GROW)	EMA (EU)	FDA (US)	TFDA (Taiwan)	TGA (Australia)	ANVISA (Brazil)	HC (Canada)	PMDA (Japan)	HSA (Singapore)	Swissmedic (Switzerland)	MFDS (Korea)
Nanotechnology		X	X	X	X		X				
Nanoscale	X		X				X			X	
Nanostructure							X				
Nanomaterial	X		X				X				
Nanomedicine	X	X	X				X				
Nanomedicines		X			X						
Nanosimilars		X									
Nanodevice							X				
Theranostic products											
Combination products			X				X				
Borderline products		X									

3.4 Discussion on selected nanomedicine terms

3.4.1 Nanomedicine

The increasing interest in nanomedicine research is reflected by the number of articles having this term as a keyword attributed by the authors. From 1996 to 2006 the term *nanomedicine* appeared as an author keyword in 80 documents from the publications dataset (Step 1) and increasing to a total of 2320 documents over the following ten years (**Figure 15**).

Figure 15 Use of the term nanomedicine as an author keyword in the publications dataset



Annual contribution of the total number of publications extracted with the search string *nanomedicine** (blue line) in the period of 1996-2016 and f the total number of publications mentioning *nanomedicine* as an author keyword (red bars) in the same period. *Source*: TIM (http://tech.timanalytics.eu)

According to the bibliometric analysis the term nanomedicine appears for the first time in 1998 in a publication title [51]; in 2001 this term appears as an author keyword in an article about future possibilities that nanotechnology will offer in the field of neurosurgery [19]. In 2004 eight publications have *nanomedicine* as an author keyword. These publications discuss a wide range of topics from the application of nanotechnology in diagnostics, drug delivery [20, 21] and molecular imaging applications [22], the possibilities offered by nanotechnology in the field of neurological surgery [23], investigation of nanorobotics system design in nanomedicine [24], to the potential social impact and ethical issues of the application of nanomedicine in health care [25]. The analysis of the term co-occurrence shows that in the scientific literature the most co-occurring terms with *nanomedicine*, i.e. terms that appear together in more than 50 publications, are *drug delivery*, *nanoparticles*, *nanotechnology*, *cancer*, *nanobiotechnology*, *liposomes*, or *theranostics nanomedicine*.

Some authors have indicated that a (regulatory) definition of nanomedicine would have implications for many aspects of translational research, potentially influencing fund allocation, patents, drug regulatory review processes and approvals, ethical review processes, clinical trials and public acceptance [26]. Other authors have expressed reservations about the use of the term *nanomedicine* to refer to nanotechnology-enabled medicine or nanotechnology in different areas of medicine [27], considering *nanomedicine* as an academic term, while explaining that industry perceives it as another advanced medical technology.

The mapping shows that the term *nanomedicine* is used almost exclusively by certain regulatory authorities in their websites. There is no regulatory definition of *nanomedicine*. Some of the authorities consulted in this report propose working definitions; however, other sources, stakeholders and organisations have defined the term from their perspective. **Table 20** in **A5.1** lists descriptions of the term *nanomedicine* retrieved from regulatory sources.

The term *nanomedicine* was mentioned in two clinical trials' summaries in the dataset: once as primary sponsor company name (Clene Nanomedicine), and once to identify the application of nanomedicine technology for diagnosis, referring to the gene expression profile evaluation as diagnosis tool in allographs recipients (WHO Clinical trial ID: NCT01929785).

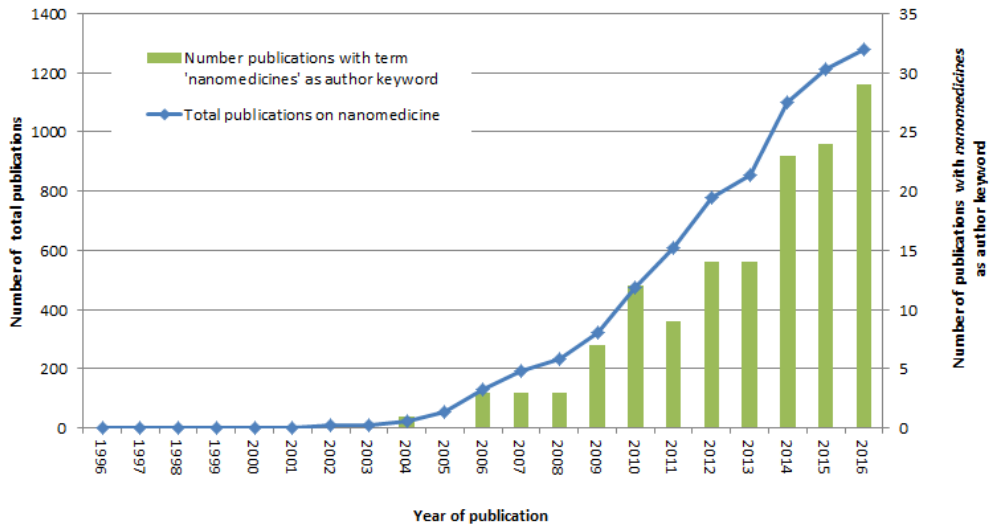
3.4.2 Nanomedicines

Table 21 in **Annex 5** presents a list of descriptions of the term *nanomedicines* extracted from regulatory sources.

The term *nanomedicines* in the literature appears for the first time in 2003 and it was used to describe a "nano-antifungal" product class [43]. In 2004, Alonso [44] used the term as an author keyword and in the article defined nanomedicines as *[products] consisting of nanosystems that are able to deliver drugs to the right place, at appropriate times*.

During the identification of terms in the scientific literature metadata, the term *nanomedicines* was among the top 20 most frequently occurring author keywords, mentioned in 146 publications (**Figure 16**, green bars). In contrast to the term *nanomedicine* that broadly defines the application of nanotechnology to the health sector and therefore could imply a variety of products including pharmaceuticals as well as medical devices, an analysis of the publications retrieved with the plural variant suggested the association of this term to the description of nanotechnology-based pharmaceutical products.

Figure 16 Use of nanomedicines term as an author keyword in the publications dataset



Annual contribution of the total number of publications extracted with the search string *nanomedicine** (blue line) in the period of 1996-2016 and f the total number of publications mentioning *nanomedicines* as an author keyword (green bars) in the same period. *Source*: TIM (http://tech.timanalytics.eu)

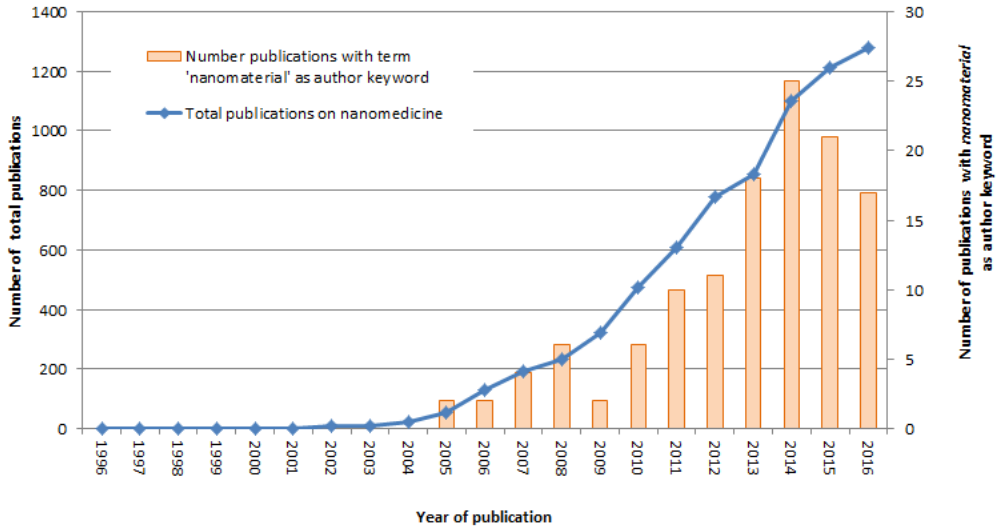
The scientific literature also presents other terms and expressions which *medicinal products containing nanoparticles*, *nanomedicines products*, *nanodrugs* or *nanopharmaceuticals* as synonyms.

In the clinical trial registry, the applied search did not find any record when mapping the ICTRP for this term.

3.4.3 Nanomaterial

The scientific publications dataset consists only of publications in the field of nanomedicine and the term *nanomaterial* in this context is among the top 10 most relevant keywords in the established set.

Figure 17 Use of nanomaterial term as an author keyword in a nanomedicine related dataset



Annual contribution of the total number of publications extracted with the search string *nanomedicine** (blue line) in the period of 1996-2016 and f the total number of publications mentioning *nanomaterial* as an author keyword (orange bars) in the same period. *Source*: TIM (http://tech.timanalytics.eu)

In a regulatory context, the term *nanomaterial* is also one of the most frequent nano-prefixed terms, both in terms of number of texts extracted from authorities' websites and in terms of number of distinct authorities using the term in their documents. A comprehensive comparison assessment of the key elements in regulatory and advisory definitions of the term *nanomaterial* already exists [52]; this report only included the descriptions that are relevant to health products applying nanotechnology or containing nanomaterials. **Table 22** in **Annex 5** presents a list of descriptions of the term *nanomaterial* extracted from regulatory sources.

Regarding the use of *nanomaterial* to describe materials containing or applying nanotechnology in the health sector, several publications and official documents used the term *nanomaterial* when referring to the type of material in the registration or authorisation forms for nanotechnology-based products. The Australian TGA has a general working definition for *nanomaterial*, which is applicable to several products, and TGA uses the term in the definition of *nanomedicines* as therapeutic products containing nanomaterials. The FDA uses the term *nanomaterial* in a general context; it has not established a regulatory definition of nanomaterial, but rather uses the term for ease of reference when generally referring to both materials in the nanoscale range and certain materials that otherwise exhibit related dimension-dependent properties or phenomena. The various Directorates of the European Commission use the term *nanomaterial* in relation to different sectors and products. The DG GROW's website mentions the term *nanomaterial* in documents involving the description of medical devices, which are described as *medical devices containing nanomaterials*. The DG SANTE's website uses the term *nanomaterial* to describe the use of nanotechnology in products other than

medicinal products (e.g. cosmetics). EMA does not describe or use the term *nanomaterial* in the information provided at its webpage, instead the agency uses the term *nanomedicine* to define the use of nanotechnology in medicinal products.

This mapping exercise in clinical trials showed only one summary referring to the term *nanomaterial* to describe a clinical research on nanomaterial-based sensors.

3.4.4 Nanotechnology

The survey of scientific publications revealed that the term *nanotechnology* was one of the most frequently used author keywords in the nanomedicine publications dataset. The term appeared in the earliest publications, and modifications of the word such as *cancer nanotechnology* or *pharmaceutical nanotechnology* were introduced in recent years, with more than 50 composed terms.

In general, there is no accepted regulatory definition of nanotechnology at international level. The definition of nanotechnology and its interpretation are essential elements in the definition of nanomedicine. Several guidance documents on requirements for marketing authorisation of drugs and health products indicate special requirement for nanotechnology–based products or they fall outside the scope of the guidance. **Table 23** in **Annex 5** lists the descriptions of the term *nanotechnology* provided in English language in the webpages and documents provided by regulatory sources.

Two main elements were identified as critical in the retrieved descriptions of the term *nanotechnology*: the size and the exhibition of unique properties related to dimensions. In general, the size ranges from 1 to 100 nm but in some of the descriptions, this range is approximate and not always consistent, even in documents from the same source. Other sources only mention the term *nanoscale* to define the size (section 4.5.4).

In some of these nanotechnology descriptions, a change of properties at the nanoscale in comparison to the non-nanoscale is indicated as a regular element of the description; whereas in others, this change of properties, either chemical, physical or even biological, is only a determining factor in the description of nanotechnology when the outcome of the technology is a structure larger than 100 nm.

A number of clinical trials (14) and patents also mentioned the term *nanotechnology* in their descriptions.

3.4.5 Nanoscale

In a literature review on challenges facing the development of nanotechnology terminology and nomenclature in the field of nanotechnology [53], Klaessig et al. claimed that *any new field derived from the application of nanotechnology methods and techniques is susceptible to the debate on the nanoscale size and how it affects the classification of the products enabled by these technologies and their regulation* [53]. In nanomedicine, size is a key element which may warrant additional safety requirements or quality attributes. Klaessig et al. [53] referred to *nanoscale* as an example of a term that may have different meanings depending the regulatory context. The author notes that *there is a tendency that those* [unique properties] *concerned with biological effects or behavioural differences have a more flexible range to define the term nanoscale*, increasing the size range of the definition beyond 100 nm. Descriptions of the term *nanoscale* found in the regulatory authorities' (RAs) websites (**Annex 5)** were compiled.

The keyword analysis of RAs' websites showed the use of the term *nanoscale* mainly as an adjective or as a synonym of the prefix "nano" in words related to health sector products differentiating them from their bulk equivalent, or to indicate the size of the molecular or structural entity or product (i.e., *nanoscale materials*, *nanoscale self-assembling peptide*, *nanoscale oil*, *nanoscale device*, *nanoscale ingredients*, *nanoscale crystals*, *nanoscale platforms* or *nanoscale therapeutics*). In other cases, the term *nanoscale* is implicit in the use of the prefix "nano" for some terms to differentiate them

from the bulk equivalent or to indicate the application of nanotechnology methods or techniques.

Almost all descriptions found in the explored regulatory sources indicated a size range that includes 1 to 100 nm for *nanoscale*. These descriptions might include the limits mentioned, leading to a more rigid application of *nanoscale*. Other descriptions use the words "around" or "approximately" allowing interpretation to consider products of larger sizes as well.

Health Canada defines in its glossary the term *nanoscale* as "*properties or phenomena* as *properties which are attributable to size and their effects; these properties are distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material*" [54].

As for the application in nanomedicine, the *nanoscale phenomena* may also cover specific physiological interactions, transitions between molecular and microscopic scales, such as increase of drug availability due to an increase of the surface, or alteration in the pK [25]. This unique behaviour could occur for sizes larger than 100 nm, and it had been taken into consideration in some descriptions concerning nanomedicine terminology. For example, Swissmedic describes the upper limit size range to 1000 nm when defining *nanoscale* and FDA's overarching final guidance explains that when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will consider whether a material or end product is engineered to exhibit properties or phenomena attributable to its dimensions up to 1000 nm.

3.4.6 Nanostructure

Table 25 presents a list of descriptions of the term *nanostructure* extracted from different sources. The only description found in a regulatory source for the term *nanostructure* was in the Government of Canada's terminology and linguistic data bank Termium Plus. This term had been also described in the CPC to explain the classification for *specific uses or applications of nano-structures.* In the description of this class, other terms such as *nanosize* or *nanoscale* are also defined as *relate[d] to a controlled geometrical size below 100 nanometres (nm) in one or more dimensions*.

In the dataset of clinical trial summaries, only one result was found to use this term to describe a clinical research project on a *nanostructured lipid carrier*.

Concerning patents, 36 patents classified under the CPC as nanomedicine used the term to identify structures with a size range larger than 100 nm. In one patent, the *term nanostructure* was described as *a structure having at least one region or characteristic dimension with a dimension of less than about 500 nm, e.g., less than about 200 nm, less than about 100 nm, less than about 50 nm, or even less than about 20 nm (*Patent number: 9,598,287; Title: *Method of synthesizing carbon nanorods and nanowires*). In other patents, the size describing a nanostructure went beyond 1000 nm, where *the nanostructure of claim, has a length of about 1 nm to about 1500 nm* (Patent number: 9,187,330; title: *Tubular nanostructure targeted to cell membrane*).

3.4.7 Nanosimilars

This term was initially proposed by EU regulators and it was described on the EMA website as *nanomedicines that are claimed to be similar to a reference nanomedicine*[19].

In the scientific literature, only 3 publications included the term in the author keyword list. In one of these publications, the term *nanosimilars* was explained *as new medicinal outcomes combining the generic drugs and the nanocarrier as an innovative excipient, in*

[19] Nanotechnology. European Medicines Agency webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000345.jsp& (Retrieved 9 March 2017)

order to evaluate them as final products [55]. Other terms or phrases, such as *generic versions of nanomedicines* or *follow-on nanomedicines* had been used to describe this concept in the scientific literature [56-58]. No results were found in the mapping of this term to the ICTRP clinical trials database.

3.4.8 Nanodevice

The only definition for this term was found in the glossary TERMIUM Plus® from the Government of Canada. In this source, *nanodevice* is defined as *an artificial eutectic mechanical device that relies on nanometres-scale components* [54]. The glossary also provides synonyms: *nano-devices delivering drugs* and *devices incorporating nanotechnology*.

The National Cancer Institute Thesaurus (NCIT) gives more relevance to the chemical or biological part of the definition and defines this term as *a functional macromolecule composed of nanoscale components*. Other definitions focused on the engineering properties of the device, thus the NanoParticle Ontology (NPO) defines this term as *an engineered nanomaterial which has an end-directed activity/function*.

3.4.9 Theranostic products (or theranostics), Combination products, and Borderline products

3.4.9.1 **Theranostic Products (or theranostics)**

In the literature, several authors define *theranostics* as *the combination of disease diagnosis and therapy* [59]: *A term created from the words "therapeutic" and "diagnostics", it refers to a class of pharmaceuticals and their directly-related diagnostic accoutrements* [60]. When applied to nanomedicine, a variety of synonyms had been used to describe the meaning including *nanotheranostics, theranostic products* or *theranostic platforms*. In these cases, the term refered to *the combination of diagnostic and therapeutic properties within a single nanomedicine formulation* [61].

The biomedical terminology of Medical Subject Headings (MeSH) included the term *theranostic nanomedicine* referring to *an integrated nano-scale approach to medicine which involves concurrent diagnosis, drug delivery, therapy, and monitoring of therapeutic response* [62].

3.4.9.2 ***Combination Products***

The term *combination products* is mainly used by the FDA, which defines it as:

> *(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labelling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (21 Code of Federal Regulations 3.2(e)).*

Also, Health Canada uses the term *combination product* in a similar concept:

> *Is a therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive nature of the drug component and device component is integrated in a singular product (Health Canada 2006).*

Inside this category, Health Canada indicated that *nano-devices delivering drugs, fell between regulatory regimes (for drugs and medical devices) and thus required different regulatory approaches which could cause administrative delays in product reviews, and also result in inconsistencies across regulatory frameworks* (Health Canada 2010).

The Australian Therapeutic Goods Administration (TGA) proposes a new term to convey the potential regulatory uncertainty over this type of products: *Device-medicine boundary products: […] therapeutic goods that are not readily identified as medicines or devices* [63].

3.4.9.3 ***Borderline Products***

Like the Australian TGA, the EMA also uses *borderline products* as a term to indicate products with an unclear regulatory path, although there is no official definition for borderline products. In a report, the EMA Innovation Task Force (ITF) uses this term to describe also *products that include combination of pharmaceuticals and device*. […] *products for which there is uncertainty over whether they fit the definition of a medicinal product or not*.

In the *Manual on borderline and classification in the Community Regulatory framework for medical devices* (version 1.17 of 09-2015)[20], the European Commission provided an explanation of the meaning of borderline cases for medical devices:

> *Borderline cases are considered to be those cases where it is not clear from the outset whether a given product is a medical device, an in vitro diagnostic medical device, an active implantable medical device or not. Or alternatively, borderline cases are those cases where the product falls within the definition of a medical device but is excluded from the Directives by their scope. Where a given product does not fall within the definition of medical device or is excluded by the scope of the Directives, other Community and/or national legislation may be applicable.*

[20] Manual on borderline and classification in the Community Regulatory framework for medical devices (283 KB) (version 1.17 of 09-2015)

4 Final remarks and conclusion

A novel, growing scientific field is usually accompanied by the generation of a myriad of terms, concepts and definitions, which might be used ambiguously by the stakeholders with diverse interests and different backgrounds, as is the case for the application of nanotechnology in the healthcare sector.

This report aims to support the establishment of a harmonised terminology, in English, for nanotechnology-based health products. Terminology related to the field of nanomedicine has been captured, mapped, and analysed. The terminology derived from different types of information sources commonly used in the regulatory framework for medical products: scientific articles, RAs' webpages, clinical trial registries and patents. This study contributes to the ongoing debate on terminology for nanomedicine, presents supporting information for obtaining an overview of the potential divergences that may appear in the use of terminology in a regulatory context, and discusses the challenges that may arise from the variety of definitions of the same (or very similar) terms.

The major outcomes of this work are summarised here.

- **Presentation of a methodology to profile the basic terminology in the emerging field of nanomedicine and construct a specialised keyword set**

The tech and text mining tools used in this study were confirmed as suitable methods to obtain an objective picture of the terminology used and allowed extraction of relevant keywords within an evolving field such as nanomedicine. By combining text mining and bibliometric methodologies, a methodology has been developed which allowed to construct a keyword set which is sufficiently comprehensive to cover a wide range of concepts related to the field of nanomedicine as well as to identify the relevant information in different types of sources.

Similar to earlier bibliometric analysis of nanotechnology-related publications [64], the analysis of keywords in the publications dataset identified an increase of the terminology associated to nanomedicine over the years, particularly in nano-prefixed terms, which can be interpreted as an increasing research activity in this field. The combination of an automatic term recognition approach, a specialised subset of publications and a simple literature review yielded a comprehensive list of general terms defining the principal areas of application of nanomedicine including therapeutics, diagnostics, drug delivery and devices incl. nanorobotics. Furthermore, specific terms that define the types of nanomaterials applied, such as dendrimers, nanocarriers, micelles, liposomes, and magnetic nanoparticles, were identified.

Based on term frequency, as an indication of terminology consolidation within the field, and term relevance, which is a text-mining algorithm that identified candidate terms from specialised scientific publications considered to be highly relevant to a field, over four hundred keywords from scientific publications related to the field of nanomedicine were selected for the applied specific keyword set. The use of a specific keyword set was particularly useful to explore sources covering diverse themes, tailoring the mapping to specific information on nanomedicine and avoiding the inclusion of terms related to topics or products outside the scope of this analysis (e.g. cosmetics, food or pesticides). Based on its completeness and robustness, this keyword set is a valid tool to map other information sources on the topic of nanomedicine.

- **Mapping and analysis of the use of specialised nanomedicine terminology in relevant regulatory sources**

None of RAs have specific regulations for nanotechnology-based medical products. The regulation of these products is covered by the general legislation addressing the health sector and available procedures to ensure products' safety, quality and efficacy. However, the RAs are aware of the need for additional regulatory guidance, requirements and testing standards to address nanomedicine and support the approval of these products [10]. A way to adapt current regulation is through a number of

nanospecific requirements, and some medicine regulatory agencies are already requesting information to identify nanotechnology-based products and providing specific guidance on how to assess the quality or toxicity of certain materials used in nanomedicine [65].

Mapping different information sources with the specialised keyword set provided an overall picture on the use of terminology, especially in a regulatory context. The analysis of the type and frequency of nanomedicine-related terms was analogous to the one applied in bibliometric studies when exploring a common lexicon on nanotechnology in the scientific literature [17]. The initial assumption of the study was that the use of nanomedicine-related terms, including nano-prefixed and non nano-prefixed terms, reflects the sharing of information and interest of the RA regarding the application of nanotechnology in the health sector. Also, the identification of differences in the use of specific terminology among the RA could be used to indicate potential regional divergences and identify areas for future discussions towards terminology harmonisation.

The analysis of the frequency of occurrence for general terms revealed an interesting trend in the use of certain terms. For example, to describe the application of nanotechnology in medicinal products, EMA uses the term *nanomedicines*, whereas *nanomaterial* is used by the FDA to describe drug products that contain nanomaterials.

The terminology analysis of the RAs' websites provided insights into the differences in the amount of information as well as the number and type of terms used in regulatory documents to describe the advancements in the nanomedicine field. The type of information provided at these websites presented a wide range of subjects and document types, including product registration forms, guidance documents, product information factsheets, patient/consumer leaflets, assessment reports from regulatory agencies or information on safety of drugs. Regarding the total amount of information extracted from the webpages, a huge variability among the regulatory authorities was observed. For non-English webpages this variability could be partially explained by the limited number of webpages in English. When English is the primary language, this variability could be explained by the level of transparency to inform different stakeholders (consumers, practitioners, registrants). A confounding source of terms was the variety of products that a health authority may regulate, from food and cosmetics to tobacco products. Among the authorities analysed in here, the FDA, Health Canada and TFDA are agencies presenting more nanomedicine-related concepts in the information shared on their websites. In particular, an extensive list of specific terms related to nanomaterials at the FDA website in a specialised section on *Science and Research* gave a significant amount of information on basic and clinical research.

Finally, the report describes interesting regional variants in the use of general terms indicating the need to establish clear terminology and definitions which would facilitate an effective communication among international stakeholders and foster a regulatory convergence for products that apply nanotechnology. An example is EMA's use of the plural form of the term *nanomedicine* that is almost exclusively used in the EU to describe the application of nanotechnology in medicinal products. Since EMA only works on medicinal products and biological products, the term *nanomedicines*, when used by EMA, should not be confused with other applications, such as medical devices. However, the term *nanomaterial* is used by EMA with a low frequency, and it is used more frequently in organisations outside the EU as a general term to refer to nanotechnology-based products or materials (e.g. liposomes, dendrimers and metal nanoparticles). Some terms, identified as used by non-European agencies to describe nanomedicine products, are compound terms such as *therapeutic products containing nanomaterials* (Health Canada), *nanotechnology-based medicines* or *nanosize drugs* (PMDA, Japan), or *drug products that contain nanomaterials*, *nanotechnology products* or *products that involve the application of nanotechnology* (FDA). However, these terms might not be solely related to medicinal products (or drugs) but also refer to medical devices or combination products. Thus, an agreed set of terms and definitions, which describe the various applications of nanotechnology in medical products unambiguously, would improve

communication among stakeholders and contribute towards global regulatory convergence for such products.

- **Increased use of nanomedicine-related terms in clinical trials and patents**

As previously reported in [25], an increase of applications of nanotechnology in health products was also identified through the analysis of terminology in the international clinical trials registries database WHO-ICTRP. Due to the nature of the information reported (for example, type of material, processes or interventions, disease targeted or studied application), clinical trial registries and patents were interesting sources of information to assess the impact of application of nanotechnology in the health sector, and therefore useful sources of specialised terminology. Researchers, industry and policy-makers might benefit from the information provided in patents to identify potential solutions to technical problems, future commercial applications, and to drive innovation and regulatory preparedness to inform decision-making [18].

In this study, the keyword set in clinical trials and patents as a proxy for the terminology used by researchers, clinicians and producers to describe the application of nanotechnology in medicinal products and medical devices in a specialised context other than scientific publications. This analysis did not aim to provide any categorisation of nanomedicines.

Within the clinical trials registry, it was evident that materials, products and research protocols described would correspond exclusively to the health sector and the approach identified a wide range of terms describing the use of nanomaterials in the health sector. The fact that only few new terms were identified querying *nano**, in comparison with the nano-prefixed terms already present in the keyword set, validated its extensiveness to be used for future evaluations of terminology in other sources.

Similar to scientific publications, the clinical trials database was enriched in specific terms describing materials and formulations but showed scarce reference to general terms. The analysis of non nano-prefixed terms showed that *liposomes*, *emulsions*, *aerosol*, *hydrogel* followed by *colloids* were the most frequent terms used to report potential nanomedicine products. However, due to the lack of detailed size information, it was difficult to reliably assess whether the material is smaller than 1000 nm and whether the extracted clinical trial could be referring to an investigation of a product applying nanotechnology. Depending on the definition of nanomedicine or nanomaterial, a number of clinical trials extracted by querying these terms could be considered outside the scope of this study. For example, several products already approved and on the market involve drugs encapsulated in liposomes with a size of several micrometres, which in some scientific publications were labelled as *nanopharmaceuticals based on its individual drug containing nano-sized chambers* [66]. A similar trend was observed in patents; however, as some patents had a well-defined classification system that indicated whether nanotechnology was involved or were directly classified as nanomedicine, the uncertainty associated to the use of non nano-prefixed term to identify nanomedicine products was reduced.

The increasing use of nano-prefixed terms for already existing concepts may suggest an effort to unambiguously identify the tested product as a nanotechnology-based product. However, the social aspect of using nano-prefixes to imply innovation or rebranding technology to receive funding had also been previously suggested as a relevant factor in the analysis of the lexicon evolution on nanotechnology [14]. Thus, the establishment of a clear terminology to describe materials and formulations applying nanotechnology or containing nanomaterials would contribute to developing a classification system for these products to strengthen the translation of research, increase transparency and enable informed decisions.

- **Compilation of relevant terms to describe the application of nanotechnology in the health sector and relevant documentation**.

Finally, the report presents a compilation of descriptions of selected nanomedicine-related terms provided in documents by RA or with regulatory relevance. Due to a general lack of information on terms related to materials and formulations within the RAs' websites, the descriptions were extracted from existing vocabularies, glossaries or available ontologies. Some of the selected terms were used also in other contexts; however, the extraction of descriptions was limited to documents that inform on the application of nanotechnology in the health sector.

This compilation presents the variety of elements in the descriptions, which may contribute to the discussion, at scientific and/or regulatory level, on the need to clarify certain terms. It also points out the inconsistencies among RA in the descriptions of a certain term and provides the foundation to work towards a harmonised terminology in nanomedicine.

In conclusion, the diversity of terms as well as their correlation and description highlight the challenges of communication in biomedical research and regulation of nanotechnology-based products. The mapping approach presented here is a first attempt to identify the key terms distinctly used by different health authorities to provide information on nanomedicine. These results show sectorial and geographical difference in the use of the key terms among authorities in different geographical areas. This diversity was also observed in the definitions extracted from regulatory sources, especially those concerning general terms. The results aim to provide a first basis for discussions towards a harmonised terminology in this area. In the future, an extension of this mapping approach to other relevant local, national and global health authorities, for example international organizations such as the World Health Organization and the World Trade Organization, may contribute to the effort to integrate terms and concepts across authorities covering the regulation of medical products applying nanotechnology. This work might provide necessary background information to allow the development of standards in the field of nanomedicines, which would stimulate innovation and foster industrial competitiveness.

Finally, as this report has been underway for some time and as the preliminary outcomes were presented to the IPRF at several occasions, various websites of the RA have been modified. Given this dynamic nature of websites, it would not be possible to exactly replicate this study.

4.1 Challenges and next steps

This initial study has shown the feasibility of the methodology, which could thus be used in future research for example in studies with an enlarged number of RAs' websites. The present study focussed mainly on authorities from countries participating in the IPRF Nanomedicines Working Group.

Since text-mining was performed over the total of information obtained from the regulatory agencies, the frequency analysis of the terminology might include documents from the application of nanotechnology in other fields, for example the use of nanoparticles in sun-screen products. This could have a significant impact in the number of documents extracted for certain terms, especially for general terms such as *nanotechnology* or *nanoscale*. In order to identify only health related documents, the current dataset needs to be further curated, and ways to systematically or (semi)automatically in-and exclude documents might be considered in future.

Due to technical challenges, it was impossible to crawl some webpages, hence manual mapping using the website's search engine was performed. Therefore, the frequency analysis was not considered for these websites but the retrieval of term definitions was performed whenever possible (Step 3). A similar approach was used for clinical trials information. The presented results could therefore be considered as an analysis of trends

rather than a report of exact frequency numbers. An automatic text-mining approach, using term variants, considering product brands or co-term analysis would have resulted in a more accurate picture of the use of nanomedicine terminology in these information sources.

The application of text mining and automatic term extraction as well as analysis of other relevant information sources that are representative of the translation of nanomedicine, e.g. automatic text mining of the clinical trials databases may provide sufficient and robust data for the analysis of the evolution of terminology in this emerging technology. Comparing the terminology used at different stages of translation (from research to commercialisation) could aid in understanding for example the maturity of the state of science, the level of integration between stakeholders and the consolidation of the terminology. A common understanding on terms relevant for innovative medical products will support a smooth translation of highly needed products from the laboratory environment to clinical applications where they are highly needed in order to adress unmet medical needs. Since most diseases are not region specific a harmonised terminology describing such emerging product class are of utmost importance to make them available to markets worldwide without unnecessary delay.

List of abbreviations

ANVISA	Brazilian Health Regulatory Agency
ASTM	American Society for Testing and Materials (ASTM International)
BSI	British Standards Institution
CORDIS	Community Research and Development Information Service (European Commission)
CPC	Cooperative Patent Classification System
CT	Clinical trial
DG GROW	Directorate-General for Internal Market, Industry, Entrepreneurship, and SMEs (European Commission)
DG SANTE	Directorate-General for Health and Food Safety (European Commission)
EMA	European Medicines Agency
EPO- PATSTAT	European Patent Office- Worldwide Patent Statistical Database
EPR	Enhanced Permeability Retention
FDA	Food and Drug Administration (USA)
HC	Health Canada
HSA	Health Sciences Authority (Singapore)
ICTRP	International Clinical Trials Registry Platform
IPRF	International Pharmaceutical Regulators Forum
ISO	International Organization for Standardization
KCO	Keyword co-occurrence network
MeSH	Medical Subject Headings
MFDS	Korean Ministry of Food and Drug Safety
MHLW	Ministry of Health, Labour and Welfare (Japan)
NCI	National Cancer Institute (USA)
NCIm	National Cancer Institute Metathesaurus (USA)
NCIt	National Cancer Institute Thesaurus (USA)
NNI	National Nanotechnology Initiative (USA)
NPO	Nanotechnology Particle Ontology
OECD	Organisation for Economic Co-operation and Development
PMDA	Japanese Pharmaceuticals and Medical Devices Agency
SPIO	Superparamagnetic iron oxide
Swissmedic	Swiss Institute of Therapeutic Products
TFDA	Taiwan Food and Drugs Administration
TGA	Therapeutic Goods Administration (Australia)
TIM	Tools for Innovation Monitoring

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Annexes

Annex 1 Description of bibliometric search engines

A1.1 Automatic extraction with Tools for Monitoring Innovation (TIM)

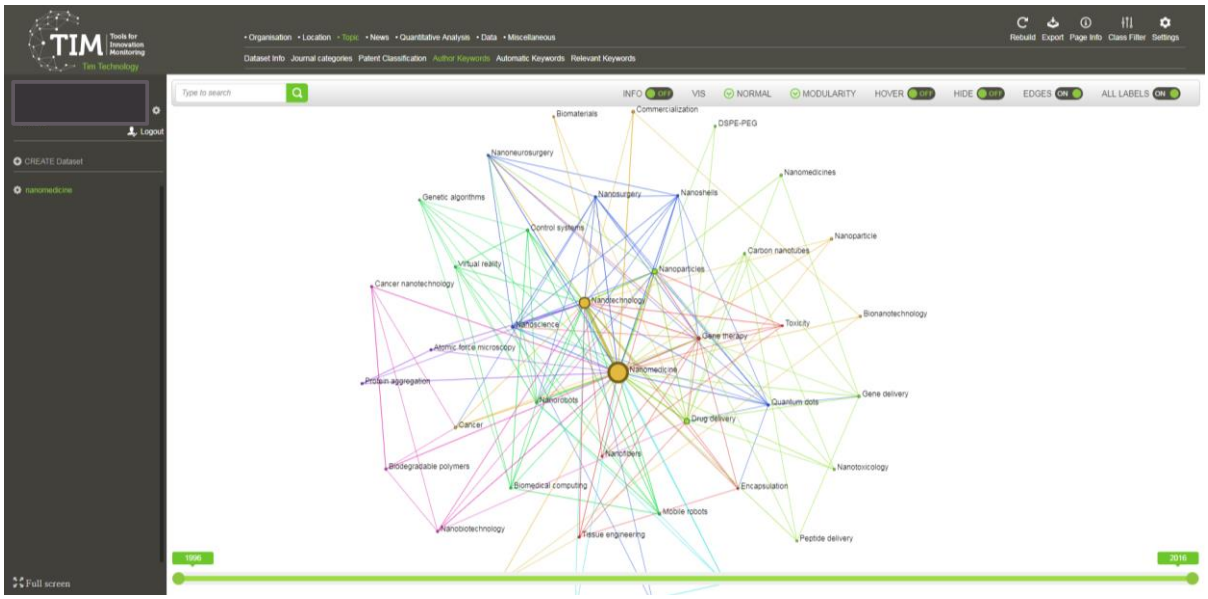
TIM is a platform being developed by the JRC's Competence Centre on Text Mining and Analysis at the European Commission, which applies text mining and computational linguistic techniques to monitor innovation through the analysis of documents on a specific topic. TIM technology editor allows its users to create and visualise datasets about specific technological issues. It gathers together datasets such as patents, scientific publications, and EU grants (http://timanalytics.eu/).

This search engine provides a wide range of text-mining and visualisation tools interesting for this purpose, such as automated extraction of keywords, information on keyword occurrence and co-occurrence frequency (Figure 2) and the application of algorithms to rank keywords according their relevance on the document set retrieved for a given search string.

A1.1.1.Keyword and topic visualisation

TIM facilitates the visualisation of the keyword extraction results through word maps, also called *keyword co-occurrence networks (KCO)*. KCOs use the most frequent author keywords of the documents to study the conceptual structure of a research field (**Figure 18**). The size of the nodes is proportional to the respective keyword's frequency (number of documents mentioning a given author keyword); the thickness of the edges represents the co-occurrence of the linked nodes (number of documents sharing keywords. Author keywords listed in one paper are linked together because they are all terms that can be used to represent the core of a research paper and stronger interrelations can be expected.

Figure 18 Visualisation of keyword frequency and co-occurrence in TIM



This platform identifies and lists three categories of keywords: *author*, *automatic* and *relevant keywords* (Box 1). In general, the *automatic keywords* category of keywords contains general terms that are unspecific for the field of nanomedicine. For this reason, only *author keywords* and *relevant keywords* extracted with TIM were considered in the construction of the nanomedicine keyword set.

Keywords generated by TIM (Tools for Monitoring Innovation) language processing algorithms

Author Keywords are keywords chosen by authors of scientific papers to describe the topic of their paper and for indexing their paper. Author keywords are frequently included in the header information of a published journal article. This category only refers to terms found in the scientific literature (articles, reviews, conference proceedings and some book chapters) and no data consolidation has been performed in this set.

Automatic keywords are terms automatically extracted from the text using language processing algorithms. They are calculated by processing the title, abstract and author keywords. The Automatic keywords are extracted from all types of documents retrieved with this query, including patents and EU projects. The list of automatic keywords goes through a process of data consolidation, for that plurals and certain type of spellings are collapsed in one simple term; i.e. the term nanomedicine shows in the literature many spelling variants: Nanomedicine, nanomedicine, Nano Medicine, nanomedicines, or Nanomedicines. This process reduces redundancy and noise but in some cases may also omit relevant information, i.e. plurals of terms with specific meaning compared to their singular form. The system applies specific calculations to rank the relevance and results in a third type of keyword list called relevant keywords.

Relevant keywords are terms ranked within the total of documents; these terms have associated a numerical score that measures the relevance of the keyword in the group of the total of identified terms of this dataset. TIM scores the relevance of the automatically extracted keywords within the pool of documents according their weight and uniqueness in this dataset. Thus, this score identifies those terms that are rarer and potentially more specialised or related to the field. This rank is calculated using the term frequency–inverse document (TF-IDF) calculation, a numerical statistic that is intended to reflect how important a term is to a document by estimating the rarity of a term in the whole document collection. TIM designates this list of terms as relevant keywords (source: http://tech.timanalytics.eu/).

A1.2 Automatic extraction with GoPubMed

To automatically extract terminology on nanomedicine, another bibliographic tool, GoPubMed was used, to validate and complement the keyword set extracted with TIM. This publication search engine explores information from PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), one of the most relevant biomedical literature databases.

Like TIM, GoPubMed provides statistics on top terms and total publications hit counts. A particularity of GoPubMed is that this platform performs an ontology-based literature search, using hierarchically structured vocabularies, and therefore allows the extraction of terms found inside the same class. This web server uses background knowledge and it associates concepts with keywords which allows going from general terms to more specific ones on the searched topic [67]. These concepts categories come from biomedical specific vocabularies such as GeneOntology (GO) for molecular biology (www.geneontology.org), MeSH (Medical Subject Headings), SNOMED, or UMLS for the medical domain (umlsinfo.nlm.nih.gov). Each of these categories nests other specific concepts related with the searched keyword.

100 top terms provided by the engine were selected and expert judgement were applied to exclude terms not specific for nanomedicine but used in the broader field of health care and toxicology (i.e. humans, cell line, culture, preparations, or temperature). In addition, to increase the specificity of the keywords retrieved selected terms were nested under certain general terms: nanoparticles, pharmaceutical preparations, drug delivery systems and nanostructures.

Annex 2 List of keywords automatically extracted with bibliometric search engines

A2.1 List of keywords automatically extracted with TIM for nanomedicine

The top 100 relevant keywords and author keywords retrieved by using TIM and (*nanomedicine**) as search string creating a nanomedicine specific publication dataset. The keywords are sorted by relevance score (**Table 11**) and occurrence frequency, respectively. Some of the differences between the keywords is whether for example it starts with a capital letter or not (e.g. 1. Nanomedicine versus 4. nanomedicine), or whether it is plural or not (e.g. 1. Nanomedicine versus 12. Nanomedicines). Author keywords having the same frequency appear in random order. The abbreviations in this table are automatically assigned by TIM, and they do not always represent the ones commonly found in the literature.

Table 11 Top 100 most relevant terms in TIM's *nanomedicine** publications dataset

Ranking	Keywords	Relevance	Ranking	Keywords	Relevance
1	nanomedicine	22492.08	51	nanotoxicity	471.94
2	drug delivery (DD)	3734.26	52	cancer nanomedicine	470.67
3	nanotechnology	3512.40	53	silver nanoparticle (SN)	465.71
4	nanoparticle	3222.09	54	protein corona (PC)	461.46
5	nanocarriers	1867.88	55	therapeutics	460.78
6	theranostics	1535.91	56	reactive oxygen species' (ROS)	456.42
7	liposomes	1494.18	57	paclitaxel	449.80
8	nanomaterial	1467.77	58	cellular uptake	449.12
9	quantum dot (QD)	1147.52	59	PEGylated	446.52
10	polyethylene (PE)	1124.41	60	active targeting	436.10
11	micelles	951.64	61	gene delivery	434.68
12	cancer therapy	909.61	62	anticancer drug	430.30
13	gold nanoparticle (GN)	903.87	63	cytotoxicity	429.12
14	deoxyribo nucleic acid (DNA)	884.94	64	nanotheranostics	427.96
15	dox	813.93	65	multifunction	427.39
16	nanobiotechnology	803.07	66	drug carrier	419.96
17	MRI	752.73	67	TEM	419.21
18	dendrimer	751.93	68	nanoscale	416.70
19	carbon nano tube (CNT)	750.77	69	theranostic nanomedicine	412.74
20	biocompatibility	749.18	70	drug targeting	408.00
21	nanorobotics	743.43	71	hydrolysis acidification (HA)	406.43
22	magnetic nanoparticles (MN)	735.83	72	cancer cells	403.58
23	nanotoxicology	743.43	73	FeO	399.90
24	Manufactured nanoparticles (MNP)	710.97	74	photodynamic therapy	399.63
25	biodistribution	664.92	75	nanotherapeutics	399.18
26	photothermal therapy	655.71	76	nanoformulation	395.31
27	targeted drug delivery	655.44	77	delivery system (DS)	384.98

Table 11 (cont)

Ranking	Keywords	Relevance	Ranking	Keywords	Relevance
28	biomedic	642.26	**78**	nanocapsule	384.85
29	targeted delivery	630.40	**79**	nanomedical	383.93
30	quantum dots (QD)	607.94	**80**	nanosystem	374.68
31	carbon nanotube (CN)	607.44	**81**	cancer	373.99
32	inf	605.53	**82**	gene therapy (GT)	372.06
33	doxorubicin	602.52	**83**	chitosan	369.73
34	pH	565.24	**84**	iron oxide (IO)	368.92
35	ML	555.56	**85**	nanogel	366.50
36	solid lipid nanoparticles (SLN)	543.26	**86**	nanopharmaceutical	359.34
37	tocopheryl polyethylene glycol succinate (TPGS)	539.33	**87**	encapsulation	356.01
38	tumor targeting	538.84	**88**	mesoporous silica (MS)	347.80
39	poly lactic glycolic acid (PLGA)	538.38	**89**	nanostructure	344.79
40	conjugation	532.21	**90**	nanodiamonds	338.84
41	cancer nanotechnology	515.27	**91**	polymer therapeutics	338.09
42	molecular imaging (MI)	509.78	**92**	super paramagnetic iron oxide nanoparticles (SPION)	337.89
43	delivery	509.48	**93**	sup	337.10
44	nanos	507.13	**94**	contrast agent (CA)	333.95
45	aunps	505.43	**95**	nanodrugs	333.87
46	ribonucleic acid (RNA)	503.80	**96**	polycaprolactone (PCL)	332.56
47	EPR effect	499.56	**97**	prodrugs	331.14
48	Central nervous system (CNS)	485.71	**98**	drug load (DL)	328.52
49	sirna	485.16	**99**	polymer	328.09
50	self assembly (SA)	483.43	**100**	ptx	325.35

Table 12 Top 100 most frequent author keywords in TIM's *nanomedicine** publications dataset

Ranking	Keywords	Frequency Number publications	Ranking	Keywords	Frequency Number publications
1	Nanomedicine	2087	**51**	Tissue engineering	45
2	Drug delivery	604	**52**	Dendrimers	44
3	Nanoparticles	594	**53**	Hyperthermia	43
4	nanomedicine	504	**54**	Micelles	43
5	Nanotechnology	414	**55**	Controlled release	43
6	Cancer	218	**56**	Endocytosis	43
7	Nanoparticle	207	**57**	Photothermal therapy	42
8	drug delivery	171	**58**	siRNA	41
9	nanoparticles	142	**59**	Inflammation	41
10	Liposomes	133	**60**	Targeted delivery	40
11	Cancer therapy	110	**61**	DNA	39

Table 12 (cont.)

Ranking	Keywords	Frequency Number publications	Ranking	Keywords	Frequency Number publications
12	Nanomedicines	106	**62**	Polymeric nanoparticles	39
13	Theranostics	95	**63**	Biomaterials	38
14	Carbon nanotubes	93	**64**	Drug delivery system	38
15	Imaging	92	**65**	Breast cancer	37
16	Gold nanoparticles	89	**66**	Oxidative stress	37
17	Cytotoxicity	86	**67**	Blood-brain barrier	36
18	Quantum dots	85	**68**	Therapy	36
19	Nanomaterials	82	**69**	Diagnosis	35
20	Gene therapy	77	**70**	Active targeting	34
21	Targeting	76	**71**	theranostics	34
22	Magnetic nanoparticles	76	**72**	Tumor targeting	34
23	Chemotherapy	73	**73**	PLGA	33
24	Nanobiotechnology	71	**74**	Polymers	32
25	Nanotoxicology	71	**75**	Nanocarrier	31
26	Toxicity	69	**76**	Diagnostics	31
27	nanoparticle	66	**77**	gold nanoparticles	30
28	cancer	65	**78**	self-assembly	29
29	Liposome	64	**79**	Atherosclerosis	29
30	Self-assembly	63	**80**	Personalized medicine	28
31	Drug targeting	63	**81**	cancer therapy	28
32	Doxorubicin	63	**82**	liposomes	28
33	Biodistribution	62	**83**	Polymeric micelles	27
34	Biocompatibility	61	**84**	Theranostic	27
35	nanotechnology	58	**85**	Protein corona	27
36	MRI	55	**86**	Docetaxel	26
37	Gene delivery	55	**87**	SiRNA	26
38	Apoptosis	54	**88**	nanomaterials	26
39	Molecular imaging	54	**89**	Polymer therapeutics	25
40	Drug delivery systems	53	**90**	Biodegradable polymers	25
41	Cancer nanotechnology	52	**91**	Polymer	24
42	Photodynamic therapy	52	**92**	photothermal therapy	24
43	Chitosan	50	**93**	Reactive oxygen species	24
44	Magnetic resonance imaging	50	**94**	Targeted therapy	24
45	Targeted drug delivery	48	**95**	drug targeting	23
46	Paclitaxel	47	**96**	Bioavailability	23
47	Pharmacokinetics	47	**97**	Dendrimer	23
48	Silver nanoparticles	47	**98**	Alzheimer's disease	23
49	Nanotoxicity	46	**99**	Regenerative medicine	23
50	Nanocarriers	45	**100**	Surface modification	23

A2.2. List of keywords automatically extracted with TIM for nano and medical devices

TIM top 100 relevant keywords and author keyword retrieved using (*nano** AND *"medical device*"*) as search string sorted by relevance score and occurrence frequency, respectively. Author keywords having the same frequency appear in random order.

Table 13 Top 100 most relevant terms in TIM's (nano* AND "medical device*") publications dataset

Ranking	Relevant Keywords	Relevance	Ranking	Relevant Keywords	Relevance
1	medical device (MD)	1991.14	**51**	nano scale	85.16
2	silver nanoparticle (SN)	538.07	**52**	nanoskin	82.82
3	nanotechnology	439.32	**53**	Food and Drug Administration(FDA)	79.37
4	agnps	324.69	**54**	electrospinning	78.65
5	implanted medical devices (IMD)	287.01	**55**	nanogenerator	78.49
6	biocompatibility	271.37	**56**	scaffold	77.50
7	biomaterials	253.26	**57**	polyurethane	76.99
8	nanoparticle	236.30	**58**	polymer	76.34
9	nanomaterial	213.66	**59**	bionanocomposite	75.96
10	biomedic	209.71	**60**	silver ions	74.80
11	nanosilver	209.47	**61**	mosquito lagoon (ML)	74.21
12	nanomedicine	206.06	**62**	antibacterial property	73.58
13	silver	202.61	**63**	catheter	73.11
14	biofilm	201.13	**64**	titanium	72.99
15	drug delivery (DD)	192.85	**65**	nanotopography	72.56
16	active implanted medical devices (AIMD)	188.47	**66**	nanobiotechnology	72.52
17	carbon nano tube (CNT)	187.69	**67**	implantable device	72.43
18	nanocomposites	168.98	**68**	nanostructured surface	71.86
19	scanning electron microscope (SEM)	155.62	**69**	antimicrobial activity	71.18
20	coating	152.96	**70**	antibacterial coating	71.16
21	nanos	150.17	**71**	anti biofilm	70.29
22	tissue engineering (TE)	147.60	**72**	surface modification	69.21
23	bias competit (BC)	138.26	**73**	stent	67.94
24	antimicrobial	135.37	**74**	x ray diffraction (XRD)	67.15
25	inf	135.00	**75**	hydroxylapatite (HAP)	65.24
26	biofilm formation (BF)	134.38	**76**	transmission electron microscopy (TEM)	64.49
27	protein undernourished (PU)	132.27	**77**	biosensors	64.17
28	carbon nanotube (CN)	131.35	**78**	block copolymer (BC)	63.89
29	antibacterial	130.67	**79**	nanotube	63.53
30	medical implants	129.65	**80**	blood compatibility	62.94
31	medical application	123.87	**81**	orthopedic	62.86
32	invention	120.93	**82**	ag nps	62.42
33	cellulose	119.77	**83**	micro-Electro-Mechanical Systems (MEMS)	59.58
34	polydimethylsiloxane (PDMS)	119.06	**84**	nanocellulose	59.39

Table 13 (cont.)

Ranking	Relevant Keywords	Relevance	Ranking	Relevant Keywords	Relevance
35	regener medicin (RM)	112.36	**85**	thereof	56.74
36	bacterial	112.00	**86**	biomimetic	56.32
37	poss pcu	111.97	**87**	nanometer	56.31
38	nanofiber	110.33	**88**	ag nanoparticle	55.91
39	wound dressing (WD)	108.66	**89**	polymere	54.59
40	nanostructure	108.38	**90**	staphylococcus aureus (SA)	54.54
41	antibacterial activity (AA)	105.80	**91**	hydroxyapatite	54.53
42	nanoscale	104.42	**92**	the coat (TC)	54.33
43	hemocompatibility	101.19	**93**	cytotoxicity	54.30
44	poly lactic glycolic acid (PLGA)	97.40	**94**	polylactic acid	54.21
45	micro nano	93.74	**95**	chitosan	54.12
46	protein adsorption	91.17242	**96**	atomic force microscopy (AFM)	53.14
47	implantable	90.60061	**97**	nanocoating	53.13
48	hydrogel	89.11189	**98**	nanopore membranes	52.82
49	adhesic	88.4455	**99**	antibiofilm	52.43
50	implants	86.3094	**100**	graphene	52.31

Table 14 Top 100 most frequent author keywords in TIM's (nano* AND "medical device*") publications dataset

Ranking	Author Keywords	Frequency Number publications	Ranking	Author Keywords	Frequency Number publications
1	Nanotechnology	47	**51**	Nanofibers	6
2	Nanoparticles	41	**52**	Hydrogels	6
3	Silver nanoparticles	41	**53**	Staphylococcus aureus	6
4	Medical devices	37	**54**	Infection	6
5	Biocompatibility	35	**55**	Stainless steel	6
6	Medical device	27	**56**	silver nanoparticles	6
7	Drug delivery	27	**57**	Osteoblasts	6
8	Biomaterials	19	**58**	Polymers	6
9	Silver	18	**59**	Hemocompatibility	6
10	Nanoparticle	16	**60**	Pseudomonas aeruginosa	5
11	Nanomaterials	16	**61**	Bionanotechnology	5
12	Antibacterial	16	**62**	Bionanocomposites	5
13	Nanomedicine	15	**63**	Mechanical properties	5
14	Tissue engineering	15	**64**	Fibroblasts	5
15	Biofilm	14	**65**	Nanoskin®	5
16	Carbon nanotubes	13	**66**	POSS-PCU	5
17	Antimicrobial	13	**67**	Collagen	5
18	Regenerative medicine	12	**68**	MEMS	5
19	Cytotoxicity	12	**69**	Biomedical	5

Table 14 (cont.)

Ranking	Author Keywords	Frequency Number publications	Ranking	Author Keywords	Frequency Number publications
20	Antibacterial activity	12	**70**	Apoptosis	5
21	Bacterial cellulose	12	**71**	Implant	5
22	Nanocomposites	11	**72**	Hydroxyapatite	5
23	Surface modification	11	**73**	Biosensors	4
24	Silver nanoparticle	11	**74**	Titanium dioxide	4
25	Electrospinning	10	**75**	Corrosion	4
26	Titanium	10	**76**	Coatings	4
27	Protein adsorption	10	**77**	Medical applications	4
28	Toxicity	10	**78**	S. aureus	4
29	Nanosilver	10	**79**	Chitosan	4
30	Inflammation	9	**80**	Nanostructured materials	4
31	Coating	9	**81**	Catheter	4
32	Nanocomposite	9	**82**	medical device	4
33	Antimicrobial activity	9	**83**	Film	4
34	Controlled release	8	**84**	Biomedical application	4
35	Biomaterial	8	**85**	Nanomaterial	4
36	Cell adhesion	8	**86**	Self-assembly	4
37	Surface functionalization	8	**87**	Scaffold	4
38	Polymer	8	**88**	Bacterial adhesion	4
39	Biofilms	8	**89**	DNA damage	4
40	Nanoindentation	7	**90**	cytotoxicity	4
41	Nanotopography	7	**91**	AFM	4
42	biofilm	7	**92**	Carbon	4
43	Biomedical applications	7	**93**	biocompatibility	4
44	Scaffolds	6	**94**	Stem cells	4
45	nanoparticles	6	**95**	Albumin	4
46	Hydrogel	6	**96**	Nanotubes	3
47	Biosensor	6	**97**	Tribology	3
48	Composites	6	**98**	Thrombin	3
49	nanotechnology	6	**99**	Gene therapy	3
50	Nanobiotechnology	6	**100**	Nanofibers	3

A2.3 List of keywords automatically extracted with GoPubMed

Table 15 GoPubMed top 100 "Top terms" sorted by keyword occurrence frequency

– Nanoparticles	– Oxides	– Apoptosis	– Antibodies
– Humans	– Liposomes	– Membrane	– Micelles
– Pharmaceutical Preparations	– Cell Line	– Spectrum Analysis	– Macrophages
– Animals	– Drug Carriers	– Nature	– Cell Proliferation
– Neoplasms	– Cell Line, Tumor	– Equipment and Supplies	– X-Ray Diffraction
– Therapeutics	– Membranes	– Personal Autonomy	– stem cell development
– Nanomedicine	– Fluorescence	– Physics	– Magnetic Resonance Spectroscopy
– Tissues	– Polymerization	– Serum	– Inflammation
– Mice	– Culture	– Polyethylene Glycols	– Ligands
– Evaluation Studies as Topic	– Peptides	– Cells, Cultured	– stem cell differentiation
– Drug Delivery Systems	– X-Rays	– Immunity	– Microscopy, Electron, Scanning
– Nanostructures	– Cell Survival	– Microscopy, Electron	– Oxygenators
– Research Report	– Medicalization	– Fees and Charges	– Breast Neoplasms
– Proteins	– Immunization	– Rats	– Carcinoma
– Genes	– Work	– Medicine	– Binding
– Patients	– Antineoplastic Agents	– Technology	– Nanotubes, Carbon
– Nanotechnology	– Forecasting	– Intracellular	– Survival
– Microscopy	– Diagnosis	– Adult	– Hydrogen-Ion Concentration
– Male	– Lipids	– Apoptosis	– RNA, Small Interfering
– Female	– DNA	– Biological Availability	– Doxorubicin
– Electrons	– Hydrophobic and Hydrophilic Interactions	– Safety	– Pharmacokinetics
– Polymers	– Lung	– Environment	– Wounds and Injuries
– Electronics	– Nanotubes	– Metal Nanoparticles	– Transfection
– Particle Size	– Stem Cells	– Microscopy, Electron, Transmission	– Lasers
	– Drug Therapy	– antigen binding	– Permeability
		– Temperature	

Source: GoPubMed (http://gopubmed.org/web/gopubmed/); search string *nanomedicine**

Table 16 List of synonyms linked to nanoparticles, pharmaceutical preparations, drug delivery systems and nanostructures.

Nanoparticles	Pharmaceutical preparations	Drug Delivery Systems	Nanostructures
– Carbon nanotubes	– Liposomes	– Liposomes	– Nanoparticles
– Metal Nanoparticles	– Drug Carriers	– Drug carriers	– Nanostructures
– Dendrimers	– Micelles	– Dendrimers	– Nanotubes Nanotubes, Carbon
– Quantum Dots	– Dendrimers	– Nanocapsules	– Metal Nanoparticles
– Nanocapsules	– Nanocapsules	– Nanoconjugates	– Dendrimers
– Magnetite Nanoparticles	– Colloids	– Excipients	– Quantum Dots
– Fullerenes	– Hydrogels	– Drug implants	– Nanocapsules
– Nanoconjugates	– Hydrogel	– Unilamellar liposomes	– Nanocomposites
– Nanospheres	– Prodrugs	– Virosomes	– Nanofibers
– Nanoshells	– Delayed-Action Preparations	– Tablets	– Magnetite Nanoparticles
– Nanodiamonds	– Suspensions	– Insulin infusion systems	– Fullerenes
– Calcifying Nanoparticles	– Nanoconjugates		– Nanoconjugates
	– Emulsions		– Nanospheres
	– Excipients		– Nanopores
	– Plant Extracts		– Nanoshells
	– Powders		– Nanodiamonds
	– Capsules		– Nanowires
	– Dosage Forms		– Calcifying Nanoparticles
	– Drug Combinations		– Nanotubes, Peptide

Source: GoPubMed (http://gopubmed.org/web/gopubmed/); search string *nanomedicine**. These terms are sorted by term frequency (number of publications mentioning the term)

Annex 3 Description of nanomedicine materials and products in the literature

The extracted categories derived from the scientitic literature review, by searching for the term nanomedicine. The 50 most cited scientific reviews on nanomedicine published until October 2016 were considered.

Table 17 Summary of list of terms identified in the literature review

Source	Terms (not official categories)	Reference
U.S. Food and Drug Administration (FDA) **List of terms applicable to nanomedicine**	Nanoparticle Polymeric nanoparticle platforms Dendrimer Liposomes Micelles Nanoemulsions Nanotube Superparamagnetic iron oxide	Oral presentation Not official document [68]
European Commission **DG Research** **European Technology Platform on NanoMedicine** **Nanomedicine**	Liposomes Micellular and micro-emulsion Systems Liquid crystal based formulations Nanocrystals Antibodies and conjugates Naturally occurring proteins as delivery systems Polymer conjugates and bio-conjugates based on the conjugation of polypeptides and polymers Biodegradable nanoparticles/nanocapsules Virus-like particles for gene delivery Delivery of small nucleic acids or mimetics Delivery of vaccines	Oral presentation Not official document [69]
Taiwan **Nanomaterial**	Liposome Micelle Nanocrystal Metal colloid Polymer-drug conjugate Solid nanoparticle Dendrimer	Scientific article [49]
Australia TGA **Nanomedicines**	Liposomes Pegylated liposomes Pegylated proteins Protein-drug conjugate Nanocrystal Nanosuspension Emulsions Polymeric nanoparticles Metal/metal oxides Vaccines Monoclonal antibodies	Oral presentation Not official document [70]

Source	Terms (not official categories) (cont.)	Reference
Scientific publications (reviews)		
Nanopharmaceuticals (Weissig, 2014)	Lipid-based (non-liposomal) formulations Pegylated proteins, polypeptides, aptamers Nanocrystals Polymer-based nanoformulations Protein–drug conjugates Surfactant-based nanoformulations Metal-based nanoformulations (SPION) Virosomes	[71]
Nanoformulation Drug nanoparticles (Wais, 2016)	Liposomes Dendrimers Block copolymer micelles	[72]
Nanoparticle therapeutics (Miller, 2013)	Liposome Albumin-bound nanoparticles Polymeric nanoparticles Dendrimers Metal nanoparticles	[73]
Nanotherapeutics or nanotherapeutic products (Hafner, 2014)	Nanocrystal Nanoemulsions Polymeric drugs Liposomes Polymer-protein conjugates Nanoparticles Virosomes Polymeric drug Nanocomplex	[74]
Nanomedicine-related terms (Etheridge, 2013)	Aerosol OR Nanoaerosol Colloid OR Colloidal OR Nanocolloid OR Nanocolloidal OR Nanosuspension OR Nanocoll Dendrimer OR Dendrimeric Emulsion OR Nanoemulsion Fleximer Fullerene Hydrogel Hydrosol Liposome OR Liposomal OR Nanosome OR Nanosomal Micelle OR Micellar Nano Nanobiotechnology Nanobottle Nanocapsule OR Nanoencapsulation Nanoceramic Nanocoating OR Nanocoated Nanocomposite Nanocrystal OR Nanocrystallite OR Nanocrystalline Nanodiamond Nanodrug Nano-Enabled Nanofiber OR Nanofilament Nanofilter or Nanomesh Nanogel Nanomaterial Nanomedicine Nanometer Nanoparticle OR Nanosphere Nanopore OR Nanoporous	[25]

Source	Terms (not official categories) (cont.)	Reference
Nanomedicine-related terms (cont.) **(Etheridge, 2013)**	(cont.) Nanorod Nanoscaffold Nanoscale Nanosensor Nanoshell Nanosilver Nanostructure Nanotechnology Nanotherapeutic Nanotube Nanowire Quantum Dot Solgel Superparamagnetic OR Iron Oxide OR SPIO OR USPIO Virosome	[25]
Nanomedicines **Nanocarriers** **(He, 2016)**	Polymeric nanoparticle Micelle Liposome Nanogel Mesoporous inorganic nanoparticles Metallic/metal oxide nanoparticle Carbon nanotube	[75]
Nanocarriers **(Cho, 2008)**	Polymeric nanoparticles (polymer-drug conjugates) Polymeric micelles Dendrimers Liposomes Viral-based nanoparticles Carbon Nanotubes	[76]
Nanomedicinal products **(Noorlander, 2015)**	Dendrimer/fleximer Emulsion Gold nanoparticle Iron nanoparticle Liposome Micelle Nanodispersion Polymer conjugate Polymeric nanoparticles Protein nanoparticle Virosome	[77]
Nanomedicine **(Min, 2015)**	Liposome and Lipid-based nanomedicine Protein nanoparticles Polymer-drug conjugates Polymeric-micelles and nanoparticles: • Polymeric micelles • Dendrimers Inorganic Nanoparticles	[78]
Clinical applications **(Riehemann, 2009)**	Lipid-based vehicles Liposomal drug carrier Polymer based delivery Metal nanoparticles Nanoshells Non-injectable nanovectors	[79]

Source	Terms (not official categories) (cont.)	Reference
Nanovectors (Bhattacharya, 2012)	Liposomes Dendrimers Micelles Polymeric nanoparticles Solid lipid nanoparticles Other nanoparticles	[80]
Nanomedicine systems (Rizzo, 2013)	Liposome Polymer Micelle Nanoparticle Antibody	[61]
Carrier systems in theranostic nanomedicines (Theek, 2014)	Liposomes Micelles Polymers Dendrimers Proteins Nanoparticles Microbubbles Antibodies	[81]
Nanomedicines (Bremer-Hoffmann, 2015)	Inorganic particles Polymer based nanocarrier Lipid based nanocarrier Virosome Protein conjugate	[82]
Nanotechnological platforms or nanocarriers (Aparicio-Blanco, 2016)	Polymer-based nanocarriers: • Polymeric conjugates • Polymer nanoparticles • Polymeric micelles • Dendrimers Lipid-based nanocarriers: • Liposomes • Solid lipid nanoparticles • Lipid nanocapsules Metal-based nanocarriers: • Magnetite/Gold/Selenium nanoparticles	[83]
Nanomedicines (material category) (Bobo, 2016)	Polymeric nanoparticles Polymeric micelles Liposomal nanoparticles Protein nanoparticles Inorganic nanoparticles Crystalline nanoparticles	[84]
Nanoparticles (Tatar, 2016)	Organic: • Drug-polymer conjugate • Protein-polymer conjugate • Dendrimer • Polymeric nanoparticle • Liposome • Micelle Inorganic: • Carbon nanotube • Silica nanoparticle • Porous nanoparticle • Gold nanoparticle • Iron oxide nanoparticle	[27]

Source	Terms (not official categories) (cont.)	Reference
Nanoparticles (cont.) **(Tatar, 2016)**	• Quantum dots Carbon nanotube	cont. [27]
Nanoplatform **(Ma, 2016)**	Lipid-based nanoparticles • Liposomes • Nanoemulsions • Solid-lipid nanoparticles Polymeric nanocarriers • Polymer-drug conjugates • Dendrimers • Micelles • Polymersomes • Microbubbles • Protein nanoparticles: (virus nanoparticles) Inorganic platforms • Carbon-based theranostic platforms (fullerene, carbon nanotubes, graphene) • Metallic nanoparticles	[85]
Nanocarriers **(Núñez, 2016)**	Micelleplexes: • Linear block copolymers • Star block copolymers • Self-Assembled Cationic Peptides Lipoplexes Dendrimers Cyclodextrins • Metallic and magnetic nanoparticles	[86]
Nanocarriers **(Luo, 2015)**	Liposomes Polymer-conjugated drugs Polymeric nanoparticles Dendrimers Inorganic nanoparticles	[87]
Type of nanoparticles **(Kompella, 2013)**	Polymeric nanoparticles Polymeric nanogels and hydrogels Liposomes Micelles Dendrimers Chitosan nanoparticles Protein nanoparticles	[88]
Nanomaterial type **(Bregoli, 2016)**	Liposomes Albumin-based nanoparticles Micelles Polymeric nanoparticles Inorganic nanoparticles	[89]
Nanoscale therapies **(Heath, 2009)**	Liposome Albumin-based Polymeric micelle Polymeric-drug conjugate Targeted liposome Targeted polymer-based particle Solid inorganic or metal particle Dendrimer	[90]
Nanotherapeutic platforms **(Wicki, 2015)**	Lipid based nanocarriers: • Solid lipid nanoparticle • Stealth liposome	[29]

Source	Terms (not official categories) (cont.)	Reference
Nanotherapeutic platforms (cont.) (Wicki, 2015)	• Liposome Drug conjugates: • Antibody-Drug conjugate • Polymer-Drug conjugate • Polymer-Protein conjugate Polymer based nanocarriers: • Polymeric micelles • Nanoparticle Albumin bound Technology (Nab) • Polymeric nanoparticle Inorganic nanoparticles: • Silica Nanoparticle • Metal Nanoparticle • Hafnium Oxide Nanoparticle Viral nanoparticle	cont. [29]
Nanoparticle strategies (Gupta, 2011)	Liposomes Micelles Polymer nanospheres and nanoshells/nanocapsules Ultrasound-sensitive nanostructures Au nanospheres and nanoshells Dendrimer nanostructures Magnetically sensitive nanostructures Base nanoparticle : • Liposomes • Micelle • Polymer particle • Gold particle or shell • Ultrasound sensitive bubble • Dendrimer • Iron oxide particle • Quantum dot Hybrid constructs	[91]
Nanoparticles (Ozcelikkale, 2013)	Polymer nanoparticle Liposome Polymeric micelle Carbon nanoparticle Quantum dot Gold nanoparticle Iron oxide nanoparticle	[92]
Nanomaterials (Zhao, 2011)	Carbon black nanoparticle Carbon nanotube Cerium oxide Chitosan Cobalt Copper oxide Fullerene derivative Gold nanoparticle Multi walled nanotube Nanocarrier Nanoceramic Nanocomposite Nanofiber Nanomaterial Nanoparticle Nanorod Nanoscroll	[93]

Source	Terms (not official categories) (cont.)	Reference
Nanomaterials (cont.) **(Zhao, 2011)**	Nanotube Nanowire Nickel nanoparticle Platinum Poly n isopropylacrylamide Polymer Quantum dot Silicon dioxide nanoparticle Silver nanoparticle Single walled nanotube Titanium dioxide Unclassified drug Zinc oxide	Cont. [93]
Nanoparticles **(Zarbin, 2010)**	Carbon nanotube Dendrimer Fullerene Nanoceria Liposome Micelle Polyplex Dendrimer Gold nanoparticle Quantum dot Superparamagnetic iron oxide) Nanowires Nanostructured scaffolds (nanowires and other support matrices with defined nanoscale features).	[94]
Nanocarriers **(Godin, 2010)**	Neutral liposomes Cationic liposomes Hemaglutin virus of Japan (HVJ) liposomes Perfluorocarbon nanoparticles Polyelectrolyte nanoparticles (RNA or polyvinyl sulfate with polyethylene imine/DNA complex) Polymeric (PLA or PLGA) Nanoparticles	[95]
Nanomedicine technologies taxonomy **(Freitas Jr, 2005)**	Raw nanomaterials: • Nanoparticle coatings Nanostructured materials: • Cyclic peptides • Dendrimers • Detoxification agents • Fullerenes • Functional drug carriers • Nanobarcodes • Nanoemulsions • Nanofibers • Nanoparticles • Nanoshells • Carbon nanotubes	[96]

Source	Terms (not official categories) (cont.)	Reference
Nanomedicine technologies taxonomy (cont.) (Freitas Jr, 2005)	• Noncarbon nanotubes • Quantum dots Nanopores: • Nanofiltration membranes Nanopores	Cont. [96]
Types of nanoparticles (Emerich, 2007)	Ceramic nanoparticles Dendrimers Hydrogels Liposomes Micelles Nanocrystals Polymer nanoparticles Solid lipid nanoparticles	[97]
Nanosized oral lipid-based drug delivery systems (Dening, 2016)	Nanosized oral lipid-based drug delivery systems. • Self-emulsifying formulations • Lipid-based micelles • Liposomes • Solid lipid nanoparticles (SNLs) • Mucoadhesive hydrogel • Nanostructured lipid carriers (NLCs) • PCL nanocapsules and submicron emulsions • Lipid nanovesicles Oral polymer-based nanocarriers. • Polymeric micelles • Polymeric nanoparticles	[98]
Types of nanoformulations (Moss, 2014)	Inorganic nanoparticles Organic-inorganic nanoparticle Solid drug nanoparticle Dendrimer Nanoemulsion Liposomes	[99]
Nanomaterials (nanoparticles) (Abeer, 2012)	Liposomes Polymer nanoparticles (nanospheres and nanocapsules) Solid lipid nanoparticles Nanocrystals Dendrimers Fullerenes Inorganic nanoparticles	[100]
Type of nanomedicines (Fattal, 2014)	Lipids: • Liposome • Nanoemulsion • Solid lipid nanoparticles Polymers: • Nanosphere • Nanocapsule • Polymeric micelles	[28]
Nanodrugs (Markman, 2013)	Lipid-based nanoparticles (liposomes) Polymer-conjugate Dendrimers Carbon-based nanoparticles Metallic and magnetic nanoparticles	[101]

Source	Terms (not official categories) (cont.)	Reference
Types of contrast agents (Mody, 2009)	Liposomes Micelles Dendrimer Magnetic polymeric nanohybrids Fullerenes Nanotubes	[102]
Polymer-based nanomedicine (Park, 2008)	Polymer-based nanomedicine • Polyethyleneimine (PEI) • Poly(L-lysine) (PLL) • Synthetic biodegradable polycations • Chitosan Polymeric micelles: • PEG– poly(amino acid) • PEG– polyester • PEG– lipid • Polysaccharides Others: • Liposomes • Microparticles • Self-aggregates • Nanoparticles Polymer–drug conjugates	[30]
Inorganic hollow nanoparticles and nanoparticles (Son, 2007)	Carbon nanotube Hollow nanoshells Porous nanospheres Nanotube	[103]
Nanodrugs (Markman, 2013)	Lipid-based nanoparticles (liposomes)Polymer-conjugate Dendrimers Carbon-based nanoparticles Metallic and magnetic nanoparticles	[101]
Nanomedicine (Martins, 2015)	Nanoparticles Liposomes Polymeric Nanocarriers Albumin Bound Nanoparticles Metallic Nanoparticles Drug Conjugates	[104]
Theranostic nanomedicines (Lammers, 2011)	Liposomes Polymers Micelle Nanoparticle Antibody	[105]

Annex 4 Mapping regulatory authorities' websites

Table 18 Number of regulatory authorities' webpages crawled for this study

Authority	URL (English version)	#Pages retrieved
Australian Gov Dep of Health	www.tga.gov.au	6,128
Agência Nacional de Vigilância Sanitária	portal.anvisa.gov.br	472
Health Canada	www.hc-sc.gc.ca	15,197
Ministry of Health, Labour and Welfare, Japan	www.mhlw.go.jp/english/	2,248
Ministry of Food and Drug Safety, Korea	www.mfds.go.kr/eng/	87
Federal Service for Surveillance in Health Care	www.roszdravnadzor.ru/en	70
Health Sciences Authority, Singapore	www.hsa.gov.sg/content/hsa/en.html	487
Swiss Agency for Therapeutic Products	www.swissmedic.ch/index.html?lang=en	35,368
US Food and Drug Administration	www.fda.gov	76,754
Food and Drug Administration, Taiwan	www.fda.gov.tw/EN/	4,052
European Medicines Agency	www.ema.europa.eu	4,704
European Commission, DG Growth	ec.europa.eu/growth/index_en.htm	71,783
European Commission , DG Health	http://ec.europa.eu/health/index_en.htm	3,383

Website crawling and data collection June 2016

Table 19 Keyword frequency (number of documents) of final keyword set analysis in the regulatory authorities' dataset.

Terms	Subgroup	DG-GROW	DG-SANTE	EMA	FDA	TFDA	HC	HSA	MFDS	MHLW	Swissmedic	TGA	Hit counts	Occurrence
aerosol	structural entity	48	4	5	323	1	50			2	182	51	666	9
aggregation	characterisation	11		26	86	9	33	3		3	3	14	188	9
borderline products	general	5	1	4			4				8	1	23	6
cancer nanomedicine	characterisation				1								1	1
cancer nanotechnology	characterisation				2								2	1
carbon black nanoparticle	structural entity						4						4	1
carbon nanotube	structural entity	1			10	3	4						18	4
carbonbased nanoparticles	structural entity				1								1	1
cationic liposome	structural entity				2								2	1
coating	chemical processing	2485	2	8	323	9	147			1	89	19	3083	9
colloid	structural entity	1	1	1	82		56	1			38	17	197	8
colloidal gold	structural entity				4		2						6	2
combination products	general	4		20	48417	3	45	4			14	48	48555	8
conjugate	chemical processing		14	50	279	8	33				12	46	442	7
conjugation	chemical processing		1	1	31	10	33				11	5	92	7
delivery system	general	3	3	1	427	10	53	2		5	233	35	773	10
deliverysystem	general										2		2	1
dendrimer	structural entity	1			5								6	2
dls	characterisation	3			8	1					13		25	4
dustiness	characterisation	1											1	1
dynamic light scattering	characterisation				5	1							6	2
emulsion	chemical processing	4		23	146	14	23				658	24	892	7
fullerene	structural entity				8	3							11	2
functionalisation	chemical processing	2											2	1
gold nanoparticle	structural entity				10	3							13	2
hafnium	structural entity	1											1	1
hydrogel	structural entity				48		10				150	6	214	4
hydrosol	structural entity				3								3	1
iron oxide	structural entity	1			44		86			8	4	5	148	6
iron oxide nanoparticle	structural entity				4								4	1

Table 19 (cont.)

Terms	Subgroup	DG-GROW	DG-SANTE	EMA	FDA	TFDA	HC	HSA	MFDS	MHLW	Swissmedic	TGA	Hit counts	Occurrence
laser light scattering	characterisation				2	3							5	2
lipid emulsion	structural entity				5		2				16		23	3
lipid nanoparticle	structural entity				1								1	1
liposome	structural entity			22	150	6	8				2	5	193	6
magnetic iron oxide	structural entity						1						1	1
magnetic nanoparticles	structural entity				2								2	1
mean particle size	characterisation				1	3	1						5	3
mesoporous silica	structural entity					2							2	1
metal nanoparticle	structural entity					2							2	1
metallic nanoparticle	structural entity				2			1					3	2
micelle	structural entity	1		3	6	19	3				1	4	37	7
microbubble	structural entity			1	16		2						19	3
microemulsion	structural entity			2	4	6						1	13	4
microparticle	structural entity				44	8	4				3	1	60	5
nano	general	11	9		78	2	15			1	16	2	134	8
nanobased	general		1	1	2		2						6	4
nanobio	general				1								1	1
nanobiophotonic	general				1								1	1
nanobiotechnology	general				3								3	1
nanobody	structural entity				1								1	1
nanocapsule	chemical processing	1				2					2		5	3
nanocarrier	structural entity					1							1	1
nanoceria	structural entity				2								2	1
nanocolloidal	structural entity			11	1						48		60	3
nanocomposite	structural entity	3			3								6	2
nanocrystal	structural entity				3		2						5	2
nanodispersion	structural entity				1								1	1
nanodrug	general				1								1	1
nanoemulsion	chemical processing	1			1								2	2
nanoenabled	general	3											3	1
nanoengineered	general				6								6	1
nanofilter	chemical processing				2								2	1
nanogold	structural entity				3								3	1
nanohealth	general				4								4	1
nanohybrid	general				1								1	1
nanoiron	structural entity				1	2							3	2
nanoliposomal	structural entity				2								2	1

Table 19 (cont.)

Terms	Subgroup	DG-GROW	DG-SANTE	EMA	FDA	TFDA	HC	HSA	MFDS	MHLW	Swissmedic	TGA	Hit counts	Occurrence
nanomaterial	general	277	39	2	127	16	41		1			3	506	8
nanomedicine	general	2	1	8	16	2	2				9	2	42	8
nanomedicines	general			713	2		1				4	1	721	5
nanometre	general	1	2	3			8					4	18	5
nanomicroarray	general				3								3	1
nanoobject	structural entity	1			1								2	2
nanoparticle	structural entity	11	13	8	110	38	21	1			50	26	278	9
nanopharmaceutic	general				4								4	1
nanoporous	structural entity				1								1	1
nanoprobe	structural entity				1								1	1
nanoproduct	general		2		1		2						5	3
nanorelated	general					6							6	1
nanorelease	characterisation						2						2	1
nanosafety	general	1											1	1
nanoscale	general	5	2	2	53	10	16				48	2	138	8
nanoscience	general	2	3		4	2	4						15	5
nanoscopy	general				1								1	1
nanosensor	general	3			1	1							5	3
nanosight	general				2								2	1
nanosilver	structural entity		4		9	2	4						19	4
nanosimilar	general			4									4	1
nanosize	general				1							1	2	2
nanosized	chemical processing		3	1	6	2	3					2	17	6
nanosphere	structural entity				10								10	1
nanostencil	structural entity				1								1	1
nanostructure	general	5			10	6	2					1	24	5
nanosurfaces	characterisation				1								1	1
nanosuspension	chemical processing						2						2	1
nanosystem	structural entity			1	1								2	2
nanotechnology	general	141	45	711	360	18	80				76	13	1444	8
nanotherapeutic	general			3	3								6	2
nanotoxicity	general				15	6	2				1	2	26	5
nanotube	structural entity	1			13	3	8						25	4
nanowire	structural entity		1		1								2	2
non biological complex drugs	general				1								1	1
particle size distribution	characterisation	1			27	3	13				4	13	61	6
personalized medicine	general	5		2	259	4	5				6		281	6

Table 19 (cont.)

Terms	Subgroup	DG-GROW	DG-SANTE	EMA	FDA	TFDA	HC	HSA	MFDS	MHLW	Swissmedic	TGA	Hit counts	Occurrence
photocatalytic activity	characterisation		1				2						3	2
polymer	structural entity	75	1	7	268	23	71	1			118	41	605	9
polymer therapeutics	structural entity			1									1	1
polymeric nanoparticle	structural entity					2						1	3	2
prodrugs	general				6	4	1						11	3
protein corona	characterisation				3								3	1
protein nanoparticle	structural entity				1								1	1
quantum dot	structural entity	1			11	3	11					2	28	5
regenerative medicine	general	2		9	57		1			1	8		78	6
silica nanoparticle	structural entity				1	2	1						4	3
silver nanoparticle	structural entity		2		19	4	4						29	4
solgel	structural entity	2											2	1
solid lipid nanoparticle	structural entity				1								1	1
specific surface area	characterisation	1					2						3	2
stability in vitro	characterisation				1								1	1
stealth liposome	structural entity				1								1	1
superparamagnetic iron oxide	structural entity				1		3						4	2
surface characteristics	characterisation	3	1		14						4		22	4
surface modification	characterisation					1						1	2	2
surface morphology	characterisation				3								3	1
targeted delivery	general		1		7		1						9	3
targeted drug delivery	general				3								3	1
targeting	chemical processing	30	50	31	372	11	71	1		67	56	25	714	10
theranostic	general	3		1	2	2					1		9	5
theranostic nanomedicine	general				1	2							3	2
tissue engineering	general	2		710	40	3					61	3	819	6
virosome	structural entity			3							25		28	2

Annex 5 Description of selected nanomedicine terms

In this annex, descriptions of general and specific terms were presented and selected as a result of the bibliometric analysis, literature review and the mapping of different information sources.

In order to compile descriptions of the selected terms several types of documents were considered, including (1) webpage: when the term is directly mentioned in webpage sections, with or without an explicit given definition (i.e., definitions given in the text context); (2) reports: when the term is mentioned in scientific or regulatory reports authored by the authority; (3) presentations authored by the regulatory authority. The content does not necessarily represent the official opinion of the institution itself; (4) glossaries or terminology: documents including glossaries or suggested terminologies; (5) official documents: this category includes legal texts, and (6) guidance documents authored by the regulatory authority and representing its official opinion.

It is outside the scope of this report to propose an official terminology or establish an official nomenclature to describe materials or products used in the area of nanomedicine.

A5.1 Nanomedicine

Table 20 List of descriptions in English of the term *nanomedicine*

Source	Descriptions for the term *nanomedicine*	Type of document
Australia Therapeutic Goods Administration (TGA) (Australia)	When used in therapeutics, nanotechnologies have been defined as the application of nanotechnologies (or nanomedicine) for making a medical diagnosis or treating disease.	**Webpage** [36]
Canada Parliament of Canada (House of Commons)	Nanomedicine is the use of an intervention that is at a molecular scale of **1 to 100 nanometres (nm)** inclusive to treat a disease or restore function.	**Report** [106]
Canada Health Canada	The Canadian Institutes of Health Research broadly defines nanomedicine as the specialized measurement or intervention - at a **molecular scale** - needed to treat disease or restore function. This definition is meant to be inclusive of techniques and methodologies relevant to health research that does **not necessarily fit within the narrower definitions of nanotechnology or nanomaterials**. Outside of assessing possible contaminants or by-products of manufacturing products, Health Canada does not regulate technologies, or whole areas of medicine, but focuses on its regulatory responsibilities regarding substances, products, and applications of technology. (Source: Canadian Institutes of Health Research)	**Webpage** [107]
Canada Government of Canada TERMIUM Plus®	Description 1: Application of nanoscience and nanotechnologies techniques in the field of medicine. Description 2: Nanomedicine is the application of nanotechnology (the engineering of tiny machines) to the prevention and treatment of disease in the human body. This evolving discipline has the potential to dramatically change medical science. Established and near-future nanomedicine applications include activity monitors, chemotherapy, pacemakers, biochips, OTC [over-the-counter] tests, insulin pumps, nebulizers, needleless injectors, hearing aids, medical flow sensors and blood pressure, glucose monitoring and drug delivery systems.	**Glossary** [54]

Table 20 (cont.)

Source	Descriptions for the term *nanomedicine*	Type of document
European Union **European Medicines Agency**	Nanomedicine is defined as the application of nanotechnology in view of making a medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometre scale.	**Report** [108]
	Nanomedicine, the application of nanotechnology to human healthcare, offers numerous potential pathways to improving medical diagnosis and therapy and even to regenerate tissues and organs. It can provide personalised yet more affordable healthcare while at the same time offering an improved quality of life for everyone.	**Report** [109]
France **Agence Nationale de Sécurité du Médicament et des produits de Santé**	Nanomedicine is one of the most promising nanotechnological applications. It uses new physical, chemical and biological properties related to the nanoscale structures of nanomaterials.	**Report** [110]
Ireland **Health Products Regulatory Authority**	Nanomedicine is defined as the application of nanotechnology to the prevention and treatment of disease in the human body. Nanomedicine, an offshoot of nanotechnology, refers to highly specific medical intervention at the molecular scale for curing disease or of repairing and replacing damaged tissue and cells.	**Newsletter** [111]
United Kingdom **Medicines and Healthcare products Regulatory Agency**	Application of nanotechnology in healthcare and disease diagnosis and treatment and prevention of disease.	**Report** [112]

A5.2 Nanomedicines

Table 21 List of descriptions in English of the term *nanomedicines*

Source	Descriptions for the term *nanomedicines*	Type of publication
Australia **Therapeutic Goods Administration (TGA)**	**Nanomedicines** or **Therapeutic products containing nanomaterials** in the form of metal oxides, liposomes, polymer protein conjugates, polymeric substances and suspensions have been registered in Australia and/or marketed overseas in the United States or the European Union. Synonyms used in the TGA: nanotechnology-based drug. products	**Webpage** [113]
European Union **European Medicines Agency**	**Nanomedicines**: The European Medicines Agency has established a working definition of nanomedicines defined as purposely designed systems for clinical applications [with] at least one component at nano-scale size [and] resulting in definable specific properties and characteristics. [Nanomedicines] are related to the specific technology application and characteristics for the intended use (route of admin, dose), associated with the expected clinical advantages of the nano-engineering (e.g. preferential organ/tissue distribution) and needs to meet definition as a medicinal product according to European legislation.	**Presentation** [114]
	Other terms used in EMA's publications are: "medicinal products containing nanoparticles", "nanomedicinal products" or "nanotechnology-based medicinal products"	**Report** [108]

Table 21 (cont.)

Source	Descriptions for the term *nanomedicines*	Type of publication
Other related terms		
Japan **Pharmaceuticals and Medical Devices Agency, Japan (PMDA)**	**Nanotechnology-based medicines** are anticipating improving the benefit-risk balance of drugs. In this project, point to consider for regulatory requirements for nanomedicine development is discussed. Other terms used for defining nanomedicines in PMDA website are: nanodrug delivery systems, nanomedical devices, nanopharmaceuticals, or nanosized drug. **Nanosized drug:** Characteristic of the drug: a. Whether the characteristics of the drug, such as extended release or nanosized (physical/chemical property, biological activity, etc.), are similar to those of approved drugs.	**Webpage** [115]
United States **U.S. Food and Drug Administration (FDA)**	**Nano-sized drug products**, such as nanoemulsions, protein-drug complexes and iron colloids, are complex drug products that require comprehensive physicochemical characterization to gain insight into product quality that can eventually affect in vivo performance. In June 2014, FDA issued final guidance for industry titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" [48]. As described in that guidance, at this time, when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask: (1) whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm); and (2) whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micro meter (1,000 nm). The agency will apply these considerations broadly to all FDA-regulated products, including food substances. For purposes of this guidance, FDA used terms and phrases such as "nanotechnology products" or "products that involve the application of nanotechnology" to refer to products that contain or are manufactured using certain materials in the nanoscale range, as well as products that contain or are manufactured using certain materials that otherwise exhibit related dimension-dependent properties or phenomena."	**Webpage** [116] **Guidance** [48]
Canada Government of Canada TERMIUM Plus®[21]	**Nanodrug**: Nanotechnology has excellent potential in revolutionizing Health Care industries. The reduction in size of pharmaceutically active ingredients should increase the stability and bioavailability of the drug. The nanodrug delivery systems will have extraordinary features such as targeted ultracontrolled release of drugs vis-a-vis existing drug delivery systems.	**Glossary** [54]

[21] The Government of Canada's terminology and linguistic databank.

A5.3 Nanomaterial

Table 22 List of descriptions in English of the term *nanomaterial*

Source	Descriptions for the term *nanomaterial*	Type of document
Canada **Health Canada**	Health Canada has a **working definition of nanomaterial**. As stated in Health Canada webpage, this working definition is a tool to help the Department gather safety information about nanomaterials. Health Canada considers any manufactured product, material, substance, ingredient, device, system or structure to be nanomaterial if: • It is at or within the nanoscale in at least one spatial dimension, or; • It is smaller or larger than the nanoscale in all spatial dimensions and exhibits one or more nanoscale phenomena. For the purposes of this definition: • The term "nanoscale" means 1 to 100 nanometres, inclusive; • The term "nanoscale phenomena" means properties of the product, material, substance, ingredient, device, system or structure which are attributable to its size and distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material; and, • The term "manufactured" includes engineering processes and control of matter and processes at the nanoscale. Health Canada adds an explanatory note **on biological substances, structures and processes are at the nanoscale**: "Materials that either naturally exist within the nanoscale size range, or exhibit nanoscale properties/phenomena in **nature will not automatically be re-classified as nanomaterials** (e.g. naturally occurring chemical or biological molecules like nucleic acids/DNA/proteins, micro-organisms or cell structures like flagella or ribosomes, etc.). Health Canada currently regulates some biotechnology-based health products, and at this time, Health Canada has no reason to reconsider those products as nanomaterials if they simply fall within the nanoscale." It also specifies: "Biotechnology incorporates products that are biologically sourced or use biological systems in their manufacturing."	**Webpage** [117]
Canada **TERMIUM Plus®** **(Government of Canada)**	A material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale range.	**Glossary** [54]
European Union	The European Commission has provided an **advisory definition** of nanomaterial that contemplates special circumstances for medicinal products and medical devices. **Commission Recommendation on the definition of Nanomaterial**: 'nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm. Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall be considered as nanomaterials.	**Official document**

Table 22 (cont.)

Source	Descriptions for the term *nanomaterial*	Type of document
European Union	(cont.) The legal text of this recommendation indicates that: (16) *It may in some cases be necessary to exclude certain materials from the scope of application of specific legislation or legislative provision even if they fall within the definition. It may likewise be necessary to include additional materials, such as some materials with a size smaller than 1nm or greater than 100 nm in the scope of application of specific legislation or legislative provisions suited for a nanomaterial*. Regarding the pharmaceutical sector the recommendation text indicates that (17) *Given the special circumstances prevailing in the pharmaceutical sector and the specialised nano-structured systems already in use, the definition in the Recommendation should not prejudice the use of the term 'nano' when defining certain pharmaceuticals and medical devices**. ***Medical devices:** The new Regulation of the European Parliament and of the Council on medical devices (EU) 2017/745, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 states that: *In order to ensure a high level of health protection, free movement of goods and legal certainty for manufacturers, it is necessary to introduce a uniform definition for nanomaterials based on Commission Recommendation 2011/696/EU of 18 October 2011 on the definition of nanomaterial, with the necessary flexibility to adapt this definition to scientific and technical progress and subsequent regulatory development at Union and international level.* The definition provided in the new legal text is: 'nanomaterial' means a natural, incidental or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm; Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall also be deemed to be nanomaterials; The use of nanomaterials in medical devices would have also a direct impact in the classification of devices: unless the nanomaterial is encapsulated or bound in such a manner that cannot be releases, devices incorporating nanomaterials will be in class III (Chapter 3, 6.7 Specials rules).	**Official document**

Table 22 (cont.)

Source	Descriptions for the term *nanomaterial*	Type of document
United States **U.S. Food and Drug Administration (FDA)**	FDA has no regulatory definition for nanomaterial. FDA states in the final guidance titled "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology": "when considering whether an FDA-regulated product contains nanomaterials, or otherwise involves the application of nanotechnology, FDA will ask: (1) Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm); and (2) Whether an material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)." This final guidance also set forth a rationale for each element within these two points FDA will consider. I*n this final guidance for industry, FDA uses the term "nanomaterial" generally to refer to both materials in the nanoscale range and certain materials that otherwise exhibit related dimension-dependent properties or phenomena. Use of the term "nanomaterial" is for the purpose of communicating FDA's current thinking elaborated in this document only and does not establish a regulatory definition.*	**Guidance** [48]

A5.4 Nanotechnology

Table 23 List of descriptions in English of the term *nanotechnology*

Source	Descriptions for the term *nanotechnology*	Type of documents
Australia **Australian Therapeutic Goods Administration (TGA)**	The term nanotechnology is used to describe a wide range of methods involved in the production and engineering of structures and systems by controlling size and shape at the nanometre scale. When used in therapeutics, nanotechnologies have been defined as the application of nanotechnologies (or nanomedicine) for the purpose of making a medical diagnosis or treating disease.	**Webpage** [36]
Canada **Health Canada (HC)**	Nanotechnology is a field of science and technology that involves the manipulation of matter at a very small scale, the nanoscale. At the nanoscale (where 1 nanometre is only a billionth of a metre) matter exhibits chemical and physical properties which differ from the properties of bulk materials and single atoms or molecules.	**Webpage** [118]
	Nanotechnology is the application of scientific knowledge to manipulate and control matter in the nanoscale to make use of size- and structure-dependent properties and phenomena distinct from those associated with individual atoms or molecules or with bulk materials. The term "nanoscale" is defined as 1 to 100 nanometers (nm) inclusive.	**Webpage** [37]
	A precise molecule-by-molecule control of products and by-products in the development of functional structures. From the Latin *nanus* = "dwarf", so it literally means "dwarf technology". The word was originally coined by Norio Taniguchi in 1974, to refer to high precision machining. However, Richard Feynman and K. Eric Drexler later popularized the concept of nanotechnology as a new and developing technology in which humans manipulate objects whose dimensions are approximately 1 to 100 nanometers. Theoretically, it is possible that in the future a variety of human-made "nano-assemblers" (that is, tiny [molecular] machines smaller than a grain of sand) could manufacture those things that are produced in factories today. For example, enzyme molecules function essentially as jigs and machine tools to shape large molecules as they are formed in biochemical reactions. The technology also encompasses biochips, biosensors and manipulating atoms and molecules in order to form (build) bigger, but still microscopic functional structures and machines.	**Webpage** [119]
European Union **European Medicines Agency (EMA)**	Nanotechnology is the use of tiny structures - less than 1,000 nanometres across - that are designed to have specific properties. Nanotechnology is an emerging field in science that is used in a wide range of applications, from consumer goods to health products.	**Webpage** [43]
	Nanotechnology is defined as the production and application of structures, devices and systems by controlling the shape and size of materials at nanometre scale. The nanometre scale ranges from the atomic level at around .2 nm (2 Å) up to around 100 nm.	**Report** [12]
France **Agence nationale de sécurité du médicament et des produits de santé**	Nanotechnology refers to the manipulation and control matter on a nanoscale to make use of size- and structure-dependent properties and phenomena distinct from those associated with individual atoms, molecules or bulk materials. The terms "manipulation and control" include material synthesis. Nanotechnologies therefore involve the production of structures, devices and systems using processes that allow the material to be structured on a nanoscale.	**Report** [110]

Table 23 (cont.)

Source	Descriptions for the term *nanotechnology*	Type of documents
United States **U.S. Food and Drug Administration (FDA)**	FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. Nanotechnology is an emerging technology that can be used in a broad array of FDA-regulated products, including medical products (e.g., to increase bioavailability of a drug), foods (e.g., to improve food packaging) and cosmetics (e.g., to affect the look and feel of cosmetics). Materials in the nanoscale range (i.e., with at least one dimension in the size range of approximately 1 manometer (nm) to 100 nm) can exhibit different chemical or physical properties, or biological effects compared to larger-scale counterparts.	**Guidance** [48]

A5.5 Nanoscale

Table 24 List of descriptions in English of the term *nanoscale*

Source	Descriptions for the term *nanoscale*	Type of documents
Health Canada **TERMIUM Plus®** **(Government of Canada)®**	Means 1 to 100 nanometres, inclusive. A size range of approximately 1 to 100 nm.	**Webpage** [120] **Glossary** [54]
European Union **European Medicines Agency (EU)**	The nanometre scale ranges from the atomic level at around 2 nm (2 Å) up to around 100 nm.	**Report** [12]
Switzerland **Swissmedic**	The term nanoscale is defined within the description of nanoparticles: The particles have at least one dimension on the nanoscale (1-1000 nm) plus a function and / or mode of action based on nanotechnology characteristics.	**Official document** [39]
United Kingdom **The Royal Society & The Royal Academy of Engineering**	Nanoscale (which was defined to be **from 100 nm down to the size of atoms (approximately .2nm)**) because it is at this scale that the properties of materials can be very different from those at a larger scale.	**Report** [121]
United States **U.S. Food and Drug Administration (FDA)**	Materials in the nanoscale range (i.e., with at least **one dimension** in the size range of **approximately 1 nanometer (nm) to 100 nm**) can exhibit different chemical or physical properties, or biological effects compared to larger-scale counterparts.	**Guidance** [48,]
U.S. Patent and Trademark Office: Cooperative Patent Classification (CPC)	On B82, classification for nano-technology: "nano-scale" relate to a controlled geometrical size **below 100 nanometres (nm)** in one or more dimensions.	**Website** [122]

A5.6 Nanostructure

Table 25 List of descriptions in English of the term *nanostructure*

Source	Descriptions for the term *nanostructure*	Type of document
Canada TERMIUM Plus® (Government of Canada)	Having an internal or surface structure in the nanoscale range. (Reference number ISO/TS 80004-4:2011(E))	**Glossary** [54]
Cooperative Patent Classification (CPC)	On B82, classification for nano-technology: "nano-structure" means an entity having at least one nano-sized functional component that makes physical, chemical, or biological properties or effects available, which are uniquely attributable to the nano-scale.	**Website** [122]

A5.7 Nanosimilars

This term was initially proposed by EU regulators and it is referred in the EMA website as *nanomedicines that are claimed to be similar to a reference nanomedicine*[22].

A5.8 Nanoparticle

Table 26 List of descriptions for the term *nanoparticle*

Source	Descriptions for the term *nanoparticle*	Type of document
Regulatory Authorities		
Australia Therapeutic Goods Administration (TGA)	A nanoparticle is a particle within the nanoscale **range of 1 to 100 nanometres** in size; a nanometre is one millionth of a millimetre. (Original source: Referenced OECD definition).	**Webpage** [123]
Canada TERMIUM Plus® (Government of Canada)	A nano-object with all three external dimensions in the nanoscale. In biomedical applications nanoparticles are used as drug carriers or imaging agents. For this purpose the nanoparticle may have a hollow structure providing a central reservoir that can be filled with anticancer drugs, detection agents, or chemicals, known as "reporters," that can signal if a drug is having a therapeutic effect. The surface of a nanoparticle can also be adorned with various targeting agents, such as antibodies, drugs, imaging agents, and reporters. Most nanoparticles are constructed to be small enough to pass through blood capillaries and enter cells.	**Glossary** [54]
European Union European Medicines Agency	No description found for nanoparticle. [Public summary of opinion on orphan designation on Nanoparticle albumin-bound paclitaxel for the treatment of pancreatic cancer]: the paclitaxel is attached to a human protein called albumin **in tiny particles** known as 'nanoparticles'.	**Report** [124]

[22] European Medicines Agency webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/08/news_detail_001875.jsp&mid=WC0b01ac058004d5c1 (Retrieved 10 April 2018)

Table 26 (cont.)

Source	Descriptions for the term *nanoparticle*	Type of document
France National Agency for the Safety of Medicine and Health Products	A nanoparticle is a nano-object with three external dimensions on a nanoscale. Nanoparticles are not all spheres but may have the shape of needles, extended rods, spring structures, etc.	**Report** [110]
Switzerland Swissmedic: Swiss Agency for Therapeutic Products	(Synthetic nanoparticles) The particles have **at least one dimension on the nanoscale (1-1000nm)** plus a **function** and / **or mode of action** based on nanotechnology characteristics. This definition is included in the form "Application for authorisation / Variation of human medicines", in which the applicant should declare whether the medicinal product contains nanoparticles.	**Official document** [39]
Other sources		
ISO	Nanoparticle: **nano-object**[23] with all three external dimensions in the nanoscale NOTE If the lengths of the longest to the shortest axes of the nano-object differ significantly (typically by more than three times), the terms nanorod or nanoplate are intended to be used instead of the term nanoparticle. [DD CEN ISO/TS 27687:2009, 4.1] **Updated to ISO/TS 80004-2:2015.**	**Standard terminology**
Taiwan Taiwan Food and Drug Administration	Description of nanoparticle in the CMC technical review checklist proposal: Nano-object with all three external dimensions at the nanoscale that is the **size range from approximately 1 nm to 100 nm**. Polymeric nanoparticle platforms are characterized by their physicochemical structures including solid nanoparticles, nanoshell, dendrimer, polymeric micelle, and polymer-drug conjugates. [49]	**Peer-reviewed article**
BioPortal	**NCIT:** A small, stable particle whose size is measured in nanometers. These particles are used in various biomedical applications in which they can be utilized as drug carriers or imaging agents. Various targeting agents, such as antibodies, drugs, imaging agents, and reporters can be attached to the surface of a nanoparticle. [Nanoparticle Type]: The classification of discrete nanoparticle entities. [Nanoparticle Topology]: The structural motif of a nanoparticle that is defined by the spatial relationship of the constituent atoms. [Nanoparticle Complex]: A nanoparticle bound to another moiety of interest via a chemical or physical interaction.	**Webpage** [126]

[23] nano-object: material with one, two or three external dimensions in the nanoscale. NOTE Generic term for all discrete nanoscale objects. [DD ISO/TS 80004-1:2010, 2.5]

Table 26 (cont.)

Source	Descriptions for the term *nanoparticle*	Type of document
BioPortal (cont.)	(Cont.) [Nanoparticle Application]: The utilization of small **(<100 nm), stable particles** in a variety of technologies. Based on an understanding of chemical, biological and physical phenomena at the nanoscale level, processes are employed to create new nanoparticle technologies. **MeSH: Nanometer-sized particles** that are **nanoscale in three dimensions**. They include **nanocrystalline materials**; **nanocapsules**; **metal nanoparticles**; **dendrimers,** and **quantum dots**. The uses of nanoparticles include drug delivery systems and cancer targeting and imaging. Any crystalline structure possessing dimensions measured in terms of nanometers. Nanometer-sized particles that are nanoscale in three dimensions. They include nanocrystalline materials; nanocapsules; metal nanoparticles; dendrimers, and quantum dots. The uses of nanoparticles include drug delivery systems and cancer targeting and imaging. **NPO:** A primary particle which has an average size in the nanoscale range; which has an identifiable and definite chemical composition, property or function that uniquely define the nanoparticle's type as known; and, which may or may not exhibit a size-intensive property. Definition is partly based on ASTM E 2456-06 (Terminology for Nanotechnology). The type of nanoparticles mentioned in this ontology are: **fluorescence NP (nanoparticle which has fluorescence property), fluorescent NP, doxorubicin-loaded NP, hydroxyapatite NP, core-shell NP, metal NP, polymeric NP, one-dimensional NP, tamoxifen-loaded NP, chitosan NP, biopolymer-coated NP, water-soluble NP, etoposide-loaded NP, NP characterization, bimetallic NP, gelatin NP, lipid NP, PLGA NP** (nanoparticle which is basically composed of poly(lactic-co-glycolic acid) polymer)**, superparamagnetic NP, drug-loaded NP, lipid-coated NP, paclitaxel-loaded NP, two-dimensional NP, PEGylated NP** (a nanoparticle which has a coating agent composed of polyethylene glycol.)**, methotrexate-loaded NP, hydrogel NP** (nanoparticle which exists while dispersed in a hydrogel)**, polymer-coated NP, gadolinium-loaded NP, three-dimensional NP, gold NP, silver NP, carbohydrate-coated NP, spherical NP, or biodegradable NP.** **[nanoparticle component]:** A chemical component which is identified as a nanoparticle based on its structure, chemical composition or function. **[nanoparticle imaging] NIFSTD:** An imaging assay that makes use of the unique properties of nanoparticles to elucidate specific targets in an image.	**Webpage** [126] (cont.)

A5.9 Magnetic nanoparticles (SPIO, SPION, USPION)

Table 27 List of descriptions for the term *magnetic nanoparticles*

Source	Descriptions for the term *magnetic nanoparticles*	Type of document
BioPortal	**NCIT: Superparamagnetic iron oxide nanoparticle (SPIO or SPION)**. Nanoparticles that have been functionalized with chemical amine groups and dextran. These particles have been utilized as magnetic resonance imaging agents and as probes to investigate thrombosis and tumor vasculature in conjunction with a CREKA peptide (cys-arg-glu-lys-ala). Synonym: Amino Dextran-Coated Iron Oxide Particle.	**Webpage** [126] [127]

Table 27 (cont.)

Source	Descriptions for the term *magnetic nanoparticles*	Type of document
BioPortal (cont.)	**NPO:** An iron oxide nanoparticle which has superparamagnetic property. **MeSH**: Ferumoxsil. A large superparamagnetic iron oxide colloid; a miscible darkening agent; see also the dextran-coated superparamagnetic iron oxides - ferumoxides and ferumoxtran.	**Webpage** [126] [127]
Scientific literature	**Paramagnetic particles** are important tools for cell sorting, protein separation, and single-molecule measurements. The particles used in these applications must meet the following requirements: uniform in size, highly paramagnetic, stable in physiological salt buffer, functionizable, and **100-1000 nm in size.** [128]	**Peer-reviewed article**
Synonyms	Metal-based nanoformulations. **Ultrasuperparamagnetic iron oxide nanoparticles (USPION)**	

A5.10 Metal nanoparticles

Table 28 List of descriptions for the term *metal nanoparticles*

Source	Descriptions for the term *metal nanoparticles*	Type of document
BioPortal	**MeSH Definition:** Nanoparticles produced from metals whose uses include biosensors, optics, and catalysts. In biomedical applications the particles frequently involve the noble metals, especially gold and silver. **NPO Definition:** A nanoparticle which is basically composed of a metal.	**Webpage** [126]

A5.11 Polymer therapeutics

Table 29 List of descriptions for the term *polymer therapeutics*

Source	Descriptions for the term *polymer therapeutics*	Type of document
Scientific literature	The term "polymer therapeutics" was coined to describe polymeric drugs, polymer conjugates of proteins, drugs and aptamers, together with those block copolymer micelles and multicomponent non-viral vectors which contain covalent linkages. These often complex, multicomponent constructs are actually "drugs" and "macromolecular prodrugs" in contrast to drug delivery systems that simply entrap (non-covalently) therapeutic agents. Polymer–drug conjugates are drug delivery technologies in which a drug is covalently bound to a polymeric carrier, normally via a biodegradable linker. Types: Polymeric drugs (dendrimers); Polymer-Protein conjugate; Polymer-drug conjugates.	**Peer-reviewed article** [129]
Synonyms	Polymeric conjugates, polymer-based nanomedicines, polymer-drug conjugates, polymer therapeutics, polymer-protein conjugates, polymer-drug conjugates, Polymer based delivery.	

A5.12 Polymeric nanoparticle

Table 30 List of descriptions for the term *polymeric nanoparticle*

Source	Descriptions for the term *polymeric nanoparticle*	Type of document
ISO	**polymer nanoparticle dispersion:** mixing of nanoparticles (2.6) into a liquid polymer matrix which is solidified to produce a polymer matrix nanoparticle composite (ISO/TS 80004-8:2013(en), 6.5.12)	**Standard**
BioPortal	**NPO Definition:** A nanoparticle which is basically composed of polymer. (National Cancer Institute 2016	**Webpage**
Scientific literature	**Polymeric therapeutics:** Describe polymeric drugs, polymer-drug conjugate, polymer-protein conjugates, polymeric micelles to which drug is covalently bound and those multi-component polyplexes with covalent linkages being developed as non-viral vectors. The authors state that to coin biomaterials (as proteins) and non-covalent drug delivery systems as polymer therapeutics is a misguided step in the Regulatory Authority positioning**.** [130] **Polymer nanoparticles** are perhaps the most influential biodegradable and biocompatible carriers. They have good surface modification potential, provide excellent pharmacokinetic control and are suitable for the entrapment of a wide range of therapeutics. Several formulations exist including those made from PLGA, PLA, PGA, gelatins, and chitosan. Some polymers exhibit cytotoxicity due to cell internalization and breakdown. Large-scale manufacturing is difficult and expensive but FDA-approved products exist including Abraxane. [97] Biodegradable polymer nanoparticles include chitosan nanoparticles, poly(ethylene glycol) (PEG) nanoparticles, and polylactide-co-glycolic acid (PLGA) nanoparticles. [128] **Polymer nanoparticles** Solid nanoparticles that consist of natural or synthetic polymers (Size: 100–1,000 nm). [131] Polymeric nanoparticles **(polymer-drug conjugates):** Drugs are conjugated to the side chain of a linear polymer with a linker (cleavable bond). [76]	**Peer-reviewed article**

A5.13 Polymeric micelle (block copolymer micelle)

Table 31 List of descriptors for the term *polymeric micelle*

Source	Descriptions for the term *polymeric micelle*	Type of document
Regulatory Authorities		
European Union European Medicines Agency	**Block copolymer micelles:** Block copolymer micelles are self-assembled micelles, and they are typically prepared from AB block copolymers. […] An active substance can be incorporated into the inner core of the block copolymer micelle product by chemical conjugation or by physical entrapment. Block copolymers with amphiphilic character spontaneously assemble into **polymeric micelles** in aqueous media, hydrophobic interactions typically drive this self-association. However, other driving forces may be used to promote micelle formation and enhance micelle stability.	**Report** [132]

Table 31 (cont.)

Source	Descriptions for the term *polymeric micelles*	Type of document
Other sources		
BioPortal	**PDQ (Physician Data Query Terminology):** **Paclitaxel-loaded polymeric micelle:** A biodegradable poly(ethylene glycol)-poly(D,L-lactide) copolymer micelle nanoparticle-entrapped formulation of paclitaxel with antineoplastic properties. Paclitaxel promotes microtubule assembly and prevents depolymerization, thus interfering with normal mitosis. The copolymer residue increases the water-solubility of paclitaxel and allows delivery of higher doses than those achievable with paclitaxel alone.	**Webpage** [126]
Scientific literature	**Block copolymer micelles OR polymeric micelles:** Micelles are biocompatible nanoparticles varying in size from 50 to 200 nm in which poorly soluble drugs can be encapsulated, which represents a possible solution to the delivery problems associated with such , and could be exploited to target the drugs to particular sites in the body, potentially alleviating toxicity problems. [128] A **block copolymer** contains hydrophilic compartments (such as polyethylene glycol (PEG), polyacrylic acid (PAA)) and a hydrophobic compartment (such as polystyrene (PS), polybutylene (PB), polylactic acid (PLA)), which induces the controlled aggregation of block copolymers due to hydrophobic interactions in aqueous media. The polymeric building blocks can assemble into various architectures, including micelles of different sizes and shapes, and vesicles, which are of great interest in theranostics, because the chemical composition, total molecular weight and the block length ratios can be fine-tuned to produce well-defined nanocarriers with certain size and morphology. [85] **Polymeric micelles** consist of self-assembled polymeric amphiphiles tailored for controlled delivery of hydrophobic drugs. Through careful design of the hydrophobic/hydrophilic balance in the amphiphile, the size and morphology of the assembled micelles can be controlled. The internal core is hydrophobic and can be used to encapsulate poorly water soluble drugs, whereas the exterior surface is polar enough to allow dissolution in aqueous solution. The use of block copolymers as the amphiphiles has led to lower critical micelle concentration (CMC) and thus higher stability in comparison to traditional surfactant-based micelles. [84] **Block copolymers** are a type of macromolecule of chemically different segments connected via their terminal groups. There exist three basic structural types for block copolymers (Fig. 9). The first is the A–B structure, so-called diblock, with A and B being two different repeating units. A block of repeating units A is thereby connected to a block of units B. The second type is an A–B–A or A–B–C structure, called a triblock. A block of B is enclosed between blocks on either side. The third type is a multiblock in the style of (A–B)n, where blocks of A and B are repeated to form areas of repeating units A and B. A special sub-group of block copolymers are radial block-copolymers. These are formed by two or more block copolymers radiating out from a central hub, forming star-shaped macromolecules with a pre-designed symmetry. In comparison to random copolymers, block copolymers exhibit well defined structures and their synthesis requires sequential architecture. [72] Supramolecular aggregates composed of **amphiphilic block copolymers** that self-assemble into aqueous media; inner core typically serves as a container for hydrophobic drugs (Size: 20–80 nm). [131]	**Peer-reviewed article**

Table 31 (cont.)

Source	Descriptions for the term *polymeric micelles*	Type of document
Scientific literature	**Polymeric micelles** are nanoparticles formed upon self-assembly of **amphiphilic (block co-)polymers** in aqueous solutions. The resulting structure is a usually spherical nanoparticle with a hydrophobic core acting as a reservoir for poorly soluble active pharmaceutical ingredients (APIs) and a hydrophilic shell which provides colloidal stability and limits protein adsorption and opsonisation, resulting in long-circulation times. [133] **Amphiphilic block copolymers** assemble and form a micelle with a hydrophobic core and hydrophilic shell. [76]	**Peer-reviewed article**

A5.14 Solid lipid nanoparticle

Table 32 List of descriptions for the term *solid lipid nanoparticle*

Source	Description for the term *solid lipid nanoparticle*	Type of document
Scientific literature	SLNs comprise a solid hydrophobic core of lipids, such as mono-, di- and triglycerides or fatty acids with a monolayer of phospholipid coating (Kaur et al., 2008). Like polymeric nanoparticles, they are capable of controlled release of up to several weeks and can also be coated or grafted with ligands for drug targeting (Kaur et al., 2008). They are also stable and biodegradable under physiological conditions (Barbu et al., 2009) with a high drug loading capacity for both hydrophilic and lipophilic drugs (Yadav et al., 2014).	**Peer-reviewed article** [134]

A5.15 Albumin-bound nanoparticle

Table 33 List of descriptions for the term *albumin-bound nanoparticle*

Source	Description for the term *albumin-bound nanoparticle*	Type of document
Scientific literature	The nanoparticle albumin-bound (nab) platform uses albumin to shuttle hydrophobic therapeutics. Albumin is a ubiquitous serum protein that naturally carries molecules in the bloodstream, attached by reversible noncovalent binding.	**Peer-reviewed article** [73]

A5.16 Liposome

Table 34 List of descriptions for the term *liposome*

Source	Descriptions for the term *liposome*	Type of document
Regulatory Authorities		
European Union European Medicines Agency (EMA)	Liposomes are classically described as artificially prepared vesicles composed of ions or more concentric lipidic bi-layers enclosing one or more aqueous compartments. They include, but are not limited to, moni- and multi-lamellar liposomes, multi-vesicular-liposomes and polymer-coated liposomes. Nanoliposomes: In this medicine, irinotecan is contained within tiny fat particles called 'nanoliposomes'.	**Report** [135] [54, 136]

Table 34 (cont.)

Source	Descriptions for the term *liposome*	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	A vesicle formed by the homogenization (emulsification) of phospholipids in dilute salt solutions. Most are uniform-sized spheres of lipid bilayers that can be isolated from the suspending solution as a clear, separate phase. Liposomes are the prototypes of membrane-bound biologic structures.	**Webpage** [54]
FDA	Liposome drug products (LDP) contain drug substances encapsulated in lipid bilayer microvesicles designed for prolonged release and/or targeted delivery of drugs. (Center for Drug Evaluation and Research; Research Programs).	**Webpage** [137]
Taiwan **Taiwan Food and Drug Administration**	Vesicles composed of one or more bilayers of amphiphatic lipid molecules enclosing one or more aqueous compartments.	**Peer-reviewed article** [49]
Other sources		
British Standards Institution	*Stealth Liposome*: liposome that has been specially designed to avoid detection by body's immune system. *Note 1 Stealth liposomes are particularly designed to avoid detection within the reticuloendothelial system. Note 2 Detection avoidance is commonly achieved by the studding of the outside of the membrane with polyethylene glycol (PEGylation) which is inert in the body and so permits a longer circulation for drug delivery*. [PAS 131:2007, 4.27]	**Terminology** [138]
BioPortal	**MeSH**: Artificial, single or multilaminar vesicles (made from lecithin or other lipids) that are used for the delivery of a variety of biological molecules or molecular complexes to cells, for example, drug delivery and gene transfer. They are also used to study membranes and membrane proteins. **NCIT**: Substances composed of layers of lipid that form hollow microscopic spheres within which drugs or agents could be contained for enhanced safety and efficacy [139]. **NCI-GLOSS**: A very tiny, fat-like particle that is made in the laboratory. In medicine, liposomes containing drugs or other substances are used in the treatment of cancer and other diseases. Drugs given in liposomes may have fewer side effects and work better than the same drugs given alone. **CRISP**: single or multilaminar vesicles (made from lecithin or other lipids) that can be used for the delivery of a variety of biological molecules or molecular complexes to cells, for example, drug delivery and gene transfer; also used to study membranes and membrane proteins. **NPO**: A supramolecular structure which is a closed vesicle that forms on hydration of dry phospholipids above its transition temperature. This definition is also used in eNanoMapper ontology.	**Webpage** [126]
Scientific literature	The sealed concentric microscopic shells formed when certain lipid substances are in an aqueous solution. [See also micelles.] [140] Liposomes are self-assembled lipid bilayer vesicles, with 20-150 nm diametres for Small Unilamellar Vesicles (SUVs) to a few micrometres in diameter for Large Multilamellar Vesicles (LMVs). [91]	**Peer-reviewed articles**

Table 34 (cont.)

Source	Descriptions for the term *liposome*	Type of document
Scientific literature (cont.)	(cont.) Liposomes are concentric bilayered vesicles with an aqueous interior surrounded by a phospholipid. The amphiphilic nature, ease of surface modification, and good biocompatibility profile has made them attractive for increasing the circulating half-life of proteins and peptides. Liposomes can be made to stick to a cell to deliver its drug or deliver it via endocytosis. Despite a relatively long history of investigation liposomes exhibit limited stability and have not made significant medical impact. [97] Liposomes are stable microscopic vesicles of natural or synthetic lipids (usually phospholipids). Liposomes are formed when amphipathic lipids spontaneously assemble in layer form in aqueous medium. Depending on the conditions, multilayer or monolayer vesicles are formed. In multilayer vesicles, lipids are either ordered in circular rings with a head-to-tail structure with aqueous compartments in between or in a tail-to-tail arrangement with an aqueous internal part. The ability to enclose water soluble and lipophilic drugs in the lipid layers as well as encompass drugs with intermediate log[thin space (1/6-em)]P makes liposomes ideal candidates for drug delivery. In drug delivery by liposomes, cell entry is not happening by plasma clearance or tissue disposition, but by fusion or endocytosis, which increases the success rate of drug delivery to cells. This trait makes liposomes highly attractive not only for drug delivery but also as carriers for enzymes and other proteins into the inner part of the cell. Surface charge, hydrophobicity, size, fluidity and packing of lipid layers heavily influence the stability and type of protein for binding of liposomes. [72] Liposomal formulations […] are spherical, layered vesicles that self-assemble when placed in water. They range in size from 50 nm to micrometers, which permits loading with a variety of therapeutics, including simultaneous small molecules and macromolecules. Liposomes are classically eliminated by the MPS system; however, PEG can be added to the liposome surface and significantly enhance circulation half-life, which allows for increased tumor accumulation. [73]	**Peer-reviewed articles**

A5.17 Dendrimer

Table 35 List of descriptions for the term *dendrimer*

Source	Descriptions for the term *dendrimer*	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	Complex nanomolecules called dendrimers can be used to map circuits. Developed at the Michigan Molecular Institute (MMI) and sold commercially through its affiliate company Dendritech, dendrimers are nested molecular spheres. Each layer has a unique composition, depending on the dendrimer's function and--most critically for circuit design purposes--dendrimers are produced in discrete sizes. [54]	**Glossary** [54]
FDA	Repeatedly branched, roughly spherical large molecules (FDA-TRACK Research Glossary)**.**	**Glossary** [141]
Taiwan Food and Drug Administration (journal article)	Definition in the CMC technical review checklist: A polymer in which the atoms are arranged in many branches and sub-branches along a central backbone of carbon atoms. **[49]**	**Peer-reviewed article**

Table 35 (cont.)

Source	Descriptions for the term *dendrimer*	Type of document
Other sources		
ISO	**Dendrimer**: molecule comprising a multifunctional core molecule with a dendritic wedge of highly branched monomers regularly attached to each functional site, leading to a monodisperse, tree-like, or generational structure (ISO 18115-1:2013(en), 4.159)	
British Standards Institution	Repeatedly branched macromolecule. NOTE Dendrimers can be configured as a sphere, partial sphere or wedge structure (i.e. dendritic wedge). [PAS 136:2007, 5.2] **Dendritic particle**: particle with a highly branched structure. NOTE Also referred to as a branched-chain aggregate. [derived from PAS 71:2005, definition 3.6] **Dendron:** dendrimer containing a single chemically addressable group**.** NOTE: The single chemically addressable group is known as the focal point.	**Glossary** [142]
BioPortal	**MeSH:** Tree-like, highly branched, polymeric compounds. They grow three-dimensionally by the addition of shells of branched molecules to a central core. The overall globular shape and presence of cavities gives potential as drug carriers and contrast agents. *Synonyms: Dendritic compounds, dendritic polymers, dendrimers, dendrons, dendrimer, or dendritic macromolecule.* **NCIT:** A polymeric molecule which has a highly-branched, three-dimensional architecture. Dendrimers are synthesized from monomers and new branches are added in discrete steps to form a tree-like architecture. A high level of synthetic control is achieved through step-wise reactions and purification at each step to regulate the size, architecture, functionality and monodispersity of the molecules. These polymers have desirable pharmacokinetic properties and a polyvalent array of surface groups that make them potential drug delivery vesicles. This definition is shared by NPO, ENM, **CHEBI:** A highly branched macromolecule. This definition is shared in NBO and BIOMODELS. [Dendritic polymer]: A polymer substance composed of dendritic macromolecules.	**Webpage** [126]
Scientific literature	**Dendrimers** are artificial, **polymer-based molecules** formed from monomers such that each layer of branching units doubles or triples the number of peripheral groups (i.e. they look like a foam ball). The void area within a dendrimer, its ease of modification/preparation, and size control offer great. Potential for targeted gene and drug delivery. Improvements in cytotoxicity profiles, biocompatibility and biodistribution are needed **[97].** The first description the term dendrimer and the method of preparation of poly(amidoamine) dendrimers [143]. Dendrimers, hyper-branched polymers of the twenty-first century, are described as three-dimensional polymers, which are organized into very symmetrical and mono-dispersed arrays. **[144]** There are various types of dendrimers: • Poly(amidoamine-organosilicon) dendrimers (PAMAMOS) • Poly(amidoamine) dendrimers (PAMAM) • Poly(propylene imine) dendrimers (PPI) • Chiral dendrimers • Liquid crystalline dendrimers • Tecto dendrimers • Hybrid dendrimers • Micellar dendrimers	**Peer-reviewed articles**

A5.18 Carbon nanotube

Table 36 List of descriptions for the term *carbon nanotube*

Source	Descriptions for the term *carbon nanotube*	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	A tube-shaped material, made of carbon, having a diameter measuring on the nanometer scale. Carbon nanotubes have many structures, differing in length, thickness, type of helicity, and number of layers. Although they are formed from essentially the same graphite sheet, their electrical characteristics differ depending on these variations, acting either as metals or semiconductors. Original source: Internet. [http://www.nanocyl.com]. Nanocyl. The Carbon Nanotube Specialist. FAQS. "What is a carbon nanotube?" (20120213)	**Webpage** [54]
Other sources		
ISO	nanotube (2.6) composed of carbon (ISO/TS 80004-3:2010(en), 4.3)	
British Standards Institution	Nanotube consisting of carbon. Note: This term is commonly used to refer to a seamless tube constructed from graphene that can be either a single-wall carbon nanotube (SWCNT), comprising a single layer of carbon atoms	**Terminology**
BioPortal	**NCIT:** Fullerene-like nanostructures that consist of graphene cylinders. The ends of the construct are closed with pentagonal-shaped rings. **Single-Walled Nanotube:** A carbon nanotube comprised of a single layer of graphitic carbon. These tubes may be metallic or semi-conducting depending on the chirality of the tube. **Double-Walled Nanotube:** A carbon nanotube comprised of two layers of graphitic carbon.	**Webpage** [126]
Scientific literature	Refers to any tiny tube composed of carbon, whose diameter is measured in nanometers. There are several potential applications for the utilization of carbon nanotubes (CNTs) within fields of biotechnology. **[60]**	**Peer-reviewed article**

A5.19 Micelle

Table 37 List of descriptions for the term *micelle*

Source	Descriptions for the term *micelle*	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	Aggregation of surfactant molecules dispersed in a liquid. *Note 1: The surfactants molecules are often sequestered into hydrophilic and hydrophobic regions. Note 2: Micelles are commonly spherical but can also be branched, rods and worm-like.*	**Webpage** [54]
Taiwan Food and Drug Administration	Vesicles composed of one or more bilayers of amphiphatic lipid molecules enclosing one or more aqueous compartments [49].	**Peer-reviewed articles**

Table 37 (cont.)

Source	Descriptions for the term *micelle*	Type of document
Other sources		
ISO	**Micelle**: An aggregate made up of molecules and/or ions, which is formed above a certain critical concentration in solutions of surface active agents. (ISO 862:1984(en), 37) **Reverse micelle process:** synthesis of nanoparticles (2.6) in solution using reagents in the presence of reaction stopping ligands that attach to the nanoparticle surface and inhibit further growth. (ISO/TS 80004-8:2013(en), 6.4.4)	**Standard Terminology**
British Standards Institution	Aggregation of surfactant molecules dispersed in a liquid. *Note 1 The surfactant molecules are often sequestered into hydrophilic and hydrophobic regions. Note 2* Micelles *are commonly spherical but can also be branched, rods or worm-like*. [PAS 131:2007, 4.10]	**Terminology** [142]
BioPortal	**NCIT:** A multimolecular colloid particle, usually formed by amphipathic molecules in solution with the polar group toward the solution and the hydrophobic group toward the interior. **NCI-GLOSS:** A tiny particle made of substances that are soluble in water and that come together to form a ball-like shape. These particles can carry other substances inside them. In medicine, micelles are made in the laboratory and are used to carry drugs to body tissues and cells. **MeSH:** Particles consisting of aggregates of molecules held loosely together by secondary bonds. The surface of micelles is usually comprised of amphiphatic compounds that are oriented in a way that minimizes the energy of interaction between the micelle and its environment. Liquids that contain large numbers of suspended micelles are referred to as **emulsions**. **CRISP**: Aggregate of lipids in which the polar head groups face outward and the hydrophobic tails face inward. **NPO:** A supramolecular structure which is an aggregate of amphiphilic molecules in a polar solvent.	**Webpage** [126]

A5.20 Quantum dot

Table 38 List of descriptions for the term *quantum dot*

Source	Descriptions for the term *quantum dot*	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	A **crystalline nanoparticle** that exhibits size-dependent properties due to quantum confinement effects on the electronic states [54]. ISO/TS 27687:2008	**Webpage** [54]
Other sources		
ISO	**Quantum dot** (QD): crystalline nanoparticle that exhibits size-dependent properties due to quantum confinement effects on the electronic states. [SOURCE: ISO/TS 27687:2008, definition 4.7]	**Standard terminology**

Table 38 (cont.)

Source	Descriptions for the term *quantum dot*	Type of document
ISO	**Quantum dot**: nanoparticle or region which exhibits quantum confinement in all three spatial directions [ISO/TS 80004-13:2017(en), 3.1.1.6] **Quantum dot**: nanoparticle or region which exhibits quantum confinement in all three spatial directions [ISO/TS 80004-13:2017(en), 3.1.1.6]	**Standard terminology**
British Standards Institution	Discrete nanoscale semiconductor or metal structure that exhibits size-dependent electronic and optical properties due to quantum confinement [derived from Occupational Ultrafine Aerosol Exposure Characterization and Assessment] [PAS 131:2007; 4.9].	**Webpage** [142]
British Society for Nanomedicine	**Nanometer-sized semiconductor crystals**, or electrostatically confined electrons. Something (usually a semiconductor island) capable of confining a single electron, or a few, and in which the electrons occupy discrete energy states just as they would in an atom (quantum dots have been called "artificial atoms"). [CMP] Other terminology reflects the preoccupations of different branches of research: microelectronics folks may refer to a "single-electron transistor" or "controlled potential barrier," whereas quantum physicists may speak of a "Coulomb island" or "zero-dimensional gas" and chemists may speak of a "colloidal nanoparticle" or "semiconductor nanocrystal." All of these terms are, at various times, used interchangeably with "quantum dot," and they refer more or less to the same thing: a trap that confines electrons in all three dimensions. [from Hacking Matter: Levitating Chairs, Quantum Mirages, and the Infinite Weirdness of Programmable Atoms. Wil McCarthy. February 2003] ***Quantum Dot Nanocrystals (QDNs):*** used to tag biological molecules, and "measuring between five and ten nanometres across, are made up of three components. Their cores contain paired clusters of atoms such as cadmium and selenium that combine to create a semiconductor. This releases light of a specific colour when stimulated by ultraviolet of a wide range of frequencies. These clusters are surrounded by a shell made of an inorganic substance, to protect them. The whole thing is then coated with an organic surface, to allow the attachment of proteins or DNA molecules. By varying the number of atoms in the core, QDNs can be made to emit light of different colours." [From The Economist print edition]	**Webpage** [145]
BioPortal	**MeSH**: **Nanometer sized fragments of semiconductor crystalline material** which emit photons. The wavelength is based on the quantum confinement size of the dot. They can be embedded in microbeads for high throughput analytical chemistry techniques. (2004). *Synonyms: Nanocrystals, Semiconductor; Semiconductor Nanocrystal; Dot, Quantum; Semiconductor Nanoparticles; Semiconductor Nanocrystals; Nanoparticles, Semiconductor; Semiconductor Nanoparticle; Nanocrystal, Semiconductor; Dots, Quantum; Nanoparticle, Semiconductor; Quantum Dot* **NCIT**: **Nanometer-sized semiconductor particles** made of cadmium selenide (CdSe), cadmium sulfide (CdS) or cadmium telluride (CdTe) with an inert polymer coating. The semiconductor material used for the core is chosen based upon the emission wavelength range being targeted: CdS for UV-blue, CdSe for the bulk of the visible spectrum, and CdTe for far red and near-infrared. The size of the particle determines the exact color of a given quantum dot. The polymer coating protects cells from cadmium toxicity but also facilitates the attachment of a variety of targeting molecules, including monoclonal antibodies directed to tumor-specific biomarkers. Because of their small size, quantum dots can function as cell- and even molecule-specific markers that will not interfere with the normal cellular functions.	**Webpage** [126]

Table 38 (cont.)

Source	Descriptions for the term *quantum dot*	Type of document
BioPortal	**(cont.)** **CHEBI:** A **nanometre sized semiconducting particle**, whose excitons (electron-hole pairs) are confined in three spatial dimensions. This definition is shared by NBO and BIOMODELS ontologies. **NPO:** A **three-dimensional nanoparticle** which is made of material that exhibits quantum effects. Types described in this ontology: cadmium selenide QD, zinc sulphide QD, and gold QD.	**Webpage** [126]
Scientific literature	QDs composed of semiconductor elements, *e.g.* CdSe, CdS, CdTe, PbS, PbSe, PbTe, SnTe, InAs and InP. [146] Quantum dots are **nanoscale crystals of semiconductor material** that glow or fluoresce when excited by a light source such as a laser. QD nanocrystals of cadmium selenide are **200-10000 atoms** wide and coated with zinc sulphide. [128]	**Peer-reviewed article**

A5.21 Colloid

Table 39 List of descriptions for the term *colloid*

Sources	Descriptions for the term *colloid*	Type of document
Regulatory Authorities		
Taiwan Food and Drug Administration	Metal colloid: Metal nanoparticles in colloidal systems where the term colloidal refers to a state of subdivision. This implies that the molecules or polymolecular particles are dispersed in a medium and have at least in one direction a dimension roughly between or, in a system, have discontinuities at distances of that order. For example, silver, gold, titanium dioxide, zinc oxide, and iron oxide. [49]	**Peer-reviewed article**
Other sources		
ISO	**Colloid:** heterogeneous substance consisting of a liquid (dispersion medium) in which nanoscale (1 nm to 100 nm) particles are uniformly retained in suspension by their electrical charge, and which exhibits Brownian movements and is subject to cataphoresis (ISO/TR 13014:2012(en), 2.4)	**Standard Terminology**
BioPortal	**NCIT:** A mixture of microscopic particles suspended in some sort of liquid medium. **CRISP:** two-phase systems in which one is uniformly dispersed in another as particles small enough so they cannot be filtered or will not settle out; the dispersing or continuous phase or medium envelops the particles of the discontinuous phase; all three states of matter can form colloids among each other. *Synonym: ferrofluid, magnetic colloid* **MeSH:** Two-phase systems in which one is uniformly dispersed in another as particles small enough so they cannot be filtered or will not settle out. The dispersing or continuous phase or medium envelops the particles of the discontinuous phase. All three states of matter can form colloids among each other. **NPO:** A suspension of particles (dispersed phase) in a liquid medium (dispersion medium or continuous phase).	**Webpage** [126]

A5.22 Fullerene

Table 40 List of descriptions for the term *fullerene*

Sources	Descriptions for the term *fullerene*	Type of document
Regulatory Authorities		
Canada **TERMIUM Plus®** **(Government of Canada)**	Compound composed solely of an even number of carbon atoms, which form a cage-like fused-ring polycyclic system with twelve five-membered rings and the rest six-membered rings.	**Webpage** [54]
Other sources		
ISO	Fullerene: molecule composed solely of an even number of carbon atoms, which form a closed cage-like fused-ring polycyclic system with 12 five-membered rings and the rest six-membered rings (ISO/TR 14786:2014(en), 3.2)	**Standard terminology**
British Society for Nanomedicine	**Fullerenes:** Fullerenes are a molecular form of pure carbon discovered in 1985. They are cage-like structures of carbon atoms, the most abundant form produced is buckminsterfullerene (C60), with 60 carbon atoms arranged in a spherical structure. There are larger fullerenes containing from 70 to 500 carbon atoms.	**Webpage** [145]
BioPortal	**NCIT**: One of three known pure forms of carbon that exhibits a spherical shape with a hollow interior. The number of carbon atoms comprising fullerenes is variable and several stable spherical carbon structures containing 70 or more atoms have been documented. **CHEBI**: A compound composed solely of an even number of carbon atoms, which form a cage-like fused-ring polycyclic system with twelve five-membered rings and the rest six-membered rings. The term has been broadened to include any closed cage structure consisting entirely of three-coordinate carbon atoms. Other ontologies adopting this definition are ENM, NBO, BIOMODELS and SOPHARM. **SIO**: fullerene is a carbon allotrope which takes the form of a hollow sphere, ellipsoid, or tube. **NPO**: A fullerene refers to any cagelike, hollow molecule composed of hexagonal and/or pentagonal groups of carbon atoms, and it is regarded as the third form of carbon after diamond and graphite. **MeSH**: A polyhedral CARBON structure composed of around 60-80 carbon atoms in pentagon and hexagon configuration. They are named after Buckminster Fuller because of structural resemblance to geodesic domes. Fullerenes can be made in high temperature such as arc discharge in an inert atmosphere.	**Webpage** [126]
Synonyms	bucky-ball, buckeyball, buckey-ball, buckminsterfullerene, footballene C60	

A5.23 Nanocrystal

Table 41 List of descriptions for the term *nanocrystal*

Source	Descriptions for the term *nanocrystal*	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	Molecular-sized solids formed with a repeating, 3D pattern of atoms or molecules with an equal distance between each part. Internet. Original source: [http://www.nanohand.eu]. Glossary. (20080207) Nanocrystals are aggregates of anywhere from a few hundred to tens of thousands of atoms that combine into a crystalline form of matter known as a 'cluster'. Typically around 10 nm in diameter, nanocrystals are larger than molecules but smaller than bulk solids and therefore frequently exhibit physical and chemical properties somewhere in-between. Nanocrystals are believed to have potential in optical electronics because of their ability to change the wavelength of light. [http://www.nanohand.eu]. Original source: Glossary. (20080207) **Nanocrystalline metal:** Magnetic Properties of Nanocrystalline Metals. Nanocrystalline materials represent one form of grain boundary engineering which increases the intercrystalline volume fraction of a material. It has been shown that this can affect mechanical, chemical, magnetic, kinetic and electrical properties. Nanomaterials produced by electrodeposition are porosity free and therefore yield their true intrinsic properties. However when assessing the intrinsic properties of nanocrystalline electrodeposits, microstructural and texture differences must be taken into consideration. Original source: (Department of Materials and Metallurgical, Engineering, Queen's University, Kingston, ON, Canada), (Department of Metallurgical Engineering, McGill University, Montreal, Que, Canada).	**Webpage** [54]
Taiwan Food and Drug Administration	Nanoscale solid formed with a periodic lattice of atoms, ions, or molecules. [49]	**Peer-reviewed article**
Other sources		
ISO	Nanocrystal: nano-object (3.1.3) with a crystalline structure (ISO/TS 20477:2017(en), 3.1.7)	**Standard terminology**
British Standards Institution	nanoscale solid formed with a periodic lattice of atoms, ions or molecules] [PAS 131:2007; 4.13]**[142].** This definition is also adopted by the British Society for Nanomedicine.	**Terminology**
BioPortal	**CHEBI:** Crystalline aggregates of atoms (100-10,000 atoms) with a diameter of approximately 10 nm. Type of nanocrystals mentioned in the ontology: gold nanocrystal, magnesium oxide nanocrystal, and cadmium telluride nanocrystal. This definition is also used in the NBO and BIOMODELS.	**Webpage** [54]
Scientific literature	Nanocrystals are aggregates of molecules that can be combined in a crystalline form of the drug surrounded by a thin surfactant coating. High dosages can be achieved and poorly soluble drugs can be formulated for improved bioavailability. Both oral and parenteral delivery is possible and the limited carrier in the formulation reduces potential toxicity. Limitations include poor drug stability. [97] Nanoscopic crystal of a hydrophobic parent drug (Size: 50-1000 nm). [131] A term that is utilized to refer to any crystalline structure possessing dimensions (e.g. overall width) measured in terms of nanometers. [60]	**Peer-reviewed articles**

A5.24 Nanocarrier

Table 42 List of descriptors for the term *nanocarrier*

Source	Description	Type of document
ISO	Nano-object[24] or objects which are at larger scale but which carry nanoscale[25] payloads able to transport a diagnostic or therapeutic agent either on its surface, within its bulk structure or within an internal cavity. *Note 1: Transport might be target a specified, precise location. Note 2: Includes transport of medical payloads to specific cells and tissues, for example, anticancer agent, antibiotic, other drug release, or for imaging and sensing functions* (ISO/TS 80004-7:2011(en), 4.4)	**Standard terminology**

A5.25 Nanocapsule

Table 43 List of descriptors for the term *nanocapsule*

Source	Description	Type of document
ISO	nano-object with more than one chemically or structurally distinct wall layer enclosing a hollow or solid core and which is designed to carry analytical, therapeutic or image enhancing components (ISO/TS 80004-7: 2011-10)	**Standard Terminology**
BioPortal	**MeSH**: Nanometer-sized, hollow, spherically-shaped objects that can be utilized to encapsulate small amounts of pharmaceuticals, enzymes, or other catalysts (Glossary of Biotechnology and Nanobiotechnology, 4th ed). **NBO**: A three-dimensional nanoparticle which consists of a shell and a space, in which desired substances may be placed. It can be cylindrical or spherical in shape.	**Webpage** [126]

A5.26 Nanoemulsion

Table 44 List of descriptors for the term *nanoemulsion*

Source	Description	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	A fluid nanodispersion with at least one liquid nanophase (International Organization for Standardization (ISO)).	**Webpage** [54]

[24] Nano-object (ISO definition): material with one, two or three external dimensions in the nanoscale. Note: generic term for all discrete nanoscale objects.

[25] Nano-scale: size range from approximately 1 nm to 100 nm. Note 1: Properties that are not extrapolations from a larger size will typically, but not exclusively, be exhibited in this range. For such properties the size limits are considered approximate. The lower limit in this definition (approximately 1 nm) is introduced to avoid single and small groups of atoms from being designated as nano-objects or elements of nanostructures, which might be implied by the absence of a lower limit.

Table 44 (cont.)

Source	Description	Type of document
Other sources		
ISO	Nanoemulsion: nanodispersion (2.79) with a liquid matrix and at least one or more liquid nano-objects (2.82) (ISO 18451-1:2015(en), 2.80)	**Standard Terminology**
BioPortal	**The National Centre for Biomedical Ontology**: Nanoemulsion: A mixture of two immiscible substances in which the sizes of the particles in the dispersed phase are defined as **less than 1000 nm**.	**Webpage** [126]
Scientific literature	**Emulsions** are formed from two immiscible phases by energy input (e.g. stirring, homogenization) and the presence of surfactants to reduce surface tension and stabilize the droplets. Emulsions are thermodynamically unstable. As such, phase separation occurs in an emulsion, giving back two immiscible phases. [72] Oil nanodroplets dispersed within aqueous continuous phase suitable for entrapment of hydrophobic drugs (Size: 20–200 nm). [131]	**Peer-reviewed article**

A5.27 Nanosuspension

Table 45 List of descriptors for the term *nanosuspension*

Source	Description	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	A fluid nanodispersion where the dispersed phase is a solid. The use of the term "nanosuspension" carries no implication regarding thermodynamic stability.	**Webpage** [54]
ISO	Nanosuspension: heterogeneous mixture of materials comprising a liquid and finely dispersed solid nano-objects (2.82) (ISO 18451-1:2015(en), 2.86)	**Standard terminology**
United States Patent and Trademark Office	Nanosuspensions are dispersions of nanosized drug particles prepared by bottom-up or top-down technology and stabilised with suitable excipients. (US PATENT: 9,775,818)	**US patent**

A5.28 Nanocomposite

Table 46 List of descriptors for the term *nanocomposite*

Source	Description	Type of document
British Standards Institution	Multiphase structure in which at least one of the phases has at least one dimension in the nanoscale	**Terminology**
ISO	Nanocomposite: solid comprising a mixture of two or more phase-separated materials, one or more being nanophase (ISO/TR 18401:2017(en), 3.12).	**Standard Terminology**

Table 46 (cont.)

Source	Description	Type of document
BioPortal	**MeSH**: Nanometer-scale composite structures composed of organic molecules intimately incorporated with inorganic molecules. Glossary of Biotechnology and Nanobiotechology Terms **NCI Thesaurus**: Heterogeneous materials comprised of nanoparticles and plastic resin to provide added strength and desirable thermal attributes. Nanocomposites are a class of compounds with unique performance profiles with respect to rigidity and transparent barrier properties.	**Webpage** [126]

A5.29 Nanoaerosol

Table 47 List of descriptors for the term *nanoaerosol*

Source	Description	Type of document
Regulatory Authorities		
Canada TERMIUM Plus® (Government of Canada)	A fluid nanodispersion with a gaseous matrix and at least one liquid or solid nanophase. (International Organization for Standardization (ISO)). Glossary [54] Nano-aerosol: term related to a category of nanostructured materials, fluid nanodispersions.	**Webpage** [54]
Other sources		
ISO	Nanoaerosol: solid or liquid nano-objects in dispersion in a gaseous medium (ISO 4618:2014(en), 2.163).	**Standard terminology**
Scientific literature	Nano-aerosols are nanoparticles suspended in a gas. These nanoparticles could be liquid droplets but are usually solid particles with at least one dimension being less than 100 nm. Most researchers consider nanoaerosol as another name of ultrafine aerosol or ultrafine particulate matter. [148] Nanoaerosols are defined here as being aerosols comprised of particles that are less than 200 nm in diameter [149]. In comparison, aerosol particles created by a standard 3-jet Collison nebulizer are usually between 1 and 5 µm in diameter. [150]	**Peer-reviewed article**

A5.30 Nanobody

In the EMA webpage two entries were found using the term *nanobody* for human medicinal products. In this document *nanobody*, is defined as a *very small antibody (a type of protein)*[26] . This term is associated to the description of nanomedicine and it could be discussed because its biological origin.

This term has not been mentioned in any other medicine agency webpage, only as part of FDA publication references. In this report, nanobodies are used to target lentivirus that would transduce to dendritic cells and macrophages (use as immunotherapeutic). The debate lies in the classification of this product as nanomedicine or simply as biological product.

[26] European Medicines Agency. Committee for Orphan Medicinal Products. Public summary of opinion on orphan designation (2009) http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500006257.pdf

Table 48 List of descriptors for the term *nanobody*

Source	Description	Type of document
Scientific literature	Refers to the smallest possible portion of an antibody which will bind to an antigen/hapten. Although nanobodies are not made naturally (i.e., the body always makes complete/full-size antibodies), nanobodies [approximately 120 amino acids in length] can be made via genetically engineered cells grown via cell culture. [60] Nanobodies, derived from naturally occurring single-chain antibodies, are the smallest fragments of naturally occurring heavy-chain antibodies that have evolved to be fully functional in the absence of a light chain. [128] One order of magnitude smaller that their parent molecules, conventional monoclonal antibodies, and thus have a greater stability as well as a reduced chance of causing immunogenic response in vivo. [151] Nanobodies are the smallest fragments of naturally occurring heavy-chain antibodies that have evolved to be fully functional in the absence of a light chain. [152] Nanobodies® (Ablynx) are among the smallest known antigen-binding antibody fragments, and are derived from the heavy-chain only antibodies that occur naturally in the serum of Camelidae. [153]	**Peer-reviewed article**

A5.31 Virosome

Table 49 List of descriptors for the term *virosome*

Source	Description	Type of document
BioPortal	**NCIT:** Virosomes are reconstituted influenza virus (A/Singapore) envelopes. The membrane of these vesicles consists of a spherical, unilamellar lipid bilayer. Purified influenza envelope glycoproteins (hemagglutinin HA and neuramindase NA) are inserted into the lipid bilayer. Virosomes with a bilayer consisting of neutral phospholipids can be used as an unspecific or a specific drug carrier system, while positively charged vesicles can be used as a transfer system for any genetic materials. **MeSH:** Semi-synthetic complex derived from nucleic-acid free viral particles. They are essentially reconstituted viral coats, where the infectious nucleocapsid is replaced by a compound of choice. Virosomes retain their fusogenic activity and thus deliver the incorporated compound (antigens, drugs, genes) inside the target cell. They can be used for vaccines (VACCINES, VIROSOME), drug delivery, or gene transfer.	**Webpage** [126]
Scientific literature	Reconstituted virion-like lipid bilayer vesicle that contains integrated surface glycoproteins that are derived from viruses (Size: 20–150 nm). [131] **Virosomes** were developed from liposomes by combining liposomes with fusogenic viral envelope proteins. Unlike viruses, virosomes are not capable of replication but are pure fusion-active vesicles. Due to the presence of specialized viral proteins on the surface of virosomes, they can be applied to the active targeting and delivery of their content at the target site. [154] Protein cages, which are multivalent, self-assembled structures.	**Peer-reviewed article**
Synonyms	Virus-like particles for gene delivery, Viral nanoparticles.	

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doi:10.2760/753829

ISBN 978-92-79-89872-3