

The Graphene Flagship Technology and Innovation Roadmap

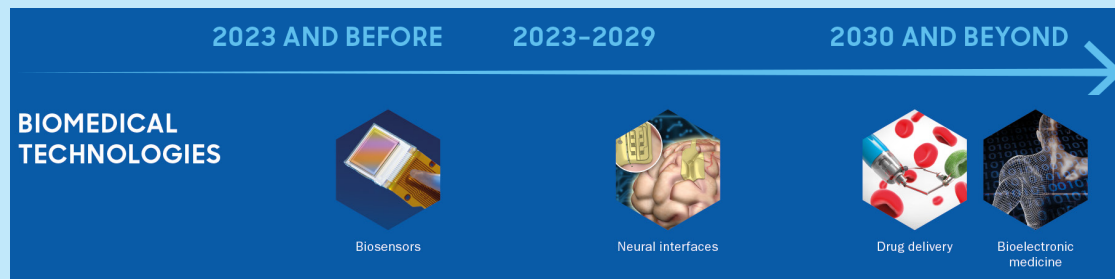
Biomedical Applications

This section covers special applications of graphene in biomedicine in a more sector oriented approach. The spectrum of applications in biomedicine proves to be quite broad and diverse, so that it is not possible to apply a single principle of GRM utilization on all biomedical applications.

GRMs promise to impact the biomedicine market in numerous segments. In particular, applications in drug delivery, biosensing, antibacterial material, bone prostheses, and small implants appear quite promising. However, the research in all fields of application is still at an early stage, and often the final proof of feasibility is still missing. However, it can be expected that further cases for application will be detected in the next years, for instance in biosensing.

A specific feature of the market in biomedicine is the requirement that all products and devices must be admitted by the public regulatory authorities of the respective countries. This brings in a delay or at least three years. In any case, there is a broad industrial basis in the EU which could adopt graphene/GO in biomedicine. Therefore, the market potential in an EU perspective is generally positive.

This is an excerpt from the complete Technology and Innovation Roadmap.



VISIT US

www.graphene-flagship.eu

CONTACT US

info@graphene-flagship.eu

FIND US



6 Biomedical applications

6.1 Potential areas of applications of GRM in biomedicine

This chapter covers special applications of graphene in biomedicine in a more sector oriented approach. The spectrum of applications in biomedicine proves to be quite broad and diverse, so that it is not possible to apply a single principle on all biomedical applications. Generally the following application areas of graphene in biomedicine prove to be relevant:

- Drug/gene delivery
 - Cancer therapy
- Bioimaging & Biosensing
- Antibacterial materials
- Biocompatible devices
 - Prostheses
 - Bioelectronic medicine
 - Small implants
 - Tissue engineering
- FOCUS: Neural interfaces

Thus the applications refer to all three broad commercial areas of medicine, i.e. drugs & pharmaceuticals, Medical Devices & Equipment, Research & Testing [613]. Wearables for consumer lifestyle health monitoring are covered in chapter 5 Electronics & Photonics. Furthermore, the more technology related area of in vitro diagnostics, POCT and biosensors is covered in 5.5 Sensors on a broader basis. Antibacterial materials and coatings that are also of interest to prostheses or for biocompatible devices are covered more broadly in 1.4

This chapter focuses on the peculiarities of the health sector and highlights particular biomedical applications. In particular, the promising application field of neural interfaces (see 6.6) served as an exemplary case to resolve the specific challenges and framework conditions for novel material implementation in the medical field.

The relevance of the above mentioned fields is reflected in patent and publication databases in different ways. Beginning with the file World Patents Index, Transnational Patents, the topics in Table 73 appear most frequently in the context of the use of graphene in biomedicine.

Table 73: Most frequent main-groups of Transnational Patents in the area of the use of Graphene in Biomedicine sorted by Frequency. [137]

Main Group	Frequency
Investigating or analysing materials by specific methods	139
Measuring or testing processes involving enzymes or micro-organisms	76
Investigating or analysing materials by the use of optical means, i.e. using infra-red, visible or ultra-violet light	45
Medicinal preparations characterised by the non-active ingredients used, e.g. carriers, inert additives	31
Measuring for diagnostic purposes	25
Medicinal preparations containing organic active ingredients	23
Medicinal preparations characterised by special physical form	27
Preparations for testing in vivo	17
Electrotherapy; Circuits therefore	13
Materials for prostheses or for coating prostheses	13
Materials for other surgical articles	11
Filters implantable into blood vessels	9
Chemical aspects of, or use of materials for bandages, dressings or absorbent pads	7

In patents, i.e. in present commercial applications, various methods of analysis and measuring biological materials dominate. In particular the first category “investigating or analyzing materials by specific methods” is linked to medical analysis. Drug delivery appears in “preparations characterised by non-active ingredients”.

In the database Web of Science, reflecting scientific publications, the clear focus is on medical engineering, whereas the treatment of special diseases is rarely addressed, in the database Compendex, reflecting scientific publications in applied fields, the focus is on biomaterials. In the following chapters, the various applications will be discussed in more detail. Before that, there is an excursus on the peculiarities of the health market.

6.2 Excursus: The specific structures of the health market

The health market has a large volume and is quite independent of economic crises. Nevertheless, it has very specific structures which make the access difficult.

Products or processes for application in the prevention, analysis, diagnosis, therapy or monitoring of human diseases or physiological processes can be either drugs or therapeutic agents such as organs, tissues, blood or cells, medical devices, or laboratory procedures. They can further be differentiated according to their use in (in vivo) or outside (ex vivo) the human body.

In order to ensure the high quality of these products and processes, especially with respect to patients' and medical staff safety and public health, a large body of legislation has been developed since the 1960s in the EU and worldwide. It is based on the principle that the placing on the market is made subject to the granting of a marketing authorization by the relevant authorities on EU or member state level [614]. Similar, but not identical regulatory regimes apply in other regions of the world, e.g. Northern America, Asia. The process of harmonization and amendment of requirements for the granting of marketing authorizations, both within the EU as well as between the different regions of the world, is ongoing. While uniform marketing authorization procedures have been implemented throughout the EU, obtaining reimbursement for the products, procedures and services from statutory and private health insurances is subject to individual EU member states' policies and regulations, and may differ significantly both in requirements to be fulfilled, procedures, and extent and timing of reimbursement.

As a consequence, the EU and worldwide health care sectors are highly regulated, and this aspect has to be taken into consideration very early in the innovation process, so that the R&D activities can be designed in a way that the regulatory requirements for obtaining marketing authorization and reimbursement by health insurances can be fulfilled: Figure 111 gives a schematic overview of the R&D and authorization process of a new drug. Mandatory for obtaining marketing authorization is preclinical and clinical research (phase I to III) in order to collect all the data that are required for obtaining marketing approval. Depending on the novelty of the drug, this process may take 7-12 years. However, different procedures apply for medical devices.

In the following paragraphs, a short overview of the relevant regulatory regimes and the procedures for obtaining marketing authorization with a focus on the European Union is given.

In the EU, two fundamentally different regulatory approaches govern the marketing authorization:

1. the medicinal products regulation, and
2. the medical device regulation.

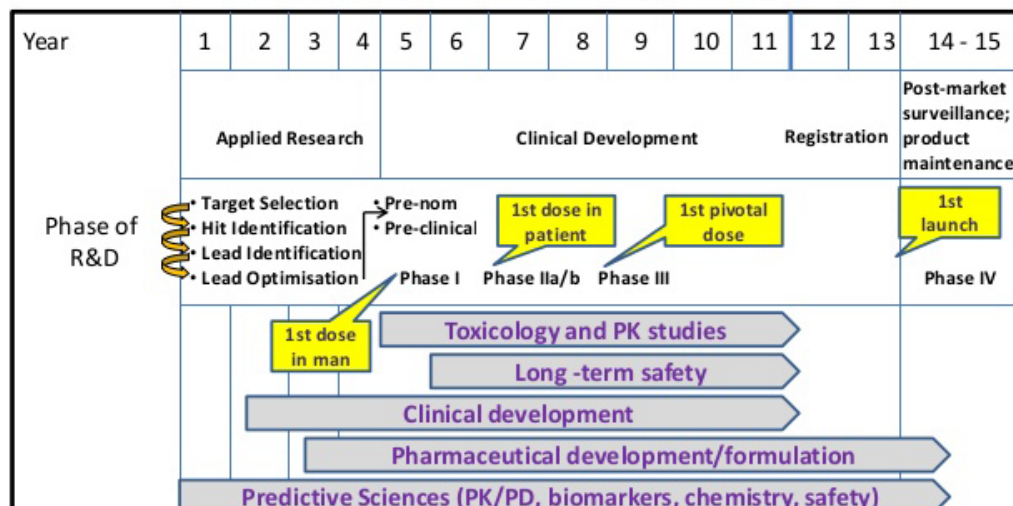


Figure 111: Schematic Overview of the R&D and Authorization Process of a Medicinal Product. [615]

6.2.1 Medicinal products regulation

Medicinal products are – in general – drugs, i.e. small chemical molecules or biopharmaceuticals, such as antibodies, therapeutic proteins, but also advanced therapies such as tissue engineered products, cell therapies etc.

Graphene and related 2D materials (GRM) are not so much considered as drugs themselves, but mainly as drug delivery vehicles, as matrices for tissue engineered medicinal products etc. Nevertheless, as the GRMs will be combined with medicinal products, (parts of) the medicinal products regulation must also be taken into account when developing GRM based drug delivery system, matrices etc.

Overall responsibility for the legislation regarding medicinal products lies with the DG Health and Food Safety. Depending on the class of medicinal products, authorisation procedures are either carried out by an individual EU member state regulatory authority, followed by a mutual recognition procedure for the whole EU; or a centralised authorisation procedure is carried out by the European Medicines Agency (EMA). This is the Community regulatory agency in charge of providing the EU institutions with scientific advice on medicinal products.

The legal basis for the regulation of medicinal products for human use in the EU is *REGULATION (EC) No 726/2004 OJ L 136* and *DIRECTIVE 2001/83/EC OJ L 311* [616, 617]. They lay down the requirements and procedures for the marketing authorisation for medicinal products, the rules for the constant supervision of products after they have been authorised, as well as provisions for manufacturing, wholesaling or advertising. The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 of the publication "The rules governing medicinal products in the European Union" [618]. In order to facilitate the interpretation of the legislation and its uniform application

across the EU, numerous guidelines of regulatory and scientific nature have additionally been adopted. They are compiled in the volumes 2-4 and 6-10 of the above mentioned publication²².: A detailed explanation of the marketing authorisation procedures and other regulatory guidance intended for applicants is contained in volume 2 (Notice to Applicants), whereas scientific guidance on the quality, safety and efficacy of medicinal products is provided in volume 3. Specific guidance on the legal requirements concerning good manufacturing practices, pharmacovigilance and clinical trials is laid down in volumes 4, 9 and 10, respectively.

In addition, various rules have been adopted to address the particularities of certain types of medicinal products and promote research in specific areas: orphan medicinal products [619], medicinal products for children [620] and advanced therapy medicinal products [621].

The key points of the medicinal products regulations with relevance for GRM at the present state of development are:

- All medicines offered for sale in the EU must have prior authorisation from either a national authority or the European Medicines Agency.
- To receive the authorisation, manufacturers must provide a range of detailed therapeutic information about the product, including any possible side-effects.
- Authorisation may be refused, if a medicine's risk-benefit ratio is not considered favourable or its therapeutic effect is insufficiently substantiated.
- National authorities should make every effort to complete the authorisation procedure within 210 days from the submission of a valid application. Authorisation is valid for 5 years and is renewable.
- A mutual recognition procedure exists to enable medicines already authorised in 1 EU country to be sold in another.
- The legislation does not apply to whole blood, plasma or certain medicinal products, such as those prepared in a pharmacy or used for research and development.
- The European Commission has also issued guidelines for good practices in the manufacture and distribution of medicinal products.

6.2.2 Medical devices regulation

Medical devices comprise a very diverse set of products, ranging from simple wound dressings, surgical instruments to high-tech diagnostic devices, such as magnetic resonance imaging devices, or medical implants, e.g. pacemakers, or software.

Most of the potential applications of graphene and related 2D materials in the health sector are medical devices for in vivo or in vitro use, e.g.

- medical implants, prostheses, e.g. equipped with GRM coatings or sensors for in vivo use

²² The different EudraLex Volumes can be accessed via http://ec.europa.eu/health/documents/eudralex/index_en.htm; accessed 2016-06-16

- diagnostic devices such as labs on chip, e.g. for point-of-care diagnostics, wearable electronics with GRM-based sensors for monitoring purposes
- Improved methods for biomedical laboratory analytical or diagnostic procedures (e.g. DNA sequencing).

Overall responsibility for the regulation of medicinal products lies with the DG Growth. Regulations relating to the safety and performance of medical devices in the EU follow the so-called “New approach”: in contrast to the medicinal products regulation which lays out product specifications in detail, the new approach only gives quite general basic requirements. The task of defining detailed technical specifications is delegated to European Standards Organisations, e.g. to Comité Européen de Normalisation (CEN) or to Comité Européen de Normalisation Electrotechnique (CENELEC). If products conform with these standards, it is assumed that they are safe and are thus marketable in all EU member states.

In the current medical device legislation, the core legal framework consists of three directives, which have been amended several times, and consolidated versions are available:

- Council Directive 90/385/EEC on Active Implantable Medical Devices [622]
- Council Directive 93/42/EEC on Medical Devices [623]
- Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices [624]

The aim of these Directives is to ensure a high level of protection for human health and safety and a good functioning of the Single Market.

In order to adapt the existing regulations to the technological and scientific state of the art, the European Commission adopted, on 26 September 2012, two regulation proposals to revise existing legislation on general medical devices and *in vitro* diagnostic medical devices [625, 626]. Revisions include the extending of the scope for legislation; better supervision of independent assessment bodies; clear rights for manufacturers/distributors; and stronger requirements for medical evidence. The ordinary legislative procedure for these proposals, involving the European Parliament and the Council, is ongoing. Once adopted, the revised regulations will replace the existing three medical devices directives.

All in all, the procedure for obtaining marketing authorisation for medical devices differs from the respective procedures for medicinal products. The key steps are the following:

1. Status of the product. It must be decided whether the product is a medical device and falls under the scope of the medical device regulation, and whether specific provisions apply (e.g. for *in vitro* diagnostics). Although the regulation provides definitions and guidance for clarifying the status (principal intended action by chemical or physical means; intended use specifically for diagnostic and/or therapeutic purposes), it may be necessary to consult the responsible regulatory authority or experts, especially if the product is a combination of medical devices and medicinal products.
2. Classification. The medical device has to be classified according to type (e.g. *in vitro* diagnostics; active implantable medical device; general medical device) and risk potential.

This classification is crucial, because it determines the scope and extent to which the conformity assessment procedure must be carried out. In general, three risk classes are distinguished (Table 74).

Table 74: Risk Classification of Medical Devices

Risk class	Description
Risk class I (incl. class Isterile and class I _{measurement function})	<ul style="list-style-type: none"> • Risk potential low • e.g. walking frames
Risk class II a	<ul style="list-style-type: none"> • Risk potential medium • e.g. hearing aides
Risk class II b	<ul style="list-style-type: none"> • Risk potential elevated • e.g. lung ventilators
Risk class III	<ul style="list-style-type: none"> • Risk potential high • E.g. active implants

3. Certification. In the certification procedure, the conformity assessment is carried out. If completed successfully, the medical device receives the CE mark and thus market authorisation. For higher risk class devices, the conformity assessment is carried out by a Notified Body, of which there are appr. 80 in the EU. The manufacturer has to submit a technical documentation to the notified body which forms the basis for the conformity assessment. While clinical trials are mandatory for the marketing authorisation of medicinal products, this is the case for only few medical devices. However, the revision of the medical device regulation will implement stricter requirements.

6.2.3 Reimbursement and users' acceptance

The reimbursement systems in Europe of novel medicinal technologies and products represent a major hurdle. Novel technologies are often more expensive and therefore the companies struggle to prove their cost-benefit over already existing and established technologies (medico-economic studies to prove effectiveness). The reimbursement schemes for health technologies are heterogeneous, also among European countries. In Eastern Europe innovative technological solutions are less frequently covered by health insurance compared to Western Europe - the expenditure per head of population is highest in Luxembourg and countries outside the EU belonging to EFTA – in excess of 4,000 Euros per person per year, it is way below 1,000 Euros in most countries that joined the EU in 2004 or later [627].

Also the users' acceptance is often a challenge for the medicinal technologies, since the majority of medical specialists have not received special training. This is especially true for point-of-care diagnostics but also other product categories, where medical specialist prefer traditional treatment schemes to innovative and disruptive technologies that require change in already existing treatment routines and habits. Some medicinal technologies reach the level of maturity to be “fully developed”, but do not manage to reach out

further into the medical world, e.g. because they do not manage to create demand for their product. There are weak links between R&D, engineering and clinicians which hold back the introduction of “intelligent” Smart Systems.

A further problem is that research-intensive medical products and devices are in general only profitable, if they reach the global market. However, the conditions of official approval, reimbursement by insurances and acceptance by users differ by country and region. In particular, it is important to get access to the US market, but the Asian market gets increasingly attractive.

To sum up, the access to the health market is highly regulated. For each product or device a detailed dossier has to be submitted and the approval process carried out by the regulatory authority in charge may require several months to even years. Furthermore, the reimbursement by the health insurances must be achieved and the acceptance by users.

6.3 Drug/gene delivery and photothermal/photo-enhanced cancer treatment

By attaching drug/gene to suitable carriers, the bioavailability of the drug/gene can be maximized due to efficient loading, target delivery, and controlled release. Following the successful use of carbon nano tubes in lab experiments (CNTs) for **drug/gene delivery**, graphene sharing a similar chemical structure with CNTs, can also be used as drug/gene delivery carrier. Graphene/GO is primarily used for drug/gene delivery in cancer therapy. In the literature, drug delivery is discussed as primary option in this context. Further potentials for the use of graphene/GO in cancer therapy are phototherapy and enhancement of drug efficiency through photo-enhancement.

In **phototherapy**, heat generated by light absorption in graphene induces thermal destruction of cancer cells containing significant concentrations of graphene [628, 629]. The scientific results in this context are very promising, but they are still in the stage of mouse models.

The photothermal effect of graphene can be also used for enhancing the efficiency of chemotherapeutic drugs such as DOX (Doxorubicin) [628]. When photothermal therapy is combined with a photosensitizer an alternative therapeutic modality called **photodynamic therapy** can be developed/achieved[630]. The results of scientific research in this context are promising, but it is still too early for relevant market estimates.

In this chapter, we will discuss drug delivery, on phototherapy and photothermal enhancement of drug efficiency.

6.3.1 Market perspective: graphene/2D materials in drug delivery and other cancer therapy

In general, the market of drug delivery is quite large and attractive reflected in a high number of patent applications in the last years (Figure 112). The US is leading in patents, but the EU has almost the same level. Whereas the total patents in drug delivery are decreasing, those with graphene exhibit a substantial increase although still at a moderate absolute level (Figure 113). In this segment, the US is in the lead, but the absolute level is moderate, so that a catch-up of the EU in this highly attractive market appears to be realistic.

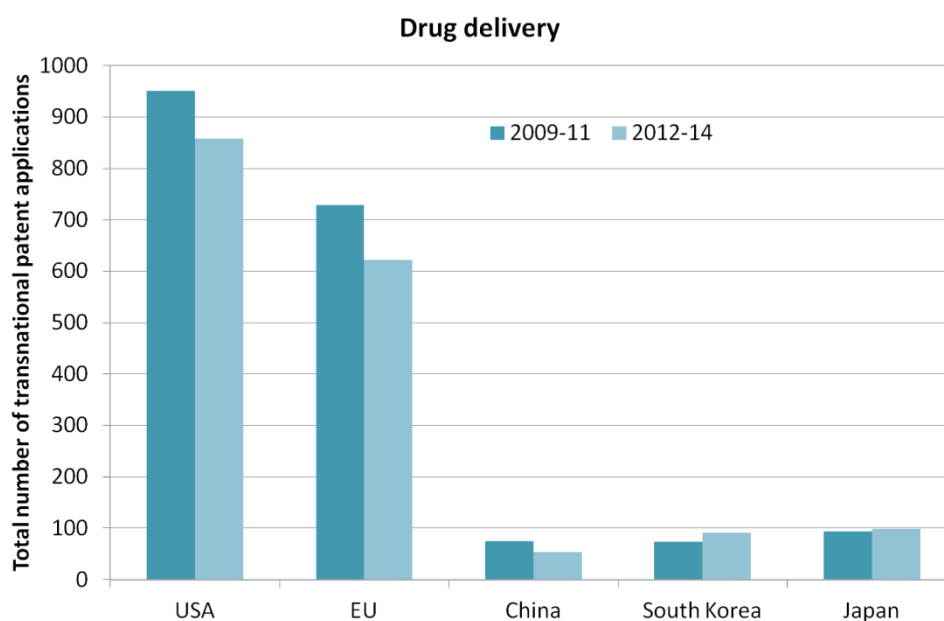


Figure 112: Transnational Patents in Drug Delivery by Priority Years. [137]

Graphene/2D in drug delivery

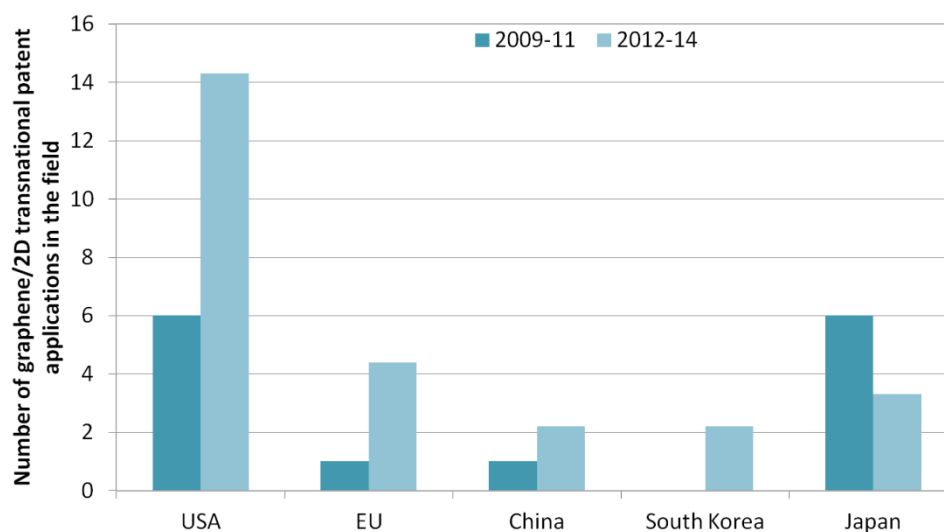


Figure 113: Transnational Patents in graphene-based Drug Delivery by Priority Years. [137]

The drug delivery based on graphene has to be considered as part of the general market of drug delivery. The worth of the global oncology drug delivery market is estimated at a level of \$96 billion in 2014 with an annual growth rate of 5 % [631]. The volume for 2020 will reach about \$141 billion. The share of the European market in 2014 was \$23 billion and will reach \$30 billion in 2020.

The number of Transnational Patents for the radiation therapy of cancer is quite high with more than 800 in the period of 2012 to 2014, thus it is a relevant market segment.

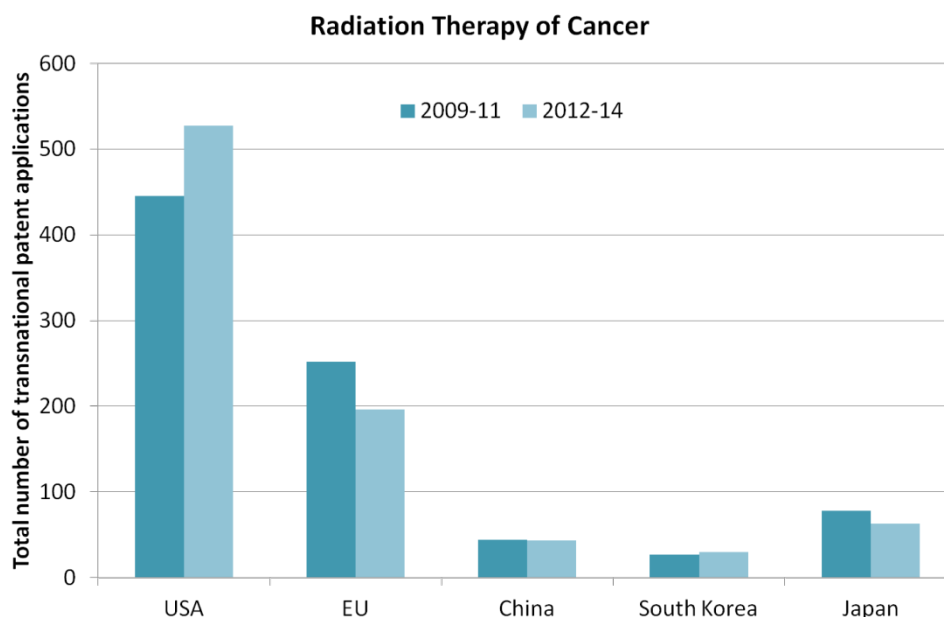


Figure 114: Transnational Patents in Radiation Therapy of Cancer. [137]

The number of patent applications for graphene based phototherapy is still very low with a level of about 10 in total, but it can be assumed that the share will grow rapidly, as soon as the usefulness in human therapy can be verified.

6.3.1.1 Market opportunities

6.3.1.1.1 Oral delivery as preferred market

The market is subdivided in oral and intravenous delivery where the oral part is about 25 %. It is assumed that nano-particles (micro-needles, patches, and orals) will lead the market in the future wherein graphene could have a major relevance. There is a preference for oral delivery, but the intravenous (IV) delivery is still more effective. With nano-particles, also oral forms of drug delivery will become more effective. In 2014, the oral drug delivery market had a size of \$24 billion and get at \$40 billion in 2020, thus the growth rate is already quite high with 8% and even increase to 14%.

At present the focus is still on basic scientific research, but there is a strong perspective to achieve reliable results in applied research until 2020.

6.3.1.1.2 Cancer therapy as a large, promising and rapidly adopting market

The potential of getting access to a large market is very high, as any promising method of improving the results of cancer therapy will be adopted rapidly.

6.3.1.1.3 Cancer therapy as first entry point

Cancer therapy is discussed as one of the potential areas of graphene, especially for delivery of combined drugs. The latter is very interesting for cancer therapy and personalized medicine both fields with increasing relevance and importance.

6.3.1.2 Market threats

6.3.1.2.1 Competing nano carrier technologies

In nano-drug delivery systems, various materials are discussed such as silica, iron gold, silver, glass, polymers etc. Thus graphene represents only a limited part of nano drug delivery. All these approaches are in early stages, so that insufficient experiences as to advantages and disadvantages exist. So it is possible that some materials exhibit positive features that cannot be reached by graphene.

6.3.1.2.2 High competition: Many stakeholders and other technologies

The market referring to cancer therapy is very large and commercially attractive. Therefore this market has attracted many enterprises, traditional pharmaceutical enterprises, enterprises in bioengineering, and enterprises in all types of medical devices. The competition is very fierce. For instance the number of patent applicants in cancer drugs comprises more than 1000 enterprises. This means that the scientific basis must be quite large and the evidence for validity of the claims must be strong.

A competitive approach is the use nano gold particles for similar purposes [632]. The market for radiation therapy of cancer is estimated at \$3.5 billion where phototherapy is a limited part besides x-radiation.

6.3.1.2.3 User acceptance

A further potential problem is the users' acceptance. The use of graphene in drug delivery will imply a change of chemical treatment of cancer from hospital-based infusion to home-based treatment with micro-needles, patches, or oral delivery. It is a question whether the physicians will be ready to reduce their monitoring in cancer treatment. At least a longer period of transition of the habits has to be taken into account.

6.3.1.2.4 Competition and strong players defending traditional systems

Furthermore, the attractive market of drug delivery is characterised by high competition and the providers of traditional delivery systems will try to defend their market shares with a vengeance.

A major problem for graphene/GO-based delivery systems will be convincing solution to the toxicity apprehension. The stigma of toxicity can stop all endeavours to bring graphene-based delivery into the market.

6.3.2 Graphene/2D materials perspective: current strengths, weaknesses and challenges for the use in drug delivery

In this very early stage it is not possible to say anything sound as to strengths and weaknesses performance, or barriers/challenges with respect to phototherapy and photothermal enhancement of drug efficiency. This chapter therefore focuses on drug delivery.

6.3.2.1 Current strengths of graphene/2D materials in drug/gene delivery

6.3.2.1.1 GO as attractive delivery system

Due to the specific features of graphene such as the high surface area available, the numerous chemical strategies and the abundant chemical functions, especially graphene oxide (GO) attracts great interest as novel drug/gene delivery system with high efficiency, multi-targeted drug delivery and controlled release [628].

Major arguments for graphene are the possibility of a targeted delivery and the delivery of a set of combined drugs. Therefore it can be assumed that graphene will get a major weight in nano drug delivery market due to these specific advantages. Compared to CNTs graphene/GO has the main advantage of a much lower risk of toxicity [633].

6.3.2.1.2 Combined drugs

In the literature, drug delivery is discussed as primary option for the use of graphene in cancer therapy. Major arguments for graphene are the possibility of a targeted delivery and the delivery of a set of combined drugs, these features can be seen as unique selling point of graphene. Therefore it can be assumed that graphene could get a major weight in nano drug delivery market due to these specific advantages.

6.3.2.1.3 First in vitro studies are promising

Numerous reports on the in vitro efficacy of the drug delivery systems based on graphene/GO have been published. Various successful ways of drug/gene delivery are documented in vitro in [628, 634, 635].

6.3.2.2 Current weaknesses and challenges of graphene/2D materials in drug delivery

6.3.2.2.1 Low maturity and missing in vivo studies

Only few examples of drug delivery with graphene/GO in vivo are reported yet. Most studies are based on in vitro models. For further investigations, in vivo studies are necessary

6.3.2.2.2 Potential toxicity

A potential barrier to the application of graphene in drug/gene delivery is the toxicity of graphene and GO. Here, [636] suggest amine-modified graphene as alternative. Zhou and Liang [628] report of a variety of studies on toxicity of graphene/GO with no clear result, [635] see a low level of toxicity of GO. Sasidharan et al. (2016) [637] see a relevant DNA-damaging potential of few-layer graphene. Bussy et al. [638] warn of generalizations on the toxicity of graphene/GO. Sunil et al. (2012) [636] suggest an amine-modified version of graphene for reducing toxicity. Tissue distribution and elimination studies of functionalized GO suggest rapid elimination. [639] Further studies on biodegradation through enzymes suggest that hydrophilicity, negative surface charge, and colloidal stability of the aqueous GO play key roles in the biodegradability. [640]

To summarize, there is a certain risk of toxicity of graphene/GO, but it is no absolute barrier for the use in gene/drug delivery. There obviously exist various ways to cope with this problem. Recent studies are rather in favour of a safely use of GO for drug delivery, but further studies are needed.

6.3.3 KPIs for of drug delivery

In the context of the use in biomedicine, it is difficult to establish simple key performance indicators (KPI), as the efficiency of a health product or a device closely linked to a health product can only be investigated in clinical tests. Clinical test take about ten years, and can be shortened only, if a very high impact appears to be probable. Clinical trials imply statistical tests which shares of the treated persons show a very positive, positive, low, no, negative, very negative impact. If the overall assessment based on a variety of parameters is better than drugs/devices of the same category, the drug/device is given a new class where higher prices can be achieved.

In any case, it can be expected that drug delivery systems are considered either as drugs (new combinations of drugs) or high risk devices requiring long and complex admission procedures.

6.3.4 Roadmap for drug/gene delivery

6.3.4.1 Current maturity: Lab scale and early investigation

There are some promising results in terms of drug delivery, mostly in vitro. But further investigations are needed, especially on how to deal with the toxicity and how efficient graphene is in comparison to other investigated drug carrier systems. Therefore benchmarking is also needed.

Photothermal therapy and photo-enhancement are at a very early stage and currently basic research.

6.3.4.2 Barriers/Challenges (summarized)

The major barriers/challenges of the use of graphene/GO for drug delivery are

- Sufficient proof of usefulness compared to other delivery systems, in particular in the context of cancer therapy
- Convincing solutions for the problem of toxicity
- Conception of easy-to-handle products home use.

Major barrier for photothermal treatment and photo-enhancement at the moment is the low maturity. Before further assessments can be made, the actual functionality and feasibility needs to be proven and benchmarked.

6.3.4.3 Potential actions

If the area of graphene/2D in drug/gene delivery is seen as promising for Europe and the topic is further pushed, the following potential actions, derived from the challenges, are suggested:

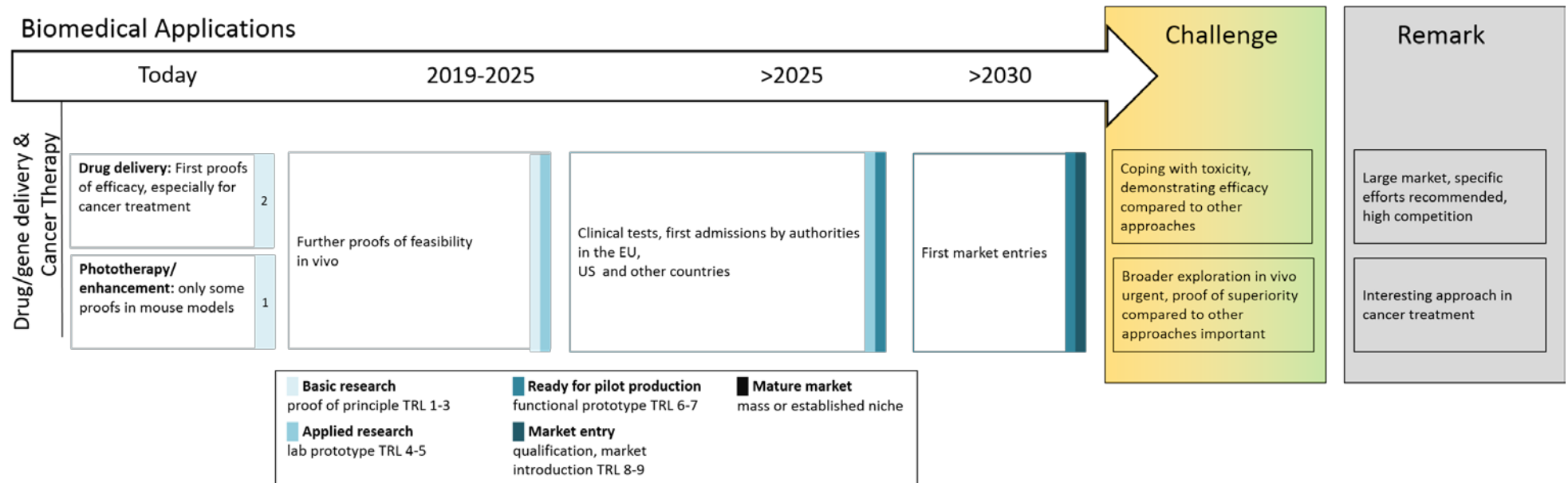
Broader expansion of in vivo investigations and clinical tests are needed for market entry of graphene/GO in drug delivery.

Benchmarking of graphene/GO with other drug delivery systems

The scientific research in photothermal effects of graphene/GO in the context of cancer should be intensified, as this is a promising market. Especially the use in human therapy has to be substantiated in a profound way. Only against such a background, it will be possible to raise the interest of enterprises for this perspective.

6.3.4.4 Roadmap

At present the focus is still on basic scientific research, but there is a strong perspective to achieve reliable results in applied research until 2020.



6.4 Biosensing & Bioimaging

Various applications of graphene in biosensing and bioimaging are reported [628, 634, 635, 641]. Thus some novel fluorescence resonance energy transfer (FRET) based biosensors were developed based on the super efficient fluorescence quenching ability of graphene. Its unique electronic property allowed for making FET type biosensors whereby important biomolecules can be detected such as nucleic acids, proteins, or growth factors. Controllable self-assembling of graphene-biomolecules enabled to build ultrasensitive biosensors for the detection of DNA and other molecules. As a matrix for the detection of molecules, a graphene-based nanopatform for matrix-assisted laser ionization mass spectrometry was conceived etc. GO-based instruments for cellular imaging were built. Manipulation of the size, shape and relative fraction of domains of GO by reduction chemistry provides opportunities for tailoring its optoelectronic properties. To summarize, graphene and GO allow for highly specific ways of biosensing and bioimaging. Please refer to chapter 5.5 Sensors for further, more generic assessments on biosensors and the roadmap.

6.5 Antibacterial material

In many research projects, the potential toxicity of graphene towards bacteria could be shown, but some other studies did not show significant cytotoxicity [628, 634]. Thus there is a controversy about the toxicity of graphene towards bacteria. Nevertheless, a filter pare with a strong antibacterial effect was developed useful for clinical applications. The general field of coatings is covered in chapter 3.3, here we will only focus on the biomedical application part.

6.5.1 Market perspective: graphene/2D materials as antibacterial material

6.5.1.1 Market opportunities

6.5.1.1.1 Potentially high volume and strong industrial base in EU

Despite the scientific controversy, various patent applications concern sterile absorbable surgical homeostatics with graphene. As the experiences are still at the early beginning and the advantages and disadvantages compared to other material are not clear yet, it is not possible to provide reliable market estimates. In any case, these applications refer to daily use in biomedicine and will have a high volume. In any case, the overall number of patent applications in this market is considerable, and enterprises from the EU are in the lead (Figure 115).

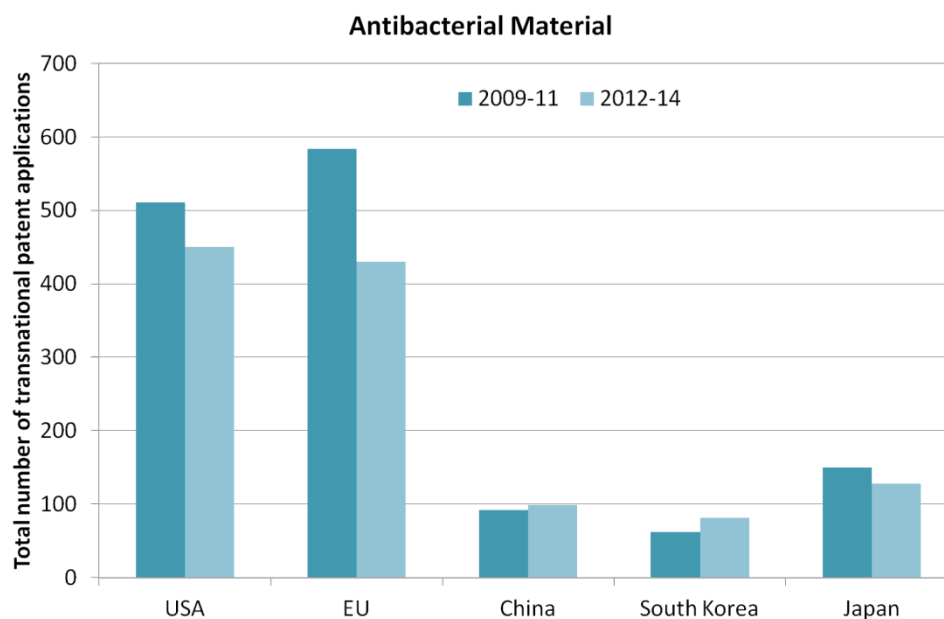


Figure 115: Transnational Patents for Antibacterial Material in Biomedicine by Priority Periods. [137]

6.5.1.1.2 Toxicity against bacteria but not human cells as an opportunity

This special market for medical devices is quite attractive. In particular, if graphene-based solutions can bring in unique selling points, e.g. toxic effects against bacteria and not against human cells. Also in this segment the studies on graphene-based approaches are still in an early stage, so that more detailed statements on the potential market volume are not possible.

6.5.1.2 Market threats

6.5.1.2.1 Highly competitive market

The market of antibacterial material for biomedicine is highly competitive. In particular, many conventional, cheap methods are available, and only if graphene-based approaches can provide specific advantages, they will succeed to establish themselves in the marketplace.

6.5.2 Graphene/2D materials perspective: current strengths, weaknesses and challenges for the use in antibacterial materials

Please refer to chapter 3.3 for a broader analysis of the topic.

6.5.2.1 Current strengths of graphene/2D materials in antibacterial materials

6.5.2.1.1 First prototypes show functionality

There are first proof of principles (e.g. a filter paper) with antibacterial properties. However, the actual effect of graphene needs to be proven.

6.5.2.2 Current weaknesses and challenges of graphene/2D materials in antibacterial materials

6.5.2.2.1 Controversy about actual cytotoxicity

As mentioned above, there is a scientific controversy on the potential toxicity of graphene towards bacteria. There are reports, where antibacterial properties could be shown, but some other studies did not show significant cytotoxicity. Benchmarking with other materials is needed.

6.5.3 Roadmap for antibacterial materials

6.5.3.1 Current maturity: open question of actual effect

The question is still open to which extent graphene can contribute to antibacterial materials

6.5.3.2 Barriers/challenges (summarized)

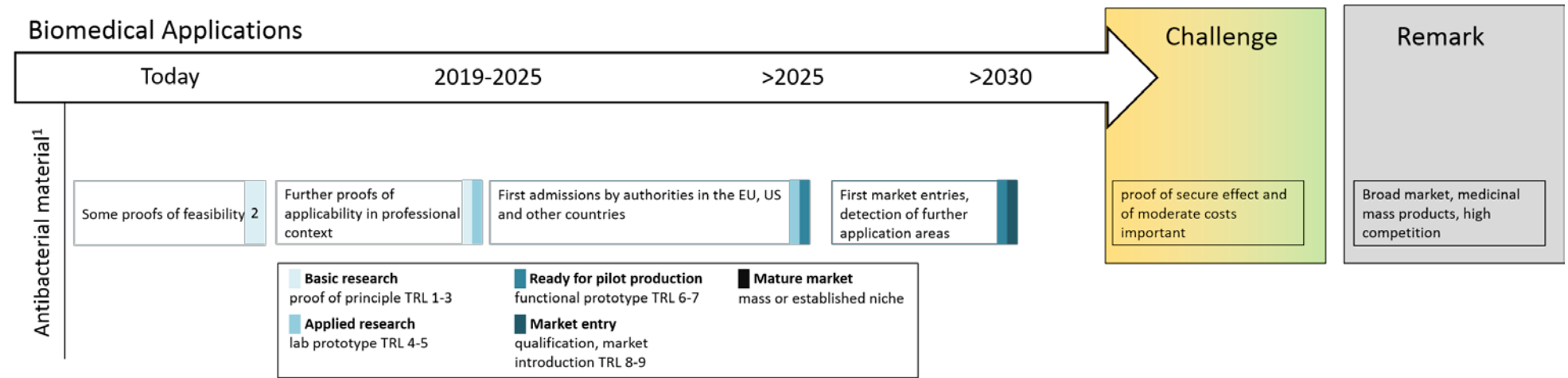
The major barrier is to show the actual potential of graphene in antibacterial applications.

6.5.3.3 Potential actions

If the area of graphene/2D in antibacterial materials is seen as promising for Europe and the topic is further pushed, the following potential actions, derived from the challenges, are suggested:

In view of the diversity of enterprises in this segment, also many European ones, it will be favorable that scientific institutions get in dialogue with enterprises for identifying attractive needs that can be met by graphene-based approaches.

6.5.3.4 Roadmap



¹: see also coatings chapter

6.6 FOCUS: Neural interfaces

6.6.1 General context: Biocompatible Devices

Due to the high biocompatibility of graphene and GO (graphene oxide), their unique parameters, notably their considerable electron mobility, thermal conductivity, high surface area and electrical conductivity, 2D materials receive high attention in the field of biomedical applications. In addition to the already mentioned areas of applications, many potential applications in the area of biocompatible devices are suggested and studied in the literature, in particular the use of graphene/GO for

- Prostheses
- Brain/nerve electrodes, bioelectronic medicine
- Small implants
- Tissue engineering

This broad variety represents an indication for many further applications likely to receive attention in the coming years.

6.6.1.1 Prostheses

Graphene and GO attract increasing interest for use as coating material of prostheses, it is easy to attach them to the surface of bones, the friction and wear are low, thus there are good prospects that graphene will become a standard in this context, although the present number of patent applications is still limited.²³

The number of patents on bone prostheses is considerable, but decreases currently, obviously indicating that new ideas with traditional approaches are lacking (Figure 116). The share of EU enterprises in patents is almost equivalent to the US ones. The number of graphene-based patents is still too low for any reliable statements. The markets for orthotics had a level of \$4.7 billion by 2015 according to Global Industry Analysts (GIA) [642], thus the market has a relevant level, as the loss or failure of bone tissue is one of the most frequent and costly problem of health care.

The major challenge for graphene/GO in this market segment is to achieve high, competitive durability, low friction and low wear, and in the case of abrasion low toxicity for humans. The strain of bone prostheses, in particular hip joints, are extreme, and high performance in comparison to competing materials such as special steel or ceramics will be important for the break-through of graphene-based solutions. In any case, the market is very promising.

²³ In this context, many considerations on coatings in chapter 3.3 of this report apply.

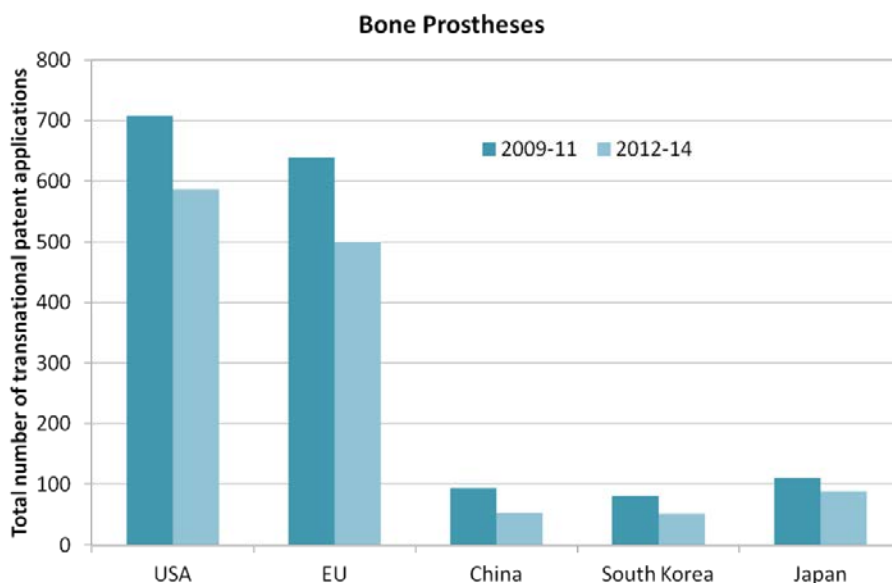


Figure 116: Transnational Patents on Bone Prostheses by Priority Periods. [137]

6.6.1.2 Small implants

Graphene proves to be suitable for extremely small implants in blood vessels as filters or stents. The whole field of small implants attracts a considerable number of Transnational Patents (Figure 117), even more than for bone prostheses (Figure 116), and relevant market volume can be assumed. The few patents refer to heart stents, but the small number does not allow for any further statement on the development of the next years.

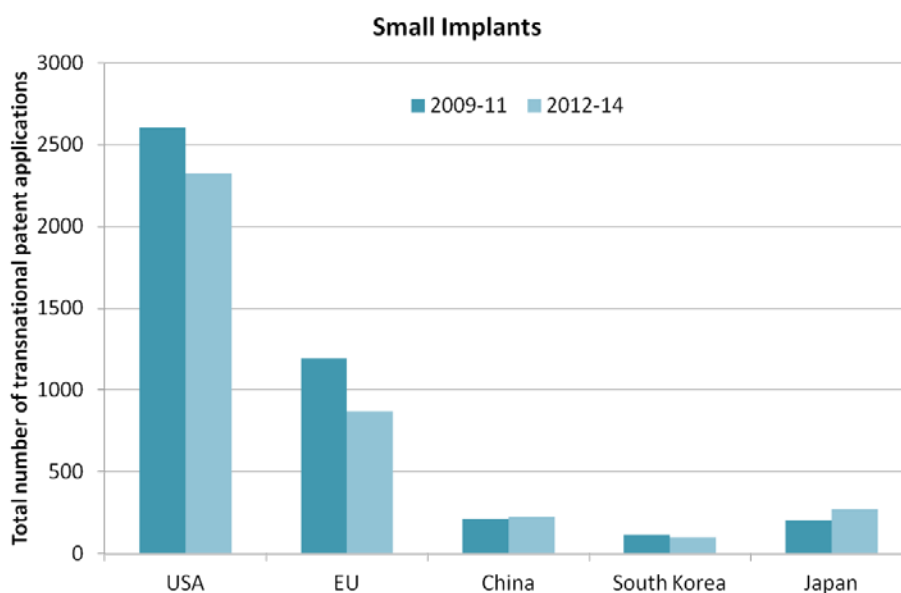


Figure 117: Transnational Patents on Small Implants by Priority Periods. [137]

6.6.1.3 Tissue engineering

Various authors have described the use of GO or RGO (reduced graphene oxide) as scaffolds in tissue engineering [628]. The whole field of tissue engineering is a dynamic area of modern medicine and graphene will bring in new prospects. For instance, substrates from stem cell differentiation or components for implant devices can be generated. In particular, tissue regeneration in the nervous area appears to be very promising. In the recent period of 2012 to 2015, 190 publications on tissue engineering were published, but only 9 Transnational Patent applications were filed. Thus the field is promising, but still in an early exploratory stage. For the whole field of tissue engineering a relevant number of Transnational Patents were registered in recent years, but less than for prostheses or small implants. Thus the market is relevant, but quite specialised.

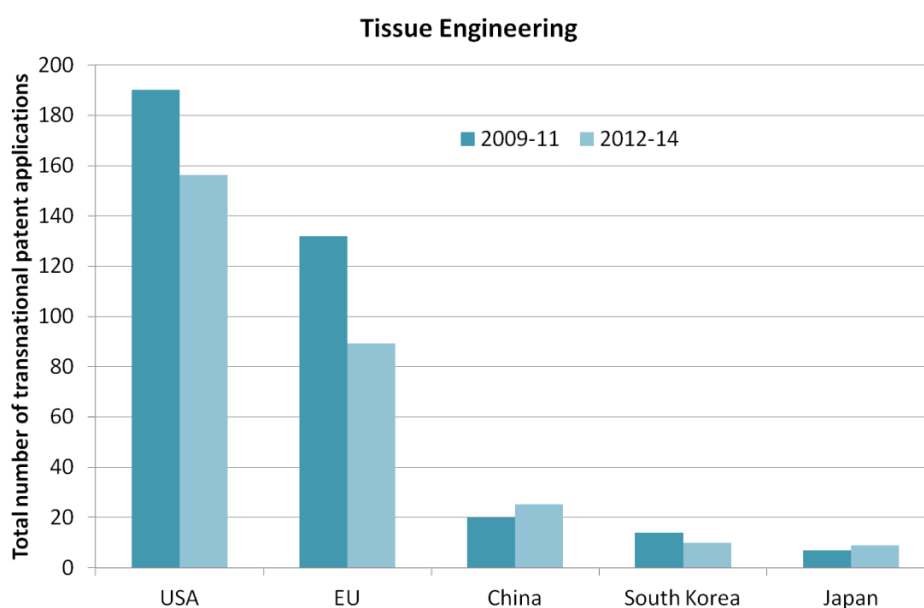


Figure 118: Transnational Patents in Tissue Engineering. [137]

6.6.1.4 Market perspective

With a predicted growth of 4.1 per cent, the global healthcare market offers interesting investment opportunities [643]. In 2015, the **global medical devices market** was estimated 317.00 billion USD and thus 20 per cent of the total healthcare market. Including exports of medical drugs and devices, the **European health market** was estimated to be 23.2 per cent of global market in 2016 [644].

6.6.2 Medical research and evaluation of neural interfaces

At present, neural interface devices rely on direct interaction with neurons in human body, with noble metal electrodes (typically Pt/Ir) connected through wires to a power supply and a digital system [644]. Their design usually only allows a single function: They either record a specific activity or stimulate tissue electrically. Despite the inert characteristics of noble metals, patients implanted with brain stimulation electrodes made of platinum for the last 20 years showed a significant extent of residual platinum traces left over in the tissue, with unclear consequences [645]. The complexity of the human nervous system as well as a high variety of specific sites, where neural implants may be used, translates into a multitude of competing clinical requirements and needs. Overall, satisfactory solutions will be hard to find, particularly based on current conventional microfabrication methods and materials. Here, we recognize a window of opportunity for novel and improved graphene based devices and technologies to offer innovative and more efficient solutions. In clinical setting, the medical doctors primary concern is not the mechanics, but the function of a device: typical clinicians will focus on how it works, and whether it works better than established solutions or not.

6.6.2.1 Market trends and framework conditions

The global electroceuticals/bioelectric medicine market is expected to reach \$ 25 billion by 2021 from \$ 17 billion in 2016 with an annual growth rate of about 8 %. [646] Although not all areas of the electroceutical/bioelectric market are relevant for graphene applications, the market size and its growth are considerable. The largest market share is currently held by implantable cardioverter defibrillators. The number of Transnational Patents for electroceuticals/bioelectrics is quite high with 279 in the period of 2012 to 2014 (see Figure 119). The USA dominates the market and, at present, the number of graphene-related patents is quite moderate. Thus, there is a good chance to seize this specific segment. European companies such as Medtronic, LivaNova, Biotronik, Cefaly Technology or Oticon Medical are active in various areas of electroceuticals.

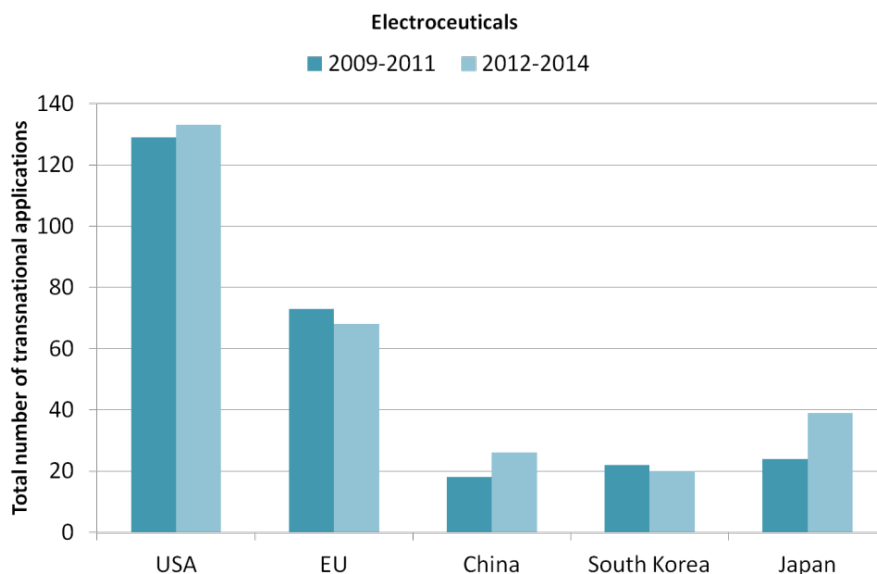


Figure 119: Transnational patent applications in the field of electroceuticals. [137]

A major area of bioelectric medicine is nerve stimulation with two primary targets of application:

- The control of artificial limbs by brain for handicapped persons
- The modulation of the immune system by neural stimulation as alternative to pharmaceutical drugs.

As to the stimulation of nerves, the transnational patent applications per country is depicted in Figure 120. Compared to that, the number referring to the modification of the immune system is much smaller (see Figure 121). Thus, this subfield is still in a very early stage. The present relation between the USA and the EU can change rapidly due to the low number of applications. Looking at the scientific publications on neuro stimulation of the immune system first prominent contributions already appeared in 2000 [647] and later in 2004 and 2009 (e.g. Steinmann [648] and Tracey [649]). Thus, a longer experience with this topic already exists. In addition, the activities of the EU are on the same level as those of the USA (see Figure 122). In consequence there are good prospects that the EU becomes a major player in this new field where a large dynamic market can be expected.

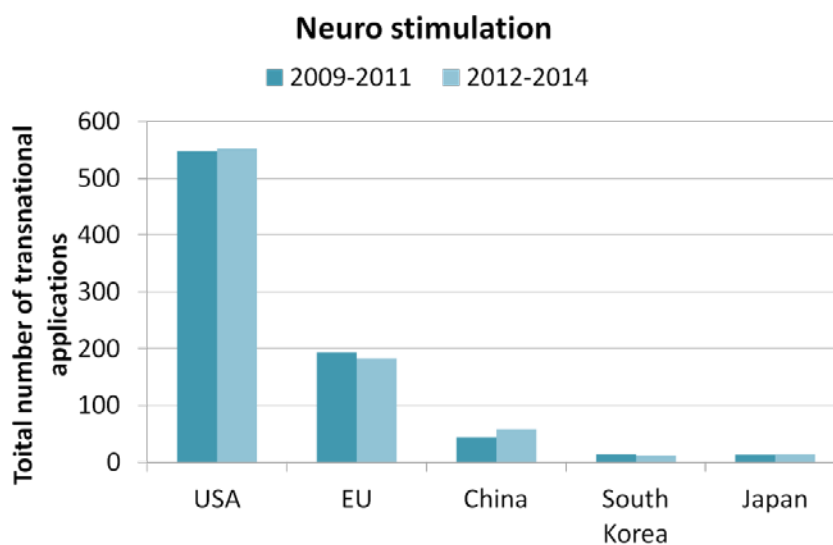


Figure 120: Total number of transnational patent applications in the field of neuro stimulation. [137]

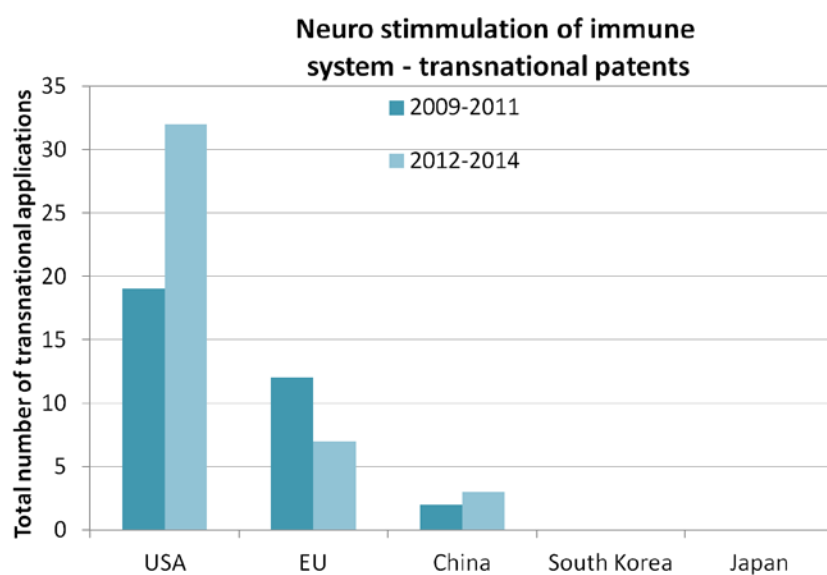


Figure 121: Total number of transnational patent applications in the field of neuro stimulation for the immune system. [137]

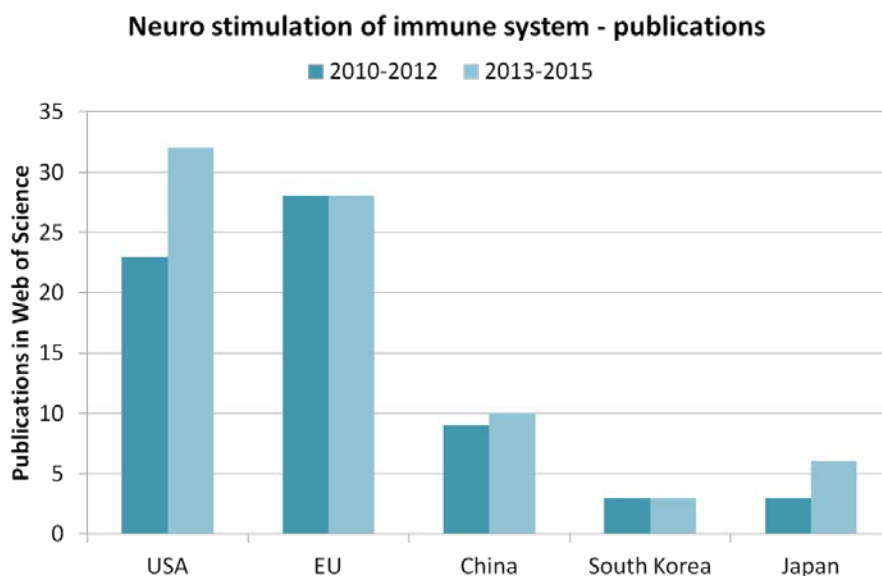


Figure 122: Total number of publications in the field of neuro stimulation for the immune system. [257]

Deep brain stimulation and neural interfaces appear interesting from a technological perspective. The growth in the **wearables** sector as well as the trend to **human enhancement** create windows of opportunity for developments such as brain-computer-interfaces, retina implants, and similar. At the same time, further development of **closed-loop-technologies** improving operational conditions are to be expected.

The specific structure of the healthcare markets constitutes an opportunity for new materials and new device technologies: Development costs of active medical devices mainly relate to the costs of approval, hence material prices and price per piece play a tangential role. Similar to other growing segments of the health market, the competition in the bio-electronic market is very fierce. Various other materials such as gold, platinum, iridium oxide, titanium nitride, or PEDOT represent established or potential solution for neural electrodes as well, and silicon might server as substrate and integration platform.

The medical devices market segment will also directly affect the pharmaceutical one, thus fierce resistance can be expected from this side. For instance, competing treatment approaches exist in the fields of epilepsy, riboflavin transporter deficiency, and of Parkinson's disease. The competition will certainly intensify as soon as bioelectronic medicine addresses widespread diseases such as hypertension treatment or diabetes. However, as the underlying concept itself is entirely new, also novel markets without incumbent technology and defense from traditional competitors will appear and as well. In the end, the effectiveness compared to chemical drugs and the cost will be decisive [650].

6.6.3 Medical treatment involving neural interfaces

Out of the wide range of neural therapies, one of the firsts and most feasible applications for the introduction of innovative electrodes, based on graphene might be monitoring and functional mapping in a clinical setting such as brain cancer surgery or epilepsy surgery. Safe removal of as much of the brain cancer or epileptic region as possible – but without causing damage to the eloquent speech and motive function areas – represents a major challenge. Today, surgeons are already familiar with similar devices based on Pt and Pt/Ir electrodes and their use in the operating field. However, current microelectrode technologies for recording electrical activity face serious shortcomings, for instance the challenge to achieve higher integration density [651].

As functional mapping lasts less than 3 hours, it seems to be the most promising area to introduce graphene-based neural interfaces in a clinical setting. Due to the rather short application span, regulatory hurdles for the producer will be much lower and less resource consuming to overcome, compared to longer application periods or even permanent implants. However, requisites for clinical use for intraoperative monitoring also derive from typical accuracy achieved by surgeons, which is on the order of mm. Here, current electrodes with a pitch of several mm might often be sufficient. Still, recording at better signal to noise level or the ability to get single unit activity in addition to mass signals and local field potentials may constitute relevant advantages. This seems to fit perfectly into the application of a functional mapping procedure where flexible graphene micro-transistors are applied to the brain surface to carry out recording and obtain more information than with large electrode area [651].

Once the medical approval has been gained for a device and the product is going to the market, new questions rise on how many patients can be actually treated with these interventions with graphene. It's all based on a number of elements, related to a specific commercial field, but also heavily influenced by the health care economics of the specific countries and market spaces. One issue under this category is the existence of a suitable support infrastructure at hospital where such products are initially taken up. In order to implant these novel devices in patients, the presence of highly qualified surgeons and an excellent surgery team constitutes a prerequisite. Traditionally, neural modulation has been established in the western hemisphere, and the question arises, how graphene could widen that market space to other countries. Today, China already performs more studies on electrocorticography with patients than most other countries, hence China might be a huge potential market.

Another emerging issue is payers – i.e. who's going to pay for the product. It is influenced again by the market place: Predominately, private insurance companies in the US, and the respective national health services in the EU. Therefore, the users (i.e. clinicians by WHO definition) and beneficiaries (i.e. the actual patients) would have to be convinced (i.e. creation of legitimacy) that these products are going to improve life quality over

standard therapies, i.e. administering a pill or injection. Patient compliance always plays a major role, too. In case, a patient has an implant or device and either they or a clinician has to trigger the stimulation, it would represent quite a burden to do that several times a day. Hence, continuous stimulation is current practice, some implants are already capable to stimulate on demand, and patient interaction is only sparsely needed then. Novel materials and innovative devices may not only improve the implant, but also enable new integrated circuit designs, close loop systems, and wearable technologies. In the end, the regular interaction with a clinician might be evitable, and the patient might not need to think about it as frequently as required today, in their everyday life.

6.6.3.1 Market trends and framework conditions

Both the European and global health markets experience **special restrictions by regulation** and related certification burdens, as compared to other less regulated markets. The European Conformité Européenne (CE), the American Food and Drug Administration Agency (FDA), and the Chinese Food and Drug Administration agency (CFDA) represent the most important regulatory bodies developing and monitoring relevant directives. In Europe, long-term²⁴ medical implants need approval for CE class 3. The recent introduction of the **Medical Device Regulation (MDR)** is increasing certification efforts, e.g. requiring more frequent (control) visits to production sites. A significant reduction of notified bodies is consequently to be expected²⁵, which might further prolong market introduction processes and thus higher market introduction costs of innovative medical devices²⁶. Still, a number of notified bodies exists all over Europe, but each one has a different competence profile narrowing down the option range for specific applications significantly.

Beyond regulation, the developments of the **European medical device market** will experience strong impact by **demographic** and **technological trends**. The most relevant demographic trend for the European [652], North-American and Japanese medical device health market will be their **aging population** and, thus, the related rise in dementia – constituting a major prospective market for neuro-stimulation therapy. Other opportunities for new technological and material developments lie within the increasing number of patients with Major Depressive Disorder (MDD), that do not respond well to drug treatment, and existing side effects of epilepsy and Parkinson drugs. Here, deep brain stimulation can serve as an alternative to drugs. The diffusion of neural interface innovation requires sufficient evidence proving benefits over risks for all the different stakeholders – first of all patients and their well-being, but also general economic benefits (in case

²⁴ Long-term meaning implants or (active) medical devices remaining more than 30 days within the body.

²⁵ According to our expert interviews, reductions will be in the range of 40-50 per cent.

²⁶ Currently, costs for a neural implant certification with a notified body lie in the range of 10-15 000 €, not including clinical trials that need to be completed beforehand.

patients are enabled to stay in their professional context longer), certainly clinicians controlling the medical treatment, as well as payers (summarizing the insurance and reimbursement market). In terms of cost, electrodes based on conventional materials can range from less than 1500 € for a simple electrode array to more than 70,000 € for a cochlea implant. Novel technologies might also be attractive, if they present cheaper alternatives to established noble metal based solutions.

6.6.4 Direct Innovation Interface: Graphene for neural electrodes

In current clinical practice, neural implantable electrode systems usually consist of silicone rubber encapsulated metal wires or plates made by means of precision mechanics. With few exceptions, silicon based systems can only be utilized for neuroscientific research in animal models at present. Furthermore, they have rather simplistic design based on arrays of around several tens of metal electrodes that are rather large. While these materials are strong and chemically relatively stable, their intrinsic stiffness and density induce glial scarring and in long term, eventual loss of electrode function. Therefore, in clinical practice, there is an urgent need for novel electrode systems, based on innovative and enhanced materials that would enable to provide better healthcare quality to patients. For instance, higher electrode numbers may be required to suppress unwanted side effects and to enhance intended effects. Here, a transition of technology appears inevitable as size and complexity is limited by precision mechanics. The choice of electrode material should primarily be motivated by the material-tissue interface interaction. In particular, maintenance of long-term functionality for recording requires a reduction of foreign body reactions, while stimulation, in certain limits, seems to be less susceptible. Hence, graphene as a novel material in the field might enable innovative solutions in the field.

6.6.4.1 Technology perspective

Recent studies have demonstrated that graphene based electrodes could offer a dramatically improved performance in neural stimulation as well as in neural recording. In neural recording, graphene has shown same level performance as platinum or gold. Beyond that, graphene enables fabrication of sensors in a field-effect transistor configuration. These reduce the sensitivity to external noise and, thus, enable the design of sensor arrays with improved integration density [643]. In general, graphene-based electrodes/transistors could be significantly thinner than conventional device designs, and would qualify for integration into flexible devices. Present research includes silicon-based devices that can already be thinned down to about 50 μm , and polymer-based electrodes that achieve thicknesses on the order of 10 μm . Certainly, soft electronic options could represent a unique selling proposition for medical applications.

Technological advantages of graphene include advanced charge injection characteristics for stimulation, better electrical and electrochemical performance, reduced impedance, and high signal-to-noise ratio for recording. Furthermore, the versatility of graphene in terms of chemical modification helps to tailor the material properties to the application. For instance, it should be easy to ingrate some functionality for electrochemical sensing of electroactive neurotransmitters like Dopamin, Serotonin and Norephedrin on a chemical route. The adoption of green chemistry principles in the production appears conceivable and may represent a distinction criterion over other available technologies. In general, graphene as a material might constitute a technological condensation point. The simultaneous exploration of many different application fields may provide transdisciplinary impulses that stimulate a faster pace of materials and device development.

6.6.4.2 Biocompatibility aspects

Initial biocompatibility tests of graphene-based neural interface devices show minimal inflammatory reaction from the surrounding neural tissue [653]. First reports describe good biocompatibility with neural cells as well as improved adhesion of neural cell cultures on graphene substrate [644]. It appears crucial to transfer these positive *in vitro* measures to *in vivo* results and beyond as soon as possible [655–657]. Extended testing may benefit from low fluorescence levels as well as from reliable stability and compliant mechanics.

Biostability of graphene in the human body constitute a critical issue, in particular for implantable devices. Among the consulted experts, we found significant concerns regarding inconsistent durability measures, such as fundamental material stability of graphene and its derivatives, their stability in solution, and *in vivo* stability, in particular first surface stability and second bulk stability of implants. Different (target) markets can be distinguished ranging from medical implants (i.e. chronic diseases requiring long term application) to the neuroscience market, where stability might be less of an issue. In general, due to reduced electrode volume and, thus lower invasiveness, graphene-base electrodes (should) leave fewer traces in neural tissues than present noble metal electrodes. Graphene also shows better compatibility (in terms of lower imaging artifacts) with MRI (magnetic resonance imaging) [654] than metallic materials.

However, the maturity of graphene-based neural interfaces remains low, so that today it is still hard to compete with established technologies that serve as benchmark. In particular, no long-term experience with graphene exists. Unforeseen issues such as impacts of the material on the tissues may arise when more long-term chronic studies become available. It may take a while to get long-term testing for graphene-enhanced devices, but the testing could also be accelerated within the community.

6.6.4.3 Specific challenges

The transition from the academic research setting into a quality managed compliance system for class 3 implant medical devices represents a particular challenge for the considered technology. Highly standardized neural electrode devices constitute a critical requisite to compare results from one medical evaluation lab to another, but their reproducibility remains a key issue based on not fully established material production and device processing routines. The production yield for graphene-base neural electrode devices might already be good on the benchtop in academic institutions. As the required quantities for medical research will remain low for quite a while, a transfer to contract manufacturers appears difficult due to the need for class 3 medical device compliance, especially since the medical evaluation demands significantly exceeds the capacities available in most academic research institutions.

6.6.4.4 Market perspective

Graphene-based neural interface devices do not only compete with established noble metal electrodes, but also with other conceivable solutions. Among a broad range of established and emerging materials, organics such as Poly-3,4-ethylenedioxythiophen (PEDOT) may represent the closest competition for graphene. Furthermore, other establishing industries might provide therapies for identical indication but on a different route. In particular, external competition from the pharma sector might be an issue to consider. In contrast to many other potential applications of graphene, the cost of the material represents only a minor factor for market access. Medical devices are very expensive, and material costs have little impact on the overall cost. Perhaps, graphene-based devices can actually become cheaper than noble metal electrodes, and a lower price could obviously have a positive effect on market creation. In general, graphene appears superior to established neural interface devices in terms of material supply. The abundance of carbon as the raw material might become an important factor in case of mass production, as no shortage in supply can occur even at high-volume demand.

However, the public perception of graphene might become a critical issue influencing the diffusion of innovations and products. Initially, the Nobel prize awarded for graphene has been considered as potentially positive marketing aspect. Today, also the impression of a research hype around the material may also have negative consequences. Spillover trends from other material perception might even be a bigger role. In general, the high skepticism associated to nano-materials in the EU (also influenced by the aftermath of asbestos) already influenced rather strict regulation (see above).

At present, toxicology research already revealed significant risks associated with carbon-nano-tubes (CNT), while graphene appears relatively bioinert so far, but the public needs to be carefully informed about further research results in that direction. As future graphene-based implants are in much more intimate contact to prospective patients than

any other conceivable (consumer) product, the acceptance of medical graphene innovations obviously has even higher impact on potential market developments. Experts explicitly described past scandals around supposedly stable silicone aesthetic implants as a source of skepticism about materials innovations in implants.

6.6.5 Indirects Innovation Interface: Advanced neural treatments

The key issue for graphene based neural interfaces at the end of the value chain is to foresee translation into the clinic and beyond, and all the obstacles, that might occur and how to best address them. Graphene can have a vast range of clinical applications in neuronal diseases and neural disorder, ranging from retinal therapies and brain computer interfaces to deep brain stimulation (DBS) [644]. Graphene neural interfaces have shown already a great potential in research. As a next step, it is important to improve on the yield and homogeneity of the device production in order to increase its manufacturing and technology readiness level. Next step towards the market access, after the proof of concept in animal studies has been demonstrated, is to move towards the first human clinical trial with graphene devices during intraoperative mapping of the brain. This also means addressing all regulatory issues associated to medical devices such as safety, biocompatibility, etc. [658].

6.6.5.1 Technology perspective

Graphene-based neural interfaces have a number of strengths that could facilitate their faster clinical uptake: (a) flexibility, (b) electrode density, (c) low impedance, (d) MRI compatibility, (e) biocompatibility, and (f) versatility (combining recording, stimulation, and chemical sensing). Once devices at sufficient quality and quantity become available, the focus will shift to translation from the R&D stage to the clinic. Overcoming regulatory hurdles takes various aspects of expertise that academics usually lack, as their responsibility usually ends with proof of concept demonstration and prototype development. However, moving forward along the value chain towards clinical uptake requires a different approach, as highest quality control requirements apply for pre-clinical evidence development. Usually, the medical devices industry takes up innovation at that stage, but still acts highly reluctant towards graphene and other novel materials based on regulatory and quality control issues requiring major changes in the complex production chain. Hence, a massive gap between lab and clinic continues to exist, but clinicians and neurosurgeons open up to device innovations as further evidence appears how novel devices could improve patients' quality of life.

6.6.5.2 Market perspective

Graphene could potentially have a very large market as a material for neural electrodes. Actors include both several large corporations (such as GSK and Alphabet with their highly active spin-off Galvani Bioelectronics) and numerous smaller start-up companies.

The latter may play a crucial role in the commercialization of novel ideas: Research laboratories develop and protect intellectual property in the field, but start-up companies could further develop the concept towards commercialization, which eventually could be acquired by large corporations that eventually bring the products to their markets. In contrast, the pre-clinical markets work differently. Its volume is much lower, but the burdens to get a product into the market is much lower. Here, it is going to be very easy to sell novel electrodes, as there is no need to go through other approval processes. Producers can directly sell to end users in case they convince them of their advantages. Early adopters may be willing to buy graphene-based electrodes, and, as a positive side effect, their usage will create valuable experience and serves as a testbed for further applications. In principle, the pre-clinical market forms an opportunity for European producers to increase their market share and build lasting competitive advantages in an emerging technology.

In general, Europe has a significant market share in the field of medical devices, where its rapidly aging society creates potentially large patient population that may need to rely on these novel technologies in the future [659]. The European Commission already supports this direction in their policies. However, limited knowledge about future market sizes makes the selection of priority topics difficult. In the worst case uncoordinated development towards all possible indications may delay success and dilute the efficacy of research efforts and funding. Hence, some experts claim that too many potential applications exists, combined with a lack of understanding regarding unmet medical needs, their urgency, and the possible impact of graphene. Several aspects may shape the user acceptance of innovative bio-electronic medicine: Its potential to enable the avoidance of chemical drugs with substantial side effects may be a significant benefit, while the long-term implantation of electrodes in the brain and at other sensitive places may be considered with serious reservation [650].

6.6.6 Innovation roadmaps

6.6.6.1 Graphene-enhanced neural devices

Few European research groups in the graphene materials and devices domain currently focus on neural interfaces. Typically, they carry out rather small projects that cover only few researchers (often PhD candidates) that mainly are motivated in their work by achieving personal progress in their own field. Small collaborations with medical experts take place, mostly on preclinical level. Despite excellent devices being produced on an occasional base, processing of larger quantities, at high yield, and reliable consistency remains out of reach under the current framework conditions. We identified the lack of sufficient capacity to provide innovative neural interface devices to the downstream medical evaluation innovation sphere as the single most important bottleneck significantly hampering the progress in the field. Therefore, the selection and prioritization of very few

(most promising) indications appears extremely urgent: Otherwise, none of the distributed efforts might ever gain sufficient momentum to create major impact, and, eventually, reach further commercialisation phases. The foreseeable end of coordinated Flagship funding in 2023 creates even further pressure. Experts suggested that the installation of a small pilot production line might close this gap, enable coordinated medical research in the field, and, eventually support market creation.

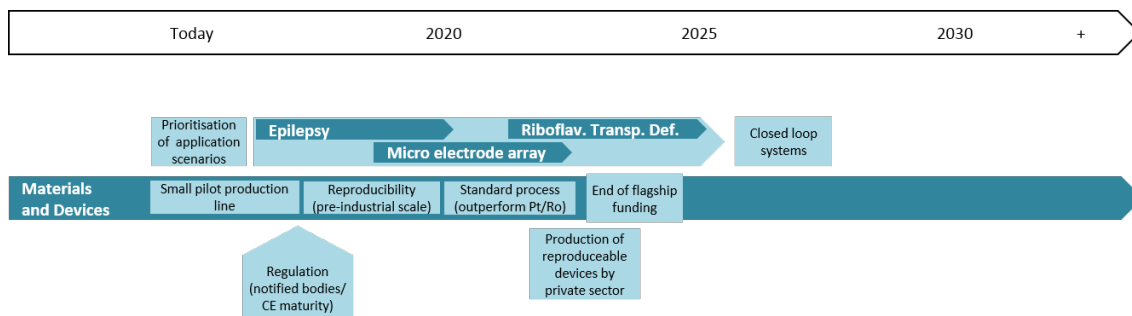


Figure 123: Roadmap for materials and device development for neural electrodes.

6.6.6.2 Medical evaluation of advanced neural interface devices

In the medical evaluation domain spanning over pre-clinical and clinical research stages, neural interface research targets various indications of both large potential volume (e.g. dementia) or high possible impact (e.g. retinal vision prostheses). The research groups are scattered all over Europe, cover a large variety of indications, but also distribute over various distinctive phases beginning with several pre-clinical *in vitro* and *in vivo* domains before possibly ever reaching the clinical domain. Limited access to advanced neural graphene electrodes further restricts the progress achieved by European actors in this field.

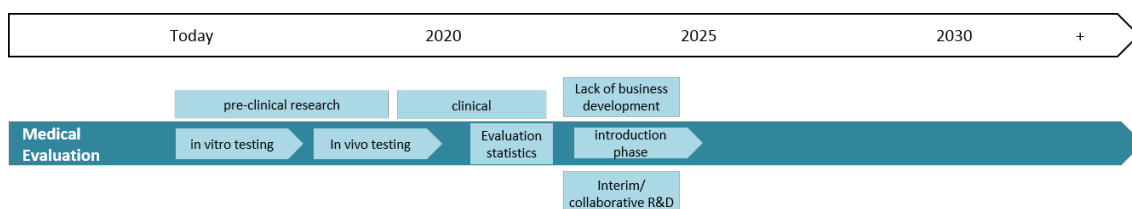


Figure 124: Roadmap for the medical evaluation of novel neural electrode concepts.

6.6.6.3 Advanced neural therapies

The majority of neural interfaces applications based on graphene remain in an early research phase. Experts expect that, with respect to the clinical market, initial acute studies on human patients may take place as early as 2020. In parallel, a smaller pre-clinical market (e.g. for neural electrodes for animal studies) might develop much faster, with first products commercially available in 7-8 years. In contrast, clinical products will require more than ten years after successful development of commercialisation strategies

and meeting all the requirements for successful market approval, set by the EU regulatory bodies. An opportunity to accelerate clinical market access for graphene-base neural interface devices would be to concentrate on short-term implants that could be used for recording in a clinical setting (e.g. during surgery). Beyond the function during surgery, the short-term implants could also serve as an initial assessment of device stability and contribute to the collection of evidence necessary for the full evaluation of long-term implants.

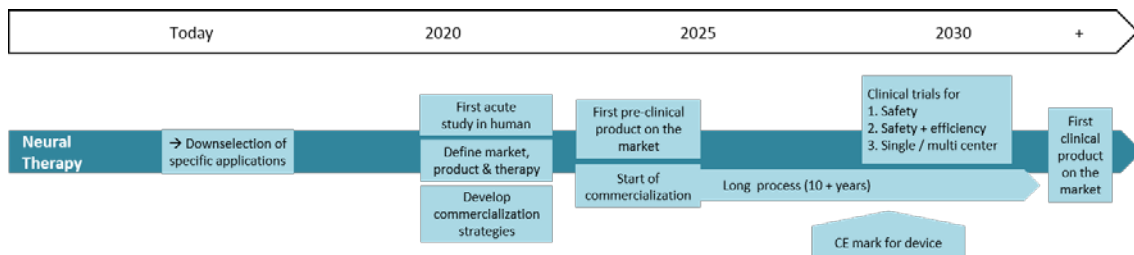


Figure 125: Roadmap for the introduction of advanced neural therapies and pre-clinical applications as an early niche market.

6.6.6.4 Joint interface roadmap

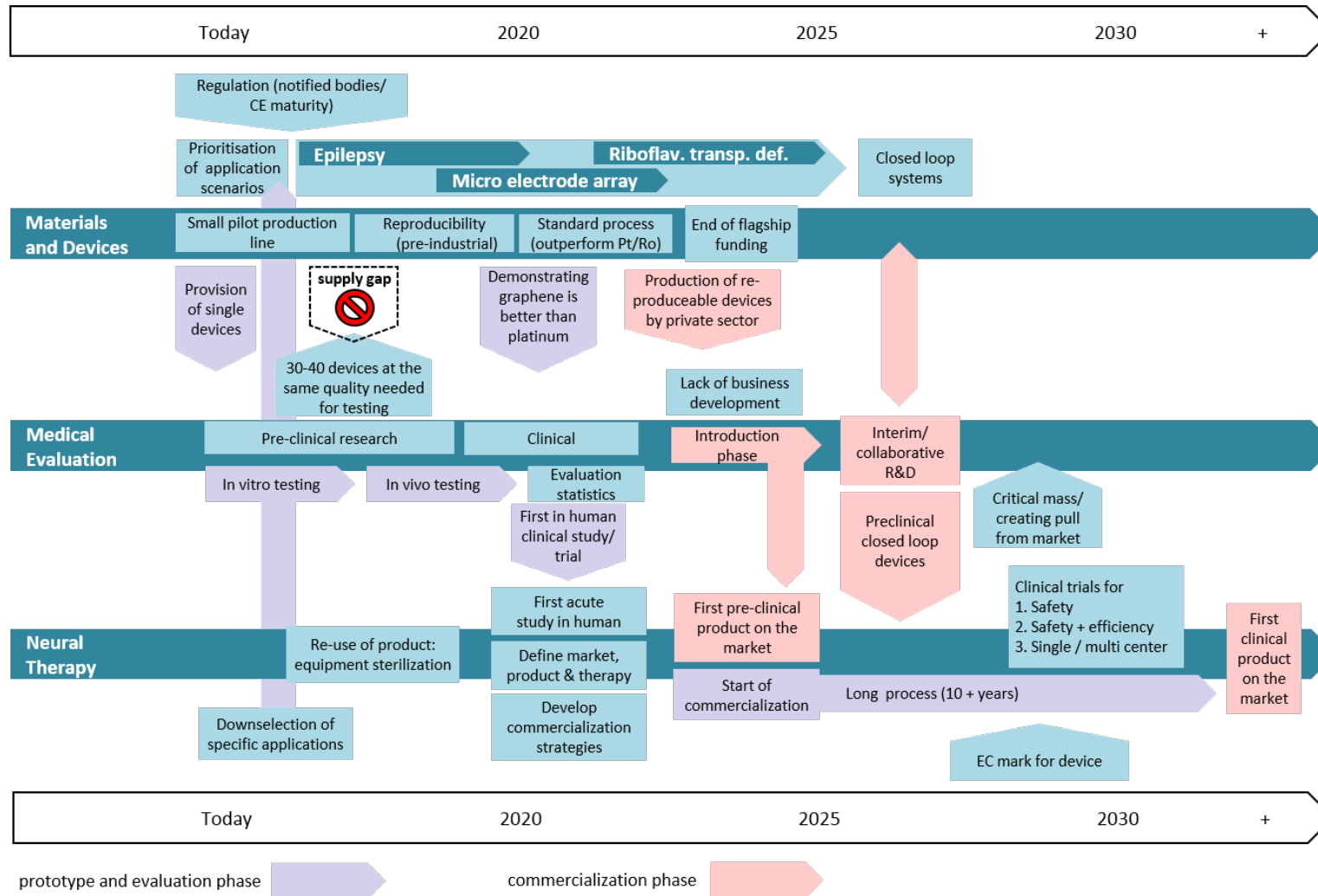
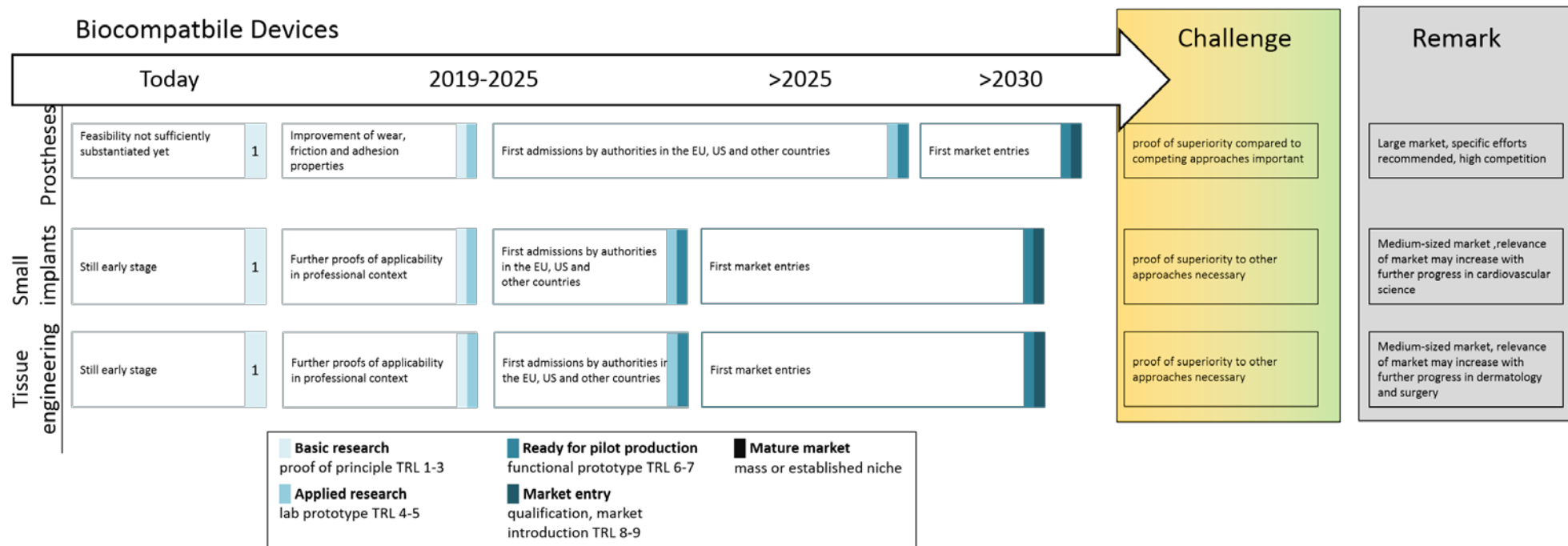


Figure 126: Interface roadmap for the introduction of graphene enhanced Si-anodes in LIBs for application in cars and wearables.

Our results show that graphene due to its striking combination of technical qualities (i.e. biocompatibility, high conductivity, high surface area etc.) holds high promise for advanced neural interfaces. However, the field is still on a basic research level, and many open questions require further research until first successful uptakes of graphene-based neural interface devices in a clinical setting can take place. Today, European research remains scattered both thematically and geographically. The present scarcity of resources (funding and device availability) demands a prioritisation of efforts to accumulate critical mass and gain sufficient momentum in order to push an initial application towards the medical market. This crucial process would ideally include the whole community involved, particularly spanning all three relevant innovation spheres. Once the down selection identifies a specific indication for treatment, demonstrating the advantages of graphene over the established solution (typically platinum-base electrodes) would be the first goal. Significant progress would then require a set of 30-40 electrodes with consistent properties to achieve meaningful test results. These numbers well exceed the capacities of academic research labs, but remain too small to involve small-scale commercial producers. That transfer might take place as soon as the transition to larger scale clinical trials occurs where even higher devices quantities would be required – and the final medical market appears much closer in reach. Initial markets could be (a) pre-clinical research and (b) short-term clinical monitoring, before (c) establishing long-term implants. Eventually, the ability to produce closed loop systems (including stimulation and recording) with graphene might open up new horizons for medical and, perhaps, even consumer markets.

6.6.6.5 Graphene for other biocompatible devices



6.6.7 Conclusions from research focus: Neural interfaces

At present, noble metal devices dominate the clinical neural electrode market. A single electrode is applied exclusively for either stimulation or recording. Due to impedance limitations, neural electrode arrays usually consist of only few but large individual contacts. Research on alternative electrode concepts based on semiconductors and/or involving graphene is still in an early stage. **In the future**, advanced neural therapy demands, electrotherapeutic treatments, and, eventually, machine-brain interface applications beyond medical markets may require advanced functionality and electrode integration density from future neural interface devices. This creates a unique **opportunity for graphene** implementation, as the demand for neural interface devices may multiply based on more widespread application and as the established technology based on noble metals fundamentally cannot provide the desired functionality.

Several requirements need to met for successful market entry:

- **Technical:** Research activities are scattered all over Europe and various indications, hence more coordination is required connect different activities and enhance the overall impact.
- **Regulation:** Safety constitutes a key requisite for market entry, and the intimate application of neural implants calls for specific attention to toxicology concerns.
- **Market:** A huge gap between public research activities and private sector exists and needs to be closed; European actors need to be aware of the US being a strong competitor in the neural interface sector.
- **Interface:** Creation of legitimacy is important and requires early diffusion of knowledge to and between the different stakeholders (payers, users, patients, regulators) involved in the final Innovation Sphere; the inclusion of medical doctors in the early R&D phases helps to dedicate efforts to actual demands and necessities of clinical practice.
- **Bottleneck:** Thorough medical evaluation of advanced neural interface technologies may demand higher production volume and reproducibility than possibly supplied by academic research facilities, but the scale is yet too small to support commercial manufacturing yet either. The installation of a dedicated small pilot line may resolve this deadlock situation.

6.7 General conclusions for graphene in biomedicine

The market for graphene/GO in biomedicine is quite segmented. In particular applications in drug delivery, biosensing, antibacterial material, bone prostheses and small implants are quite interesting. However, the research in all fields of application is still at an early stage, and often the final proof of feasibility is still missing. However, it can be expected that further cases for application will be detected in the next years, for instance in biosensing.

Table 75: Summarized assessment table of biomedicine application areas primarily sorted by European market potential and secondary sorted by USP.

Application sub topics	Current technological potential (USP)	Market potential (EU perspective)
Drug/gene delivery	+	++
Protheses	+	++
Brain electrodes/bioelectronic medicine	+	+ / ++
Biosensing & bioimaging	+	+
Small implants	+	+
Tissue engineering	+	+
Antibacterial material	+?	+
Phototherapy	?	+
Enhancement of drug efficiency	?	+

It is recommendable to get in close contact to enterprises which are already present in the marketplace to get information on specific requirements of the different market segments and thus focus the research in graphene/GO. Furthermore the enterprises could be sensitized to the specific advantages of graphene/GO-based approaches. A specific feature of the market in biomedicine is the requirement that all products and devices must be admitted by the public regulatory authorities of the respective countries. This brings in a delay or at least three years.

In any case, there is a broad industrial basis in the EU which could adopt graphene/GO in biomedicine. Therefore the market potential in an EU perspective is generally positive.

A.1 Appendix: Readiness Levels



Figure 127: Coarse readiness scales used in the roadmaps

Table 76: TRL and MRL scales

Coarse	TRL (Technology Readiness Level)	MRL (Manufacturing Readiness Level)
Basic Research	1 basic principles observed	1 Basic manufacturing implications identified
	2 technology concept formulated	
	3 experimental proof of concept	2 Manufacturing concepts identified
Applied research	4 technology validated in lab	3 Manufacturing proof of concept developed
	5 technology validated in (industrially) relevant environment	4 Capability to produce the technology in a laboratory environment
		5 Capability to produce prototype components in a production relevant environment
Prototype/ Pilot production	6 system/subsystem model or prototype/technology demonstrated in (industrially) relevant environment	6 Capability to produce a prototype system or subsystem in a production relevant environment
	7 system prototype demonstration in operational environment	7 Capability to produce systems, subsystems or components in a production representative environment
Market Entry	8 actual system complete and qualified	8 Pilot line capability demonstrated. Ready to begin low rate production.
	9 actual system proven in operational environment/competitive manufacturing	9 Low rate production demonstrated. Capability in place to begin full rate production.
		10 Full rate production demonstrated and lean production practices in place