



National Institute for Public Health  
and the Environment  
*Ministry of Health, Welfare and Sport*

**Developments in novel medical products  
with modern biotechnology and  
specifically synthetic biology**

A quick scan

RIVM Letter report 2016-0056  
C. de Vries et al.





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## Colophon

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## Synopsis

### **Developments in novel medical products with modern biotechnology and specifically synthetic biology**

#### A quick scan

Our scientific ability to understand, build and apply the programming language of life – the genetic code - is increasing at a rapid pace. In modern biotechnology and including the emerging field of 'synthetic biology' several scientific disciplines specifically aim to apply and make use of this genetic programming language in a way that is beneficial for man and society. Synthetic biology has a broad range of possible fields of application, one of which is medical products. Here we report on a *quick scan* to identify medical products which are currently being developed using synthetic biology. Additionally, we identified the applicable regulatory frameworks.

On the basis of our investigation we identified three groups of medical products: biosensors, targeted drug delivery products and engineered human cell products. The results confirm that the evolving field of synthetic biology indeed holds promise with regard to medical applications. It will, however, probably take time before most of the products will actually reach broad application in the clinic. Two types of regulatory frameworks are applicable: to cover the use of genetically modified organisms and to regulate medical products. New medical products obtained using synthetic biology might challenge the existing regulatory frameworks and this quick scan can serve as a basis to identify such challenges in cooperation with key opinion leaders in the field.

Keywords: modern biotechnology, synthetic biology, biosensor, targeted drug delivery, engineered cell products, medical devices, *in vitro* diagnostic medical devices, medicinal products, advanced therapy medicinal products, genetically modified organisms, regulatory framework



## Publiekssamenvatting

### **Overzicht van nieuwe medische producten op basis van moderne biotechnologie en specifiek synthetische biologie**

Een 'quick scan'

De huidige wetenschappelijke kennis stelt ons in staat om 'de programmeertaal van het leven' - de genetische code - in toenemende mate te begrijpen, zelf te bouwen en ook toe te passen. In de moderne biotechnologie en specifiek de 'synthetische biologie' richten verschillende wetenschappelijke disciplines zich op het ontwikkelen en toepassen van de genetische programmeertaal voor een groot aantal gebieden, waaronder die voor medische toepassingen. In dit 'quick scan' onderzoek is gekeken welke medische producten op dit moment worden ontwikkeld met behulp van synthetische biologie. Vervolgens is nagegaan welke regelgevende kaders van toepassing zijn voor deze ontwikkelingen.

Op basis van dit onderzoek identificeren we drie productgroepen: biosensoren, producten voor gerichte geneesmiddeltoediening en bewerkte menselijke celproducten. De meeste producten zijn nog ver van een daadwerkelijke toepassing in de kliniek. Het meest veelbelovend zijn toepassingen met stamcellen voor herstel van beschadigd weefsel en met biosensoren die buiten het lichaam worden toegepast voor diagnostiek. Bezien vanuit de regelgeving zijn twee soorten regulerende kaders van belang: regelgeving gericht op genetisch gemodificeerde organismen en regelgeving voor medische producten. Dit 'quick scan' onderzoek kan gebruikt worden als basis voor een analyse van mogelijke uitdagingen voor de bestaande regelgeving met behulp van opinieleiders in het veld.

Kernwoorden: moderne biotechnologie, synthetische biologie, biosensor, gerichte geneesmiddeltoedieningssystemen, gemodificeerde celproducten, medische hulpmiddelen, *in vitro* diagnostica, geneesmiddelen, geneesmiddelen voor geavanceerde therapie, genetisch gemodificeerde organismen, regelgeving.





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## 1. Introduction

### 1.1 Background

Biotechnology has enabled scientists to make medical products for many years now. For example, genetically modified micro-organisms have been used to produce therapeutic drugs, e.g. human insulin and other peptides. Human insulin has been available since the eighties, and is produced using genetically modified *Escherichia coli* or *Saccharomyces cerevisiae*. Innovations in biotechnology and bioengineering have resulted in significant changes in biotechnology practice. These changes have led to a new discipline called synthetic biology. Synthetic biology allows scientists to design and construct new biological parts, devices and systems. Although there is still wide debate about a definition of synthetic biology, it is often regarded as a new subfield of modern biotechnology. A distinctive feature of synthetic biology however, is the strong focus on the engineering aspect of genetic circuitry and genomes. Using synthetic biology, scientists are now trying to improve the design of well-known cell factories, such as *S. cerevisiae*, by building new genetic pathways from DNA fragments encoding enzymes, transcription factors, and translation control elements [1]. Already a number of *S. cerevisiae* strains have been developed using synthetic biology for the production of therapeutic drugs. A well-known example is artemisinic acid, an important precursor of the antimalarial drug artemisinin [2].

Synthetic biology enables the production of new types of therapeutic drugs. Not only by engineering micro-organisms which produce e.g. peptides, but also by modification of the peptides themselves. This may lead to the production of very much needed 'novel' medical products such as new antibiotics. With the advent of synthetic biology, lantibiotics have been developed. These are peptides derived from micro-organisms and using synthetic biology tools modified to biologically active forms of drugs against pathogenic micro-organisms [3].

The promise of synthetic biology, however, extends far beyond just engineering micro-organisms to enable them to produce a specific medicine. Much work is being done for example on biosensor applications, which can be used as either an *in vitro* or *in vivo* diagnostic device. In the field of theranostics, this is taken a step further, by combining the diagnostic property of a genetically engineered micro-organism with a therapeutic action. Yet another development is to use synthetic biology to develop not only new active compounds but overall new strategies to combat the huge problem of anti-microbial resistance.

Thus, although still in its infancy, the potential of designing novel medical products with synthetic biology holds great promises. By combining engineering and biology, genetic circuits, biosensors, engineered cells and cellular vesicles lacking key features of life can be designed for biomedical applications. Synthetic biology, which can be considered as "biotechnology 2.0", gives rise to a new kind of complexity in 'new-to-nature biological parts, systems, organisms, and cells' used in future medical products.

While synthetic biology has great advantages as a tool to develop novel types of medical products, it also presents some challenges. Converging technologies, which may be defined as combining different technologies into a single product, lead to a range of new types of medical products, including combination products and “borderline products”, i.e. products for which it is difficult to categorize them as either a medicinal product or a medical device. Synthetic biology products can be expected to give rise to a new kind of complexity, challenging the regulatory frameworks for medical products. Questions to be raised are whether the current regulatory frameworks are appropriate to deal with these new types of medical products and whether we need new guidance documents to describe how regulatory requirements should be applied to them. Moreover, a vast majority of medical products rising from synthetic biology will meet the definition of a genetically modified organism (GMO). When a medical product complies with the GMO definition, it is subject to an environmental risk assessment as prescribed by the GMO regulations in the EU. New medical products obtained using synthetic biology might thus challenge the existing regulatory frameworks and early knowledge on the development of these products will prepare both risk assessors and developers.

## **1.2 Aim of this report**

The aim of this report is to present a quick scan of the latest developments in novel medical products designed using synthetic biology. Additionally, we propose which of the regulatory frameworks for medical products and GMO's are applicable. This report aims to serve as a starting point to identify potential challenges for the current regulatory frameworks.

## 2 Definitions and regulatory frameworks

### 2.1 Definition of Synthetic Biology

#### 2.1.1 *Description of the field*

Modern biotechnology is a term adopted by international convention on Biological Diversity to refer to biotechnological techniques for the manipulation of genetic material and the fusion of cells beyond normal breeding barriers [44]. Synthetic biology can be regarded as a subfield of modern biotechnology, but with a very distinct focus on the engineering aspects of genetic circuitry and genomes.

Synthetic biology is an interdisciplinary branch of biology and engineering. It combines various disciplines, such as biotechnology, evolutionary biology, molecular biology, systems biology, biophysics, computer engineering, and genetic engineering [4]. Using the genetic software of life (the DNA code), scientists apply engineering principles to genetics, in order to reassemble catalogued and standardized biological components in a systematic and rational manner to create and engineer functional biological designer devices, systems and organisms with predictable, useful and novel functions not found in nature [5, 6]. This engineering strategy finds its way in environmental applications, in the biobased economy and in human health. Novel strategies for diseases which are difficult to treat such as cancer, immune diseases, metabolic disorders and infectious diseases are in development [7]. Not only the production of existing drugs can be improved with synthetic biology, but also completely new substances can be developed. In particular personalized medicine approaches are expected to benefit from synthetic biology.

#### 2.1.2 *Definitions*

Many definitions have been proposed to describe synthetic biology. These may provide useful insights as well as distinguish between “old biotechnology” and the novel approaches that synthetic biology provides. Three potentially useful definitions for synthetic biology are:

- The design and construction of new biological parts, devices and systems [8].
- The re-design of existing, natural biological systems for useful purposes [8].
- The application of science, technology, and engineering to facilitate and accelerate the design, manufacture, and/or modification of genetic materials in living organisms [9].

The first two definitions are used in many scientific publications on synthetic biology and the latter is proposed by the European Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). For this quick scan the first definition is adopted, because novel medical products involve more than the re-design of systems or living organisms. The third definition limits synthetic biology to living organisms only. This would similarly limit the scope of this report to only those novel medical products which meet the definition of a living organism. A broad view on synthetic biology and the development of

novel medical products was, however, preferred as a starting point for this quick scan.

## 2.2 Regulatory frameworks

Two main regulatory frameworks are relevant in the context of this report, the medical products regulatory framework for market authorization of medical products and the regulatory framework for GMOs.

### 2.2.1 *Medical products regulatory frameworks*

For medical products, separate regulatory frameworks exist for medicinal products and medical devices. For medical devices, three main directives are applicable:

- Directive 93/42/EEC on medical devices [10].
- Directive 90/385/EEC on active implantable medical devices [11].
- Directive 98/79/EC on *in vitro* diagnostic medical devices [12].

For medicinal products, the main directive and the specific regulation for advanced therapy medicinal products (ATMP's) are applicable:

- Directive 2001/83/EC on medicinal products [13].
- Regulation 1394/2007 on ATMP's [14].

The ATMP Regulation is a so-called "lex specialis", which introduces additional provisions to those laid down in Directive 2001/83/EC. Because of their novelty, complexity and technical specificity, specially tailored and harmonised rules were considered needed for ATMPs to ensure the free movement of those products within the Community, and the effective operation of the internal market in the biotechnology sector. Thus, for ATMP's both documents are applicable.

In Appendix 1, the official definitions of the various medical products, i.e. for medicinal products, medical devices, ATMP's and *in vitro* diagnostics are provided.

In general, medical products are products used to diagnose, treat or care for patients. However, there are substantial differences between medicinal products and medical devices. To determine the legal identity of a medical product, in general a differentiation based on the mode of action is applicable.

- Medicinal product is a substance presented as having properties with pharmacological, immunological or metabolic action, or administered with the aim to make a medical diagnosis.
- A medical device function is achieved by physical means, including mechanical action, physical barrier, replacement of or support to organs or body functions. It does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means [15].

A category of products that should be mentioned specifically are combination products, which contain component(s) that are a medical device and component(s) that are a medicinal product. In these cases, only one of the frameworks will be applicable, although some cross-references are made within one regime to specific provisions of the other regime. In general, the primary mode of action of the combination

products will decide which of the frameworks is applicable [15]. For ATMP's, however, it has been specified for combined ATMP's that "Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product", and thus the medicinal products framework is applicable for all combined ATMPs [14]. For most products the classification is straightforward, however, it can be expected to be more complex for synthetic biology products with new to nature biological features or products with diagnostic and therapeutic mode of action.

### 2.2.2 *GMO regulatory framework*

In addition to the European regulatory frameworks for authorization of medical products, the European regulatory framework on genetic modification is relevant for medical products if they are produced by or consist of a GMO. Directives applicable to GMOs are:

- Directive 2009/41/EC on the contained use of genetically modified microorganisms [16].
- Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms [17].

In both Directives a GMO is defined as a genetically modified organism (with the exception of human beings) in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. Techniques of genetic modification resulting in a GMO or not are listed as such in an Annex to the Directives. According to these Directives each GMO is subject to an environmental risk assessment (ERA) in order to establish measures to reduce potential risks for human health and the environment. Applications of synthetic biology comprising genetic modification of a living organism will fall within the scope of the GMO Directives. For example, when a therapeutic drug is produced by a GMO in a bioprocess facility, the GMO is regulated by the contained use Directive 2009/41/EC. For the purified drug, free of GMOs, the GMO regulatory framework is not applicable.

The requirements for an ERA according to 2001/18/EC are specifically included in the medicinal products directive 2001/83/EC. In the medical devices regulatory framework, such an explicit reference is not included, however, the GMO framework is applicable in addition to it. In the Netherlands use of a GMO in clinical trials is regulated by Directive 2001/18/EC. This differs from some other European countries where this is regulated by Directive 2009/41/EC or by a combination of these directives.





### 3. Method

To identify novel medical products designed using synthetic biology we performed a quick scan of the scientific literature and news websites. We used a search profile (see Textbox 1) to identify novel medical products. Medline was used to perform a literature search over the years 2010-2015. News websites from March-June 2015 were reviewed using HowardsHome.

#### **Textbox 1.** Search profile

Synthetic biology AND/OR medical AND/OR medicine AND/OR synthetic antibiotics AND/OR synthetic proteins AND/OR genetic switch AND/OR genetic circuits AND/OR CRISPR-CAS9 AND/OR mRNA AND/OR synthetic RNA/DNA AND/OR siRNA AND/OR genetic modification AND/OR metabolic pathway engineering AND/OR synthetic minimal cells AND/OR semi-synthetic minimal cells AND/OR protocells AND/OR liposome AND/OR risks.

At first a selection of relevant articles based on the abstracts was made. An article was included when:

- it contained information on medical products such as medicines, medical devices or artificial products with a clear relation to synthetic biology and,
- the products described in the article were already developed in a laboratory and tested in an experimental, pre-clinical or clinical setting and,
- the article was in Dutch, English or German.

Articles on food, food supplements or food additives, and articles with descriptions of theoretically designed medical products were excluded.

Different types of medical products designed using synthetic biology were identified from the selected articles. These medical products were placed in product groups, based on the descriptions in the articles. Subsequently, information on the intended use, e.g. identifying biomarkers for diseases, repair of tissue or organs, as found in the corresponding articles, as well as the mode of action was collected for each product type and combined in tables.

Finally, the potentially applicable regulatory frameworks were identified and added into the result tables, indicated in column a-f, with a plus (+) or a minus (–) sign. It was noted that the regulatory framework for medical devices is under revision. Since only draft texts are available of the future revised framework, it was decided to include only the existing framework in this analysis.



## 4. Results

### 4.1 Selection of relevant articles

The Medline search and web search resulted in 210 publications. In most (n = 179) of these publications ethical aspects of synthetic biology, mathematic design models (computer models), description of approaches to design parts or entire genetically engineered cells were addressed. In 18 publications out of the remaining 31, novel medical products were identified. Most of these are still in the development stage, in *in vitro* tests or *in vivo* models. Some of the products are already being tested in clinical trials, such as the engineered human cell products. None of the products are placed on the European market yet.

### 4.2 Identified novel medical products

In the literature and news website, 18 publications presented 12 types of novel medical products (Tables 1-3). Based on information in the literature, the products were categorized in product groups. Three main product groups were identified:

- Biosensors: a sensing device in which a biological component is coupled to a transducer. Biological components can be non-living such as nucleic acids, proteins including enzymes and antibodies, or living such as an engineered micro-organism. When the biological component interacts with the analyte being tested (e.g. glucose), the biological response will be converted by the transducer in an electrical, optical, or thermal signal (Table 1).
- Targeted drug delivery products: engineered human cells or micro-organisms carrying and delivering a chemical therapeutic drug specifically to diseased tissue in the body of a patient (Table 2).
- Engineered human cell products: an engineered cell as therapeutic drug (e.g. to recognize and kill tumor cells) or engineered somatic cells to repair tissue (Table 3).

Based on the described intended use and mode of action, the legal frameworks under which these products could potentially fall were identified. In the next paragraphs the product groups of 'novel' medical products are described in more detail.

#### 4.2.1 Biosensors

The biosensors identified here are generally composed of one or more genetic circuits able to detect an external stimulus (a pathogenicity factor or metabolite) and to respond with a visible signal like luminescence.

Biosensors are being developed to be used outside the body (*in vitro*) to detect e.g. cancer cells or pathogens, or inside the body (for *in vivo* use), e.g. inside the intestinal tract. The newly developed biosensors differ from conventional diagnostic products, because they contain an engineered biological component or a living microorganism instead of being based on a physical or chemical reaction solely.

Among the novel medical products, 6 biosensors were identified (Table 1). These biosensors are designated as non-living sensors (n=2) as they

exist of engineered pieces of DNA or as living biosensors (n=4) as they consist of engineered living micro-organisms.

The non-living biosensors are composed of a genetic circuit, i.e. comprising DNA only, and the cells to be tested need to be transfected with this DNA (nr. 1, Table 1). As this involves genetic modification, the Directive on contained use (2009/41/EC) will be applicable when this biosensor is used in a diagnostic laboratory. As this particular biosensor is intended as a diagnostic application for *in vitro* use, it will fit best in the regulatory framework for *in vitro* diagnostic medical devices (see appendix 1 for the definition *in vitro* diagnostic medical device).

The second group of biosensors is the group of living biosensors. These biosensors are GMOs and will have an intended use which can be either inside (*in vivo*, nr. 2, Table 1) or outside (*in vitro*, nrs. 3 and 4, Table 1) the body. Regarding the possible legal medical framework in which these biosensors could fall, differentiation on this intended use should be made. Biosensors with diagnostic application used outside the body (*in vitro*) fit best in the regulatory framework for *in vitro* diagnostic medical devices. Living biosensors with diagnostic application for use inside the body (biosensor 2, Table 1) fit best in the regulatory framework for medicinal products. It can be debated whether they also fit the framework for ATMP's (see Chapter 5 for discussion on this). All living biosensors meet the definition of a GMO. Again, depending on its use in humans or in a laboratory, requirements from Directive 2001/18/EC will be applicable for a living biosensor used in humans (nr. 2) and Directive 2009/41/EC will be applicable when biosensors are used in a diagnostic laboratory (nrs. 3 and 4). It can be foreseen that living biosensors for *in vitro* diagnostics may also be used as a medical device at the patient's home. As this use is outside a laboratory, the requirements from Directive 2001/18/EC instead of 2009/41/EC will be applicable.

#### 4.2.2 Targeted drug delivery medical products

A disadvantage of many therapeutic drugs is that their route of administration, e.g. oral or intravenous, hampers a direct and localized delivery at the diseased tissue. Their efficacy may be reduced by dose limiting systemic toxic side effects [18]. Much research is carried out on development of more precise and efficient drug delivery systems to target the drug to the diseased cells and to improve the efficacy of the therapeutic drugs, for example using liposomes. An alternative approach for targeted drug delivery is being developed using synthetic biology. Two types of such medical products were identified in this quick scan: engineered cells and engineered micro-organisms (Table 2).

The engineered cell products harbor a gene circuit which is activated when the circuit is induced by an external stimulus, such as light (nr. 2, Table 2) or lotion (nr 1, Table 2). Clearly, the ATMP regulation is applicable for the engineered cell part. It is not quite clear how the external stimulus should be regulated. The medical device framework could be considered for the light source. It is therefore marked with a question mark in Table 2. For the lotion, the medicinal products framework could be considered. Since this is already applicable for the engineered cell part, no question mark was added in Table 2.

Engineered microorganisms comprise the second type of targeted drug delivery systems (numbers 3, 4, Table 2). Bacteria from the normal microflora of the body can be used as targeted delivery systems to diseased parts of the body in which these bacteria normally live. The products identified in this quick scan were developed in laboratories and applied in mouse models. Based on the definitions, micro-organisms re-built to carry therapeutic drugs fit best under the regulatory framework for medicinal products.

Both types of targeted drug delivery systems comprise cells or microorganisms, which are genetically modified with genetic circuits with primary function targeted drug delivery. As they are intended for use in the human body, Directive 2001/18/EC is applicable.

#### 4.2.3 *Engineered human cell products*

The last group of products identified in this study is the group of engineered human cell products, such as engineered chimeric antigen receptor (CAR) T-cells used for cancer therapy and induced pluripotent stem cells (iPSC) used for stem cell therapy and tissue regeneration.

Engineered CAR T-cells are originally derived from T-cells from a patient with cancer (nrs. 1, 2 and 3, Table 3). These T-cells are genetically modified with sequences that encode re-engineered T-cell receptors that enable the retargeting of T-cell activity towards cells with the targeted surface antigen, e.g. cancer cells. After the *ex vivo* modification, the CAR T-cells are transferred back to the patient as a therapeutic drug.

Relatively new cell products are the induced pluripotent stem cells (iPSCs, nr. 4, Table 3). Pluripotent stem cells (PSCs) can develop into every other cell type in the body. In 2006, Japanese scientists demonstrated for the first time that they could produce iPSCs from adult mouse fibroblast cultures [19]. Today, the generation of human iPSCs is relatively simple. All kinds of human cells, such as stromal cells, cardiomyocytes and cells from the bladder, can be used as a source for iPSCs [20] [21] [22] [23]. The field of regenerative medicine is benefiting greatly from the discovery of iPSCs. In 2014, in the first in man clinical trial pilot study, autologous iPSCs were transplanted in patients with an eye disease [24]. A step forward towards the clinical application of iPSCs could be the generation of iPSCs from GMP-grade blood derived cells, such as hematopoietic progenitor cells and peripheral blood mononuclear cells [25].

The engineered cell products mentioned above all meet the definition of a GMO. As the transfer of the genetically modified cells into the patient needs authorization under Directive 2001/83/EC, the requirements from Directive 2001/18/EC will be applicable for the environmental risk assessment. For their intended use as medical products also the ATMP regulation is applicable.

Table 1. Novel medical products designed with synthetic biology: biosensors

Product group	Medical product	Mode of action	Intended use	Potentially applicable legal framework when placed on the market:					
				a	b	c	d	e	f
Biosensor	1. Non-living: Synthetic DNA circuit [26, 27]	Cellular response: triggers cell death of specific cancer cells	<i>In vitro</i> : Identification of specific cancer cells (tumor marker)	-	-	-	+	+	-
	2. Living: Reprogrammed <i>E. coli</i> Nissle 1917 [28, 29]	Detection of enzyme (LacZ) activity (luminescent signal)	<i>In vivo</i> : detection of presence of liver metastases	+	?	-	-	-	+
	3. Living: Engineered bacteria [30]	Detection of enzyme activity (fluorescence signal)	<i>In vitro</i> : detection of glucose in urine	-	-	-	+	+	+
	4. Living: Engineered <i>E. coli</i> [31]	Detection of biomolecules, induces bioluminescence emission by the biosensor	<i>In vitro</i> : detection of biomolecules in sputum (main signal produced by human pathogen <i>Pseudomonas aeruginosa</i> , infections in lungs of cystic fibrosis patients)	-	-	-	+	+	+

(a) - Directive 2001/83/EC medicinal product; (b) - Regulation 1394/2007 advanced-therapy medicinal products; (c) - Directive 93/42/EEC medical device; (d) - Directive 98/79/EC *In vitro* diagnostic medical device; (e) - Directive 2009/41/EC on the contained use of genetically modified microorganisms; (f) – ERA according to Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.

Table 2: Novel medical products designed with synthetic biology: targeted drug delivery medical products

Product group	Medical product	Mode of action	Intended use	Potentially applicable legal framework when placed on the market:					
				a	b	c	d	e	f
Targeted drug delivery products: engineered cells	1. Lotion to induce drug producing cells [32]	Induced expression of transgene (e.g. therapeutic drug) in subcutaneous cell implant by administering skin lotion	Controlled gene expression in subcutaneous cell implants	+	+	+	-	-	+
	2. Engineered cells containing an optogenetic transcription network and light source [33]	Metabolic action under influence of light	Increases blood glucose homeostasis under the influence of light	+	+	?	-	-	+
Targeted drug delivery products: engineered micro-organisms	3. Novel live bacteria drug-delivery system [34].	Xylan-regulated delivery of growth factor by bacteria	<i>In vivo</i> : diagnostic and therapeutic. Treatment for the inflamed colon	+	?	-	-	-	+
	4. Novel live bacteria drug-delivery system [35, 36]	Bacteria that find infected cells, then express, secrete, and deliver heterologous anti-inflammatory proteins into mammalian cells	<i>In vivo</i> : diagnostic and therapeutic. Treatment for infections	+	?	-	-	-	+

(a) - Directive 2001/83/EC medicinal product; (b) - Regulation 1394/2007 advanced-therapy medicinal products; (c) - Directive 93/42/EEC medical device; (d) - Directive 98/79/EC *In vitro* diagnostic medical device; (e) - Directive 2009/41/EC on the contained use of genetically modified microorganisms; (f) - ERA according to Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.

Table 3: Novel medical products designed with synthetic biology: engineered human cell products 1

Product group	Medical product	Mode of action	Intended use	Potentially applicable legal framework when placed on the market:					
				a	b	c	d	e	f
Engineered human cell products	1. Engineered T-cells : CAR T-cells [37, 38]	Cytotoxic (immunological action: target tumor-associated antigen)	Therapy for cancer	+	+	-	-	-	+
	2. Engineered Treg cells: regulatory T-cells [39]	Specific immunological action	Treatment for anti-FVIII inhibitory antibody formation hemophilia A	+	+	-	-	-	+
	3. Modified dendritic cells (with recombinant adenovirus carrying IL-12) [40, 41]	Specific immunological action	Induce tumoricidal T-cell response	+	+	-	-	-	+
	4. Induced pluripotent stem cells (iPSCs) [42] [24]	Repair function	Cell/tissue engineering	+	+	-	-	-	+

(a) - Directive 2001/83/EC medicinal product; (b) - Regulation 1394/2007 advanced-therapy medicinal products; (c) - Directive 93/42/EEC medical device; (d) - Directive 98/79/EC *In vitro* diagnostic medical device; (e) - Directive 2009/41/ on the contained use of genetically modified microorganisms; (f) - ERA according to Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.



## 5. Discussion and conclusion

### 5.1 General

The increasing number of claims on the advent of synthetic biology as an engineering discipline for the development of many new applications including medical products raises the question what the actual current status is in development and application. High expectations of new medical applications from synthetic biology include strategies for diseases that are difficult to treat, such as cancer, immune diseases, metabolic disorders and infectious diseases [7]. To gain insight into the latest developments a literature scan was performed over the period 2012-2015. In addition, for the identified medical products we checked which regulatory framework on medical products and which GMO Directive would be applicable.

The results confirm that the evolving field of synthetic biology indeed holds promise with regard to medical applications. It will, however, probably take time before most of the products will actually reach broad application in the clinic, as most of these products are still in the development stage, in *in vitro* tests or *in vivo* models. The engineered human cell products, which have been entered into small clinical trials, seem the most promising development. The medical products identified from the literature could be grouped into biosensors, targeted drug delivery medical products and engineered human cell products.

With regard to the applicable regulatory framework for medical products, in general it can be concluded that the medicinal product regulation appears to be applicable whenever a product is intended to be administered to the human body. Additionally, the specific regulation for advanced therapy medicinal products (ATMPs) could be applicable, however, that is not clear in all cases.

Where the products are intended to be used for diagnosis in an *in vitro* application, the *in vitro* diagnostic medical devices directive appears to be applicable.

With regard to the applicable regulatory framework for GMO, applications of synthetic biology comprising genetic modification of a living organism fall within the scope of one of the GMO Directives. When the application is in a laboratory suitable for contained use, Directive 2009/41/EC is applicable, otherwise Directive 2001/18/EC.

This report is aimed to serve as a starting point to identify potential challenges for the relevant regulatory frameworks. An important question to answer is whether the provisions in the applicable frameworks are adequate to cover the quality, safety and efficacy of the products. Interaction with key opinion leaders representing the various stakeholders that can be involved will be needed to create a full picture.

### 5.2 Biosensors

Biosensors are 'devices' able to detect an external stimulus and subsequently react with a corresponding signal. Biosensors can either be

living, i.e. engineered micro-organisms or living cells, or non-living, like pieces of DNA and RNA only. In addition, application of a biosensor in for example the detection of cancer cells can either be inside the human body (*in vivo*) or in samples outside the human body (*in vitro*). The discrimination between *in vitro* and *in vivo* application has impact on the applicable regulatory frameworks. For the *in vitro* biosensors, the *In Vitro* Diagnostics IVD Directive (98/79/EC) would be appropriate as the intended use of these products fits well in the definition of IVD's (see Appendix 1).

For the *in vivo* biosensors, the medicinal products framework fits best. It is a subject for debate whether they also fit the framework for ATMP's. In the definition of substance, as used in the definition for medicinal products, micro-organisms are included. Since they are administered with a view to making a medical diagnosis, they fit the definition of medicinal product. Given analogies to gene therapy and somatic cell therapy products, the framework of ATMPs would seem to be appropriate as well. However, although several aspects of the definition of a gene therapy medicinal product (see Appendix 1) are applicable, it also requires that it is used or administered with a view to regulating, repairing, replacing, adding or deleting a genetic sequence, which is not the case for the product at hand. Classification as somatic cell therapy products could be argued because the bacteria can be considered engineered living cells that are administered to humans. However, although the current definition (see Appendix 1) only refers to "cells or tissues" without further specification, the related requirements appear to imply that this is intended to include only human or animal cells, and not micro-organisms.

Regarding the GMO Directives, when a living biosensor or a non-living biosensor yielding a GMO is applied in a diagnostic laboratory (*in vitro*), Directive 2009/41/EC is applicable. It can be foreseen, however, that future use of these biosensors would be in a medical practice or at the patient's home. In that case the biosensor needs authorization under Directive 2001/18/EC for commercial use. As one biosensor is currently being developed for use in the human body, this application is a medicinal product and will involve Directive 2001/18/EC.

### 5.3 Targeted drug delivery products

Targeted drug delivery medical products can either be systems of engineered cells, or systems of engineered micro-organisms. These products can for example be used to enhance the efficacy of a therapeutic drug.

As identified by the European Commission's New and Emerging Technologies WG (NET) previously, technologies like optogenetics present a borderline/classification issue between medical devices and ATMPs [43]. A combined ATMP must incorporate one or more medical devices, as an integral part of the product. However, the light emitting device is not an integral part of this kind of product. It is a separate device, and it could be debated whether it should be regulated as a medical device, or as part of an ATMP after all. An additional complication if the two components are considered to be separate

products, is caused by the fact that there is no efficacy of the ATMP without the light source to switch it on, and there is no clinical benefit for the light source without an ATMP to be switched on. In order to assess the benefit-risk ratio, the two must thus be evaluated jointly, which is complicated when the two different regulatory frameworks must be applied. For the example of the lotion (see table 2, example 1), a similar complicated situation could occur, although it might be classified as a medicinal product, in which both components of the product at least are under the umbrella of medicinal products.

All targeted drug delivery medical products identified comprise engineered cells or micro-organisms which meet the GMO definition. The requirements for an environmental risk assessment from Directive 2001/18/EC are applicable.

#### **5.4 Engineered human cell products**

The third category consists of engineered human cell products, for example induced pluripotent stem cells (iPSCs) used for cell therapy, like tissue regeneration. The ATMP regulation is applicable. With regard to the GMO framework, the *ex vivo* modification of the cells needs authorization under the Directive 2009/41/EC on contained use. The transfer of the genetically modified cells into the patient needs authorization under Directive 2001/83/EC, which requires an environmental risk assessment according to Directive 2001/18/EC.

#### **5.5 Limitations of the study**

Information for this study was obtained by performing a literature and web search. Efforts have been made to identify as many 'novel' medical products as possible. However, it must be emphasized that this quick scan has its limitations. Many research groups around the world are working on the development of 'novel' medical products with synthetic biology tools, leading to new products every month, making it difficult to maintain an up-to-date list of products. Furthermore, data are collected with a quick scan of available literature and web search in the public domain. There is a possibility that some 'novel' medical products are missing in this study. Nevertheless, this study does provide a proper insight on the most common classes of 'novel' medical products currently in development in the area of synthetic biology.



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## Appendix 1. Definitions medical product types

### **Medicinal product:**

Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

(Source: Directive 2001/83/EC,

[http://ec.europa.eu/health/files/eudralex/vol-1/dir\\_2001\\_83\\_consol\\_2012/dir\\_2001\\_83\\_consol\\_2012\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_consol_2012_en.pdf))

### **Substance:**

Any matter irrespective of origin which may be:

- human, e.g. human blood and human blood products;
- animal, e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;
- vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts;
- chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

(Source: Directive 2001/83/EC,

[http://ec.europa.eu/health/files/eudralex/vol-1/dir\\_2001\\_83\\_consol\\_2012/dir\\_2001\\_83\\_consol\\_2012\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_consol_2012_en.pdf))

### **Advanced therapy medicinal product (ATMP):**

- *A gene therapy medicinal product:* Contains an active substance, which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. Exception: gene therapy medicinal products shall not include vaccines against infectious diseases as defined in Part IV of Annex I to Directive 2001/83/ECA
- *Somatic cell therapy medicinal product:* A biological medicinal product which has the following characteristics: (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor; (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
- *Tissue engineered product:* Contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. A tissue

engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices. Cells or tissues shall be considered 'engineered' if: the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. Non-viable human or animal cells and/or tissues, which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

- *Combined advanced therapy medicinal product*: It must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/ EEC or one or more active implantable medical devices within the meaning of Article 1 (2)(c) of Directive 90/385/EEC; and its cellular or tissue part must contain viable cells or tissues; or its cellular or tissue part containing nonviable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

(Source: Regulation (EC) No 1394/2007, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>)

#### **Medical device:**

Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of: disease, diagnosis, or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of physiological process, control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, that device shall be assessed and authorized in accordance with the Directive 93/42/EEC.

(Source: Directive 93/42/EEC, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF>)

#### ***In vitro* diagnostic medical device:**

Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for

the purpose of providing information: concerning a physiological or pathological state, or concerning a congenital abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures.

(Source: Directive 98/79/EC <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31998L0079&from=EN>)

### **Defining biotechnology**

The provisional single definition of biotechnology is deliberately broad. It covers all modern biotechnology but also many traditional or borderline activities. For this reason, the single definition should always be accompanied by the list-based definition which operationalizes the definition for measurement purposes. The single definition is: The application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services.

The list-based definition

The following list of biotechnology techniques functions as an interpretative guideline to the single definition. The list is indicative rather than exhaustive and is expected to change over time as data collection and biotechnology activities evolve:

- DNA/RNA: Genomics, pharmacogenomics, gene probes, genetic engineering, DNA/RNA sequencing/synthesis/amplification, gene expression profiling, and use of antisense technology.
- Proteins and other molecules: Sequencing/synthesis/engineering of proteins and peptides (including large molecule hormones); improved delivery methods for large molecule drugs; proteomics, protein isolation and purification, signaling, identification of cell receptors.
- Cell and tissue culture and engineering: Cell/tissue culture, tissue engineering (including tissue scaffolds and biomedical engineering), cellular fusion, vaccine/immune stimulants, embryo manipulation.
- Process biotechnology techniques: Fermentation using bioreactors, bioprocessing, bioleaching, biopulping, biobleaching, biodesulphurisation, bioremediation, biofiltration and phytoremediation.
- Gene and RNA vectors: Gene therapy, viral vectors.
- Bioinformatics: Construction of databases on genomes, protein sequences; modelling complex biological processes, including systems biology.
- Nanobiotechnology: Applies the tools and processes of nano/microfabrication to build devices for studying biosystems and applications in drug delivery, diagnostics etc.

(Source: OECD. Statistical definition of biotechnology (updated in 2005).

<http://www.oecd.org/sti/biotech/statisticaldefinitionofbiotechnology.htm>)

