



SYNTHETIC BIOLOGY

A joint report by the

the Spanish Bioethics Committee and the

Portuguese National Ethics Council for the

Life Sciences

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Synthetic Biology

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Members of the Spanish Bioethics Committee

Victoria Camps Cervera (President)
Carlos Alonso Bedate (Vice President)
Carmen Ayuso García
Jordi Camí Morell
María Casado González
Yolanda Gómez Sánchez
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Javier Arias Díaz (Secretary)

Members of the Portuguese National Ethics Council for the Life Sciences

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Maria do Céu Patrão Neves
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Rosalvo Almeida
Ana Sofia Carvalho (Reporter)
Carolino Monteiro
Duarte Nuno Vieira
José Lebre de Freitas
Lucília Nunes
Pedro Nunes
Raquel Seruca

The Spanish Bioethics Committee
Instituto de Salud Carlos III-Campus de Chamartín.
Avda.Monforte de Lemos.5 Pabellón 5.
28029-Madrid.
www.comitedebioetica.es

Portuguese National Ethics Council for the Life Sciences
Avenida D. Carlos I, nº 146-2º Esq.
1200-651. Lisbon
<http://www.cneqv.pt>

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I. INTRODUCTION

We are living in a period in which there is an important paradigm change in the relationship between ethics and scientific research. The time gap between scientific discoveries and parallel ethical reflection is gradually disappearing. It could even be said that ethics has found its own rhythm. What is currently referred to as the bioethics of emerging sciences (cloning, obtaining and using stem cells, nanotechnology, synthetic biology, etc.) has contributed decisively to this change. Nowadays science pursues its development and bioethics its reflections; reflections on the possibilities, evaluating the risks and putting forward proposals which, without being scientific, impose important nuances upon the pace of scientific development.

It can be argued that it is in our times that the new paradigm on this issue is emerging. Ethics has gradually moved towards science, and today ethical reflection seems to be not an appendix but rather an important chapter in any scientific research. The article published in *Science* by the Craig Venter group announcing the creation of "Synthia", the new bacteria, is an example of this. In fact, at the end of the article the authors stress: "We have been driving the ethical discussion concerning synthetic life from the earliest stages of this work. As synthetic genomic applications expand, we anticipate that this work will continue to raise philosophical issues that have broad societal and ethical implications. We encourage the continued discourse."

Currently, ethics finds itself increasingly frequently in the uncomfortable situation of the scientific facts that it has to evaluate, especially those linked with scientific research, being based to a large extent on mere working hypotheses, where the results may not be sufficiently measurable and predictable. This makes it difficult to anticipate the potential benefits and risks.

The considerations outlined above are applicable to synthetic biology. Some people became alarmed when the media reported a sensational event: a celebrated North American researcher (Craig Venter), after years of intense and costly work, had manufactured a cell: that is to say, created artificial life. The way in which this discovery was presented by the media contributed to the spreading of opinions that ranged from the discovery being marvellous to being terrible. It was considered fantastic, a notable event that enables us to anticipate the creation of useful cells that will produce molecules for drugs or even fuels. But is there not a risk of such activities being diverted to the manufacture of cells or even aggressive multi-celled life forms, capable of causing harm, damage or even the death of humans? Will the scientists not exceed their proper limits and end up playing God?

The current discussion regarding synthetic biology can produce fear and perplexity rather than new, important moral dilemmas. But it is true that the prospect of its development in the coming years is provoking a great deal of conjecture.

In relation to the issue as a whole, just as occurred with other research related to the life sciences, it is necessary to establish a balance between the potential benefits and risks. Let us briefly consider them.

There is no doubt that the synthetic biological products that can be obtained thanks to the progress made in synthetic biology, and their employment in the treatment of human illnesses will be very significant. But it is also predicted that they will be of great interest in other productive areas in industry such as agriculture, cattle rearing and food, amongst others. Producers' costs and consumer prices will also probably be lowered. At the same time companies and researchers in this new market will be able to make significant profits.

In considering the risks involved with synthetic biological products, currently there is uncertainty regarding the level of risk, primarily in relation to biosecurity. In fact, the initial discussions about synthetic biology have led to demands relating to security, or if preferred biosecurity, since it is feared that new risks to the life and health of living beings may result from synthetic biology. There have also been demands for the preservation of the environment, through fear of harm possibly being caused accidentally. Synthetic biology could even become a new and effective tool for the production and intentional use of particularly harmful biological weapons (the theory of dual use).

The patentability of these new "living" biological products is another matter for discussion. This is not because their application in this field is questioned or there is a desire to prevent profits being made, but for other reasons. Their patentability is not exempt from important moral dilemmas, in addition to other technico-legal and financial issues. In the first place, the issue of the patentability of life in all its forms, human and non-human, arises again with the development of synthetic biology. Secondly, there is the issue of the financial consequences that patenting can involve for third parties, not only for consumers but above all for competitors in this sector, if an attempt were made by means of patenting to achieve a monopoly over the exploitation of the products and processes discovered. In relation to this, it may be that steps are currently being taken in this direction to achieve monopolies. Regarding this concern, account has to be taken of the fact that the complexity of creating bioproducts based on different elements that have been obtained separately, as well as the need for interdisciplinary collaboration, can complicate the awarding of a patent to the researchers and also its approval by the patent offices, both at the national and regional level.

The possibility of creating synthetic or artificial life, as some scientists often emphasise, does not only pose the moral acceptability of this activity, but also calls for profound reflection on the meaning of life in general and how synthetic biology in particular should treat it.

In the literature on synthetic biology other problematic issues have been raised which in principle seem less specific to synthetic biology itself and for this reason less important here. They can therefore be debated and, if appropriate, resolved in other forums. Some of these issues concern the preservation of biodiversity and the protection of genetic information, but they also concern the current perception of ownership as a social and moral construct. The potential for synthetic biology as a technique for the biological enhancement or perfection of human beings has also

been raised, a matter which is currently the object of general debate. However, sufficiently clear definitive positions have not yet been adopted and agreed about the possibility and acceptability of such a use. In the medium term, it is said that synthetic biology could affect our moral and cultural perceptions and once again require the attention of future generations.

In conclusion, there are four main aspects that we consider must be examined and which we are going to consider briefly below. This will be preceded by a brief discussion about the significance of synthetic biology from the scientific point of view:

1. The creation of synthetic or artificial life as such.
2. The responsibility of the scientist.
3. Biosecurity in the context of synthetic biology. And,
4. Patents.

II. SCIENTIFIC ASPECTS

For the purposes of this paper it seems appropriate to provide a definition of synthetic biology, as it may help to establish the area to be considered. The following, for example, may serve for this purpose: “Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems.” (*Royal Academy of Engineering, 2009*). Other definitions or descriptions have been proposed, such as those that distinguish between a system that can be understood to be natural as distinct from one that is artificial. It is precisely in this latter description that the contradistinction between life and non-life, between a live being and a mere biological product, can be made clear.

The term synthetic biology was first used in 1912 (the date that Stephan Leduc published his *Biologie synthétique* in Paris), as the title of a book which, given its publication date, could clearly not be about this new technology. Scientific questions regarding synthetic biology arose in the last decade of the 20th century, when scientists began to try to design and synthesise genetic regulatory circuits.

The word biology is not very old, as it was coined less than two hundred years ago by Lamarck and only became popular during the 20th century. Even when scientists were not satisfied with observing and describing life forms, when the form and function of cells began to be unravelled, the dynamics of enzymes studied, constituent cells isolated, the genome itself unveiled, when tests were carried out that were increasingly demanding technically and that were more restrictive in relation to the size and weight of their reactive agents, when the tests became molecular biology, biology kept its fundamental character of observing and studying living beings and the mechanisms and processes that occur in them. In other words, biology advanced through discoveries and not through inventions and creations.

Subsequently, in the second half of the 20th century, this paradigm was profoundly altered. The best known example is that of genetically modified organisms. Through genetic manipulation it is possible to add one or more genes to the genome of a living being, conferring on it new properties never before manifested by that being. We know that this practice has been rejected by some people. However, despite the debate that it can generate, it is a well established scientific fact, widely accepted in many situations.

Intervention in the genome of bacteria or rodents with the aim of modifying them in such a way that they produce substances of therapeutic interest that are difficult or very costly to obtain by other means should not be rejected by anybody. This is so with insulin or growth hormone, and many other biological products of high therapeutic value. In relation to this, we should remember that insulin, the only medication capable of keeping patients with some types of diabetes alive, was originally extracted from the pancreas of cows or pigs and then modified. This process was very expensive and had the disadvantage that the resulting molecule was different from human insulin and brought with it the risk of sensitisation as a side effect. Through the technology of recombinant DNA it was possible to alter the

genome of a non-pathogenic bacterium (*Escherichia coli*), so that it produced insulin that was same as that manufactured in the Langerhans cells of the human pancreas i.e. a "domesticated" bacterium produced a human hormone. That is to say, it ceases to be, at least in this regard, a typical bacterium and instead becomes a "new" bacterium.

From this point on, we could say that we are in the presence of a "new" biology which, following profound advances, has come to be referred to as synthetic biology. The expression "synthetic biology" does not really seem to be a quite appropriate one. However, perhaps because of its rhetorical and metaphorical value, it has been attributed with the idea of active intervention by scientists in biological processes. This intervention is no longer limited to observing, describing and understanding, but instead to manipulating, modifying and innovating.

In general terms, the term synthetic biology describes those lines of research in the field of life sciences that are interested in the synthesis of parts of biological systems or in the construction of biological systems that are different from those that exist in nature. This technique involves a variety of different disciplines: bioengineering, synthetic genomics, protocells and artificial (unnatural) molecular biology.

Bioengineering is based on the conception and generation of new metabolic and regulatory pathways. Synthetic genomics highlights another aspect of synthetic biology, namely the creation of organisms with a chemically modified genome or a minimal genome. In addition, the objective of scientists who carry out research in the synthetic biology sector linked to protocells is to construct artificial cells in vitro. The "unnatural (artificial) molecular biology" approach has as its objective the synthesis of "new life forms", for example new types of nucleic acids or a different genetic code. In the paper referred to above, published in *Science* (2010) the genome of the bacteria was only very slightly modified. The technique that had been used for a long time involved the addition of a gene, for example in the case of the human insulin producer *collibacillus*. Instead, in this new technique the genome was completely replaced by another synthetic genome. This was a new, radical approach. The DNA inserted was not that of another bacterium, but instead was obtained in the test tube by the deliberate and ordered assembly of blocks of sequences. This had never been done before.

Enormous progress can be anticipated in this area which will make it possible to improve and extend our current ability to "domesticate" bacteria or even multicellular life forms, converting them into producers of substances for therapeutic purposes (cytostatics, immunomodulators, vaccines, antibiotics, etc.) or of commercial interest (raw materials, hydrocarbonates, fuels, etc.).

In this context the hopes and fears generated by the announcement of this discovery must be examined rigorously, both in terms of their foundations and their origin. In fact, in science there is no such thing as discoveries that come out of nowhere, that do not have any predecessors or spring from a brain that is so privileged or original and intelligent that there is no need to consider what others have already discovered, described or intuited. Consequently, caution must be exercised when evaluating the

creation in Craig Venter's laboratory of the bacterium discussed above. In the first place, it has been demonstrated that, strictly speaking, a new genome has not been created but rather a genome that already exists in nature has been reproduced or copied in the laboratory. Neither can it be described as life or the creation of a living cell, as the synthetic genome was transferred to the cytoplasm of an existing cell, and the bio-product obtained is not capable of self-reproduction. The research carried out in recent years by various scientists into synthetic biology suggested that something like this was going to occur and it is predicted that similar events will occur more frequently in the future as these experimental strategies continue.

Based on these reflexions, the least important issue, at the moment, is whether Venter's finding represents the creation of artificial life, as he maintained in his bold and self-interested claim, a claim which scientists have set about refuting. It invites very important reflection; however it is more important to evaluate what the synthesis of these bio-products represents from the scientific point of view. Undoubtedly, a biotechnological tool has been created. These possibilities, as they are developed and perfected, will substantially increase its uses in health, industrial processes and the agro-food industry.

Before enumerating the various ethical questions involved, we think that it is important to stress that the questions derived from the use of synthetic biology are not, in essence, different from those which have arisen in other emerging areas. Thus, tackling the ethical issues arising as a result of the development of synthetic biology is in every way similar to tackling the ethical issues that arise in other recently developed areas (e.g. nanotechnology, genetics, and neuroimaging). We also consider it important to stress that to our way of thinking exceptionalisms in the ethical analysis of these diverse emerging areas, such as nanoethics, genethics, must be avoided when they affect the same knowledge area. Consequently, accepting that the intensity of the ethical questions appears to be different depending on the specific area under study, the grand principles are, in essence, the same.

III. ARTIFICIAL LIFE OR SYNTHETIC BIOLOGICAL MATERIAL?

In either case, it seems reasonable to expect that soon, thanks to synthetic biology, unicellular life forms, and later very innovative multicellular life systems, will be created. Perhaps less important for the current debate which, due to its nature, must remain open, is the question: "What is artificial about these life forms?" i.e. "What is it that human beings have deliberately created, or more precisely will be able to create in the future, without copying a pre-existing model?" At lower levels of complexity and of biological organisation, the problem is not based on their identity or close similarity to other life forms that we find in nature. On the contrary, and in the same way that the possibility of creating hybrid or chimerical superior life forms has been raised, the problem lies in their identity as a species, particularly in whether they have a phenotype or genotype that is very different from other pre-existing life forms.

It would not therefore be a question of preserving biodiversity, but rather of limiting it, insofar as synthetic biology could influence it, with the aim of preserving the identity of species. Changing ideas and positions, considering advantages and disadvantages, resorting to the principle of proportionality, establishing limits and if necessary prohibitions, are matters about which decisions will have to be taken. These will be more restrictive the higher the phylogenetic profile of the life forms is involved.

There has also been a desire to remove any relevance regarding the artificial origin of these hypothetical life forms in relation to ownership. It is true that it would be necessary to accept that if they have been created artificially by someone, they could be the property of their creator (in the broad sense) unlike in nature, where wild animals do not belong to anyone, although they can be appropriated. However, these entities merit further consideration beyond the question of ownership itself, namely the exercise of rights of ownership by someone from the point of view of industrial property.

Furthermore, in ontological terms, the question will be to establish the social value that has to be given to these new organisms, as we have been doing with various living beings. Consequently, they will have to be recognised and the moral status and corresponding legal protection applied to them. This derives from their specific condition as life forms, i.e. from their intrinsic characteristics, whether they are identical to or different from other pre-existing life forms, possessing a moral status that can be recognised, and which will have to be taken as a reference point for evaluation.

In addition, ascending the phylogenetic scale and advocating this type of reflection about human beings (leaving aside the issue of enhancement) at the moment seems a luxury and excessive and there is a risk of slipping into fictitious ethics. In any event, it would probably be necessary to start from that discussed above, while also keeping an open mind to other, more profound considerations that may arise, such as those that concern the legitimacy of the life form itself.

IV. THE RESPONSIBILITY OF THE SCIENTIST.

Progress in science and technology requires absolute freedom of scientific investigation, which is generally recognised as a fundamental human right. However, this right, like any other, has its own limits, which can be defined as the responsibility of the scientist in relation to his or her own work.

The question of scientific responsibility leads us to consider how our times are characterised by a proliferation of means, but at the same time also by confusion about the ends. The German philosopher Hans Jonas criticised human beings as being capable of increasing their power but of not having tried as hard to discover the consequences of that power

In addition, the twentieth century was witnessing the substantial development of science. In fact, philosophers of science have been critical that science no longer limits itself to rationally explaining the universe and all that which exists or can exist in it, including living material. Instead, although still in a limited way, science can increasingly and ever more accurately predict the future and events. Above all, it can influence and modify these events, and as discussed above, do this particularly in the case of living material. Consequently, science has exceeded its own boundaries, as it no longer only seeks the truth, i.e. knowledge, but instead can create it, at the whim of a human being. But if human beings are moral beings, thereby capable of self awareness and reflection about their own actions and the consequences of these actions, and if they have the freedom to make decisions and consequently to act according to these decisions. This means that if they are responsible human beings, scientists also have to be responsible. They have to be capable of going from knowledge and power to assuming the inescapable responsibility which is incumbent upon them in relation to that knowledge and power.

As is well known, it was Max Weber who elaborated an "ethic of responsibility" when he was trying to develop a political ethic of consequences. In fact, this ethic evaluates action, taking into consideration the consequences anticipated as being possible or probable. It is essential to take note of the relationship between the means and the ends and the actual situation in which human action must be carried out. However, this ethic is of limited use in relation to the evaluation that the action in itself deserves.

It was Hans Jonas who with great conviction took up the notion of an ethic of responsibility applied to technology, in particular biotechnology, seeing it as an ethic for the future which commits all of us to the natural environment:

"Given that it is nothing less than human nature that is involved in the field of human intervention, caution will be our first moral mandate and hypothetical thought our first task. To think of the consequences before acting is no more than common sense. In this special case, wisdom requires us to go further and examine the eventual use of capabilities before they are completely ready for use." (*Verantwortung Prinzip*)

This premise of anticipation advanced by the German philosopher is particularly applicable to synthetic biology. He insists that the biotechnological revolution has to

take into account the fact that while mechanical errors are reversible, biogenetic errors are irreversible. Jonas summarises his proposal with the following maxim: "Act so that the effects of your action are compatible with the permanence of genuine human life" (*Verantwortung Prinzip*).

It seems that in this debate on synthetic biology and the creation of life that we should focus our attention on the expression "playing God" used above, because it has arisen on numerous occasions in relation to developments in this area. The expression seems to have been used for the first time by Paul Ramsey in his *Fabricated Man*, 1970: "Men ought not to Play God before they learn to be men, and after they have learned to be men they will not Play God". In the meantime, the argument regarding "playing God", which as well as being used in this debate has also been used in relation to other emerging technologies, has itself been criticised in various ways. Thus, it has been considered to be of no cognitive use when used within a theological perspective (Dabrock, 2009; Van del Belt, 2009), or as a dubious way of rejecting the cultural duty of human beings to mould the world (Dworkin, 2000).

V. SYNTHETIC BIOLOGY AS A NEW SOURCE OF RISK TO BIOSECURITY

1. The risks of synthetic biology to the security of life forms and ecosystems

The ability to recombine DNA, albeit in the laboratory, that is, in a closed environment, never fails to raise doubts about the behaviour of this new entity in an open environment, its interaction with other life forms and its own ecosystems. Going further, and based on proposals about the dual use of procedures and techniques, synthetic biology can be an efficient tool for the production of biological weapons, or to put it more neutrally, genetically modified organisms (GMOs) and other synthetic biological entities with the potential of destroying human beings, other life forms and the environment.

The question that has arisen in this area is whether this type of research, and the products and procedures that could result from it, is morally justifiable, given the risks that could be involved. Clearly the opposite question has also been asked, namely why should this type of activity be restricted or prohibited, if at present its harmful potential has not been established.

However, synthetic biology is not the only biotechnological activity about which there has been a debate regarding the potential risks involved. Consequently, treating it differently or more restrictively does not seem justified. Therefore the principles, rules and guidelines that have been outlined and consolidated in the past about biosecurity would also be applicable to synthetic biology since, in fact, there is currently no evidence that would justify the imposition of more restrictive measures. It is precisely in the current situation, more conjectural than based on facts, that it is appropriate to keep the principle of precaution in mind.

Let us consider, then, whether and to what extent the established system is applicable to synthetic biology and what particular issues could arise.

2. Principles of general application

When considering putting specific actions into practice, it is reasonably easy to use low risk products and procedures based on synthetic biology through the application of various principles which provide an adequate response to the anticipated risks.

2.1. The principle of precaution

Amongst the various principles applicable to the use of GMOs, the principle of precaution has become particularly prominent.

The principle of precaution arises as a consequence of seeking the protection of human health and the environment in relation to certain activities, characterised by a lack of sufficient knowledge about the possible consequences of these activities i.e. current scientific knowledge cannot reliably establish the extent of the possible harm that these activities could cause. Consequently the principle of precaution is applied in an environment of scientific uncertainty and suspicion, where it has not yet been shown that the activity subjected to evaluation could be very harmful. The

application of this principle, which has been developed in various fields, is also of great interest to the emerging biotechnologies, including its application to synthetic biology.

The principle of precaution requires a transition from a predictive model (knowledge of the risk and the causal nexus) to uncertainty regarding the risk, because possible harm cannot be determined, and the possible nexus between the one and the other has to be established. This involves statistical calculations and calculating probabilities. Nevertheless, both models come together in the prevention of feared harm, which is their common objective.

It is, therefore, in the context of a lack of, or the limitations of, the conceptual construction of predictability where the principle of precaution plays its role. This also seems to be so in our case, in relation to synthetic biology. Nevertheless, the precautionary principle is not applicable to all risk situations, but rather only to those situations which have two principal characteristics: firstly, a context of scientific uncertainty, and secondly the possibility of particularly serious harm being caused which could be uncontrollable or irreversible.

The principle of precaution does not start from an absolute lack of predictability regarding the future, as it is based on suspicion regarding the risks that a particular activity could bring with it. In short, recourse to the principle of precaution presupposes that the potentially dangerous effects deriving from a phenomenon, a product or process, have been identified, and that scientific evaluation does not make it possible to determine the risk with sufficient certainty.

In the context of the biotechnologies, Jonas himself proposes a fundamental rule for the treatment of uncertainty: "*in dubio pro malo*, when in doubt consider the most pessimistic predictions rather than the optimistic ones, because the stakes have become too high."

Consequently, synthetic biology involves activity where the risks fit well with cautious thought. As a consequence the principle of "*in dubio pro malo*" will also be applicable to such activity. However, synthetic biology impacts on areas where it is difficult to apply certain aspects of the principle of precaution.

The principle of precaution demands a consequent reaction or response. This must always be governed by its moderate or reasonable use, applying measures aimed at the evaluation, quantification and communication of the risk, followed by the adoption of appropriate measures to prevent particularly serious harm. Consequently, in its true meaning (The European Group on Ethics in Science and New Technologies, 2009) despite what has been stated on some occasions the principle of precaution does not advocate paralysing the action under discussion. Neither does it advocate relaxing the application of measures only when science has demonstrated that the possibility of harm is low.

The precautionary principle proposes a different focus. The principle is more widespread in North America. According to this principle it is assumed that the emerging biotechnologies must be considered to be safe, economically desirable,

intrinsically good, except insofar as, and to the extent that, the contrary is demonstrated. (*Presidential Commission for the Study of Bioethical Issues*, 2010). A perspective that is not very different, but more opposed to the principle of precaution, has been defended by Cass R. Sunstein. He describes the principle of precaution as incoherent, as risks exist in all social situations, while precautionary measures themselves can generate their own dangers. Consequently he proposes as an alternative a limited anti-catastrophe principle, designed for more serious risks, and which takes into account costs and benefits and tries to respect freedom of choice.

As can be seen below, there is no shortage of guiding or regulatory principles about biosecurity that in turn mention, are inspired by or derived from the principle of precaution.

2.1.1. The principles of authorisation and inspection

The European Community's legislative policies have from the start wanted to face up to the risks that could result from the biotechnologies, adopting a different perspective to that which was common until then and that has become predominant in other countries (such as the United States). This change of attitude means that the evaluation of risk is not based solely on the analysis of a genuinely or supposedly dangerous product, or on the risks that could derive from it when it is put on the market. Risk is also evaluated before there is a product in the very production process itself, that is to say the hypothetically dangerous techniques or processes are also evaluated. This focus, described as horizontal (as opposed to the previous focus, which was vertical) insists on the idea of prevention. It is inspired by the principle of precaution and is what European Law has ultimately been based on in the last two decades.

In relation to the implementation of these policies it has rightly been indicated that the most important action by the public authorities and civil servants responsible for public health and the environment consists not so much in direct actions for eliminating or preventing risks, as that would be impossible, but instead in managing them with the aim of keeping them within acceptable limits.

Implementing these control and follow up mechanisms in the field of the emerging biotechnologies is achieved on occasions through national commissions responsible for certain activities related to these biotechnologies.

2.1.2. The principles of "step by step" and "case by case"

These principles are very similar to the principle of precaution. In every case they involve taking precautionary measures that prevent leaps in the dark. Each decision or authorisation has to be supported by the requirements of each specific situation and is always based on the experience accumulated in other cases or situations that have already been inspected or authorised.

The "step by step" principle means that a new activity (e.g. freeing biological systems obtained synthetically) is only carried out when the evaluation of the previous steps reveals that it is possible to proceed to the next step without risk.

For its part, the principle of "case by case" consists of evaluating the risks associated with each biological procedure or product individually, without making excessive generalisations.

2.1.3. The principle of traceability

The principle of traceability contributes decisively to ensuring the quality and safety of life forms and biological materials of any nature and origin. From this derives the tendency for it to be required as principle.

Traceability can be defined in our case as the ability to follow the retrospective trail of GMOs and the products obtained that are based on them through the production and distribution chains and similarly for biological systems obtained synthetically. Traceability facilitates the control of the quality of materials and products. If necessary, it is possible to withdraw them from circulation (that is, from unconfined use and commercialisation) or to take other relevant measures in the event of some adverse incident occurring unexpectedly. It is worth pointing out that an effective traceability policy constitutes an important "safety net" when unforeseen adverse events occur, facilitating the adoption of risk management measures, in accordance with the principle of precaution.

The problem that synthetic biology poses in relation to this precautionary measure is the very difficulty of its application, as in reality it is not possible to trace the new biological system as such, as it did not exist previously. Instead, at most, the elements that have been created in the laboratory can be monitored. For this reason, and given the present state of research in this area, it does not seem possible to establish the traceability of each system separately or contribute much to such an aim, and even less so when considering new parts or systems. Nevertheless, in the future, as new and more complex biological systems are developed it will be possible to establish their traceability, but to do this scientists must design specific mechanisms that will make it possible to trace the origin of these products.

VI. ARE THERE LIMITS TO PATENTS IN RELATION TO THE ACHIEVEMENTS OF SYNTHETIC BIOLOGY?

1. The ethical dimension of patents, especially in relation to biotechnology.

In contrast to what the lay person usually thinks, patents, as well as having their own technical and legal aspects, also cause specific moral uncertainties. This is reflected in the very regulation of the sector, something that does not usually occur in other regulatory areas. There was a major ethical debate when the European authorities were considering the explicit recognition in legal regulations of patenting human gene sequences. The decision, taken finally on a second attempt in the European Parliament, was criticised by some specialists on the grounds that it would mean patenting the human body and with it its appropriation. It was also alleged that such recognition could lead to an increase in research costs. Based on various legal decisions that have alluded to this question recently, it is likely that controversy will recur if patenting is extended to mere genetic analysis that predicts certain pathologies.

These problems can still be substantial in the field of synthetic biology. The problems are also more complex in relation to the application of general patenting rules and rules specifically established for biotechnologies. In the latter case, there are notable problems concerning how to recognise a patent in the area of a technology where various sub-products and procedures which are already patentable are combined, as well as problems resulting from their interdisciplinarity and interdependence.

In addition, it is anticipated that there will be conflicts if patents with very wide coverage are awarded. These could arise through the possible use of these patents as mechanisms to achieve the monopolistic use of a product or procedure, when they are used in an abusive manner beyond the legal protection of creative effort and invention. This would probably be contrary to the principle of benefit sharing and would bring the principle of justice into doubt.

2. Are synthetic products obtained through biotechnologies excluded from the patents system?

Notwithstanding the above, the first area to be studied consists of whether or not the particular system established for patenting biological innovations, established in the European Directive (98/44/CE), and the evaluative system implicit therein, would also be applicable to synthetic biology.

2.1. Patents as a form of legal protection for biotechnological inventions: Progress to date

In response to the extensive debate provoked by this issue some years ago, the general response in the European arena has been that the biotechnologies will be protected by law, principally or exclusively through patents. Ultimately any solution other than patenting was ruled out. Establishing the relevant factors that differentiate a discovery from an invention was one of the most controversial points, and has still not been completely resolved.

Special care has been taken to point out that in every case it must be demonstrated that the alleged biotechnological advance or innovation fulfils each and every one of the traditionally recognised requirements of a patent. In addition, European regulations specifically insist that whoever presents the request for the patent must reliably demonstrate the industrial application of the biotechnological product. That is to say, its usefulness must be fully defined and clearly demonstrated. It is, though, true that the interpretation of the two other requirements of the patent (new inventions and not being obvious) have been made more flexible where biotechnologies are concerned.

A great deal of attention has also been given to clarifying precisely what can be patented in biotechnical material and what cannot, both in relation to human biological elements or when the human body is involved in some way, and when animals or plants are affected: in other words, inventions that involve the manipulation of living material, whether plant, animal or human.

So what can be understood to be living material? The regulatory development of the European Patent Convention defines biological material as “material containing genetic information and capable of reproducing itself or being reproduced in a biological system”. As can be seen from this report, whether or not biosynthetic products are capable of reproducing themselves is of key importance in relation to synthetic biology.

In accordance with the general principle, it is possible to patent products that are composed of or contain biological material or procedures which produce, transform or use biological material, provided that they satisfy the traditional requirements of patents, namely that they are new inventions which involve inventive activity and are capable of industrial application. Consequently, a solution can be found to this very sensitive ethical question by considering biological material isolated from its natural environment or produced by means of a technical process to be patentable, even if it already exists in its natural state.

2.2. Non-human biological materials: animals and plants

Inventions involving plants or animals can be patented, if the technical viability is not limited to a particular variety of plant or breed of animal. That is to say, plant varieties and animal breeds, and what are essentially biological procedures for obtaining such plants or animals, cannot be patented.

However, microbiological procedures, or any other technical procedure or product obtained by means of such procedures are patentable. This solution is not new, because their patentability had already been accepted before any consideration was given to their specific regulation. Nevertheless, this recognition still constitutes, at least formally, an exception to the exclusion from patenting of essentially biological processes for the production of plants or animals. The explanation for this regulatory system can be found in that once a micro-organism has been produced it is capable of rapid and abundant self-replication or self-reproduction. Consequently, this requirement would also apply to synthetic biology if the biological product had the ability to reproduce itself. But if the product lacks this ability, it could be patented as inert material.

Based on this more flexible regulatory system, the European Patent Office (EPO) has accepted the patenting of transgenic animals (such as the Harvard OncoMouse), despite opposition to it based on the argument that this patent would be contrary to morality and public order. The patenting of plants, specifically certain varieties of maize, soya and medicinal plants has also been recognised.

2.3. The specific regulation on elements of the human body

Regarding human biological material, as has already been discussed above, the ethical debate resulted in a favourable attitude towards such patenting. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene,[...] even if the structure of that element is identical to that of a natural element, can be considered as a patentable invention. By contrast, the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.

Consequently, the classic system of biopatents will apply to biosynthetic products and procedures since, given their more specific technical characteristics, in many cases they would not consist of the mere isolation or reproduction of gene sequences in the laboratory, but rather in new combinations of them. This observation is relevant in relation to the debate that has been generated, and which from time to time re-emerges leading to heated discussion about the true nature of the isolation or reproduction of parts of genes in the laboratory. Those who are against such patenting argue that these products and procedures be excluded.

In fact, this crucial discussion is on-going, at least intermittently, focussing on whether the sequencing of a gene or a genetic fragment that has been isolated in the laboratory or obtained by another technical procedure really constitutes inventive activity. It has been pointed out that a gene or a functional fraction of DNA can be linked to a chemical molecule, but an essential difference persists. This is based on what is really interesting about this molecule, namely the genetic information it carries and not the medium as a whole. If the structure of the information is identical to a natural element, it constitutes a discovery and not an invention. Consequently,

given the official European position, the technical reproduction or isolation of that information would not constitute an inventive activity, which is an essential prerequisite for the recognition of a patent. This is without prejudice to the fact that the technical procedure of reproduction or isolation of the human body element (the DNA sequence) can, in itself, constitute an inventive activity.

This discussion is not yet closed. In fact, in 1998 the United States Patents and Trade Marks Office accepted the patenting of two human genes responsible for breast and ovarian cancer in women (BRCA1 and BRCA2) the early detection of which is highly effective in preventing these cancers. However, subsequently in 2010 a North American district judge annulled the patent of both genes, because it was considered that the mere purification of these genes does not on its own modify an essential characteristic of the DNA, namely, its nucleotide sequence, or more precisely the capacity to detect mutations in these genes. The susceptibility of these patients to develop a cancer depends on whether the essential characteristics of the genes remain unaltered. Consequently, the purified genes are not something different from that which exists in nature. But in July 2011, an appeal to the Supreme Court partly overturned the decision, partly reverting to the previous situation, by recognising the patent under discussion in its ruling. However, warning was given that this would not extend to analyses of genetic sequences to determine the predisposition of patients to these illnesses. The discussion has resumed and nobody fails to recognise the major importance it can have from many different points of view (clinical, ethical, legal, economic).

This discussion of more ethical profiles could be presented in a different way in the area of synthetic biology, given its procedures and the characteristics of the most innovative products that could be obtained.

2.4. The general limit of public order and morality and its specific impact on biosynthetic products

The European patents system excludes patents on inventions where their exploitation is contrary to public order or morality. However, in reality it has never been applied, either by the EPO or by any other national court within the European Union, except as described below. Nevertheless there is no doubt that, at least theoretically, these general exclusion clauses could serve to object to some inventions derived from synthetic biology through their being especially alarming in the broadest ethical-social terms.

In any event, it constitutes an explicit recognition that the patenting of certain inventions poses moral dilemmas, as they involve both the concept of public order and, yet more clearly, moral order. This ethical dimension of patenting becomes yet more apparent when it has been considered necessary to specifically state that there is a risk to public or moral order but only in the field of biotechnologies. Certain products or procedures related to biotechnologies have been explicitly excluded from patenting as a consequence. This, as we have said, has not been considered to be necessary in relation to patents on inert objects.

We can see now how this type of restriction extends to synthetic biology.

2.5. The explicit exclusion from patenting of some procedures or biotechnological products.

As a result of the implementation of this general clause on unpatentability, some specific exclusions have been established, all of which concern biotechnologies. Thus, in relation to human biological material, the processes for cloning human beings, processes for modifying the germ line genetic identity of human beings and the uses of human embryos are excluded.

Recently, the European Court of Justice (Grand Chamber) in its sentence of 18 October 2011 established an interpretation for all the member states regarding the patenting exclusion clause in relation to procedures which use human embryos. Understandably, this sentence could have direct repercussions on the emerging biotechnologies, and it is likely that there will be intense debate in the sector.

In regard to animals, processes for modifying the genetic identity of animals which are likely to cause them suffering or physical harm without any substantial medical benefit to man or animal, and also animals resulting from such processes, are not considered to be patentable.

3. Hypothetical limits specific to patenting the products and processes of synthetic biology

Some possible conclusions related to biopatents and synthetic biology:

If material not capable of replication is involved, the products and procedures obtained will be subject to the general rules on patenting i.e. will lie outside the area of law relating to biotechnologies. From the point of view of the legal requirements of such a regulatory system, material capable of replicating itself will be excluded from patenting.

If, on the contrary, material capable of replicating itself and which constitutes some new, simple life form (artificial life) is involved, the invention would be subject to the specific rules intended for this type of living organism. That is to say, as has been discussed above, currently the patenting of micro-organisms is allowed, from the legal point of view, understanding these to be not only unicellular organisms but also other simple multicellular forms that could be created in the laboratory.

The laboratory creation of more or less complex multicellular living organisms seems to be an aim of synthetic biology that is only achievable in the medium to long term. And it is unthinkable, at least based on current scientific knowledge and technology, that it would be possible to "create" or "recreate" higher animals, specifically mammals. Consequently it seems unnecessary to evaluate this possibility, taking current axiological parameters as a starting reference point. Therefore it seems advisable at the moment to leave their evaluation for some time in the future. Nevertheless, according to current European legislation, the patenting of such

hypothetical, substantially "recreated" mammals would be acceptable. However, the hypothetical future creation of human beings would probably come under the limiting clause on morality and public order, particularly during the initial embryonic phase.

VII. FINAL CONSIDERATIONS

There is no doubt about the interest synthetic biotechnology generates, both as a scientific achievement, although it has yet to show more innovative achievements, and in relation to the contributions that it could make towards the strengthening of biotechnological applications in various sectors of industry.

We will probably have to wait for some time in the future to examine what a more developed and powerful synthetic biology, by then capable of creating various life forms, can mean for our understanding of life and life forms, both in their simplest and more complex forms.

From the ethical and legal point of view, the existence of synthetic biology may not lead to totally new regulation and reflection as, except for some specific aspects, it shares the essential features of other, currently better known and better evaluated emerging biotechnologies.

In fact, an objective axiological analysis of the biotechnologies, especially the emerging biotechnologies, which for us includes synthetic biology, has made it possible to accommodate a set of regulatory principles that have been specifically developed in this very particular context. Thus, principles and duties, such as freedom of research and responsibility, effectiveness, precaution, biosecurity and sustainability or sustainable development, amongst others, have been included in and covered by the regulations for the sector, in general in a highly efficient manner.

The regulatory principles established in the European framework for certain biotechnologies, particularly those relating to GMOs, are also applicable to the procedures and products associated with synthetic biology. If in the future such regulations are found to be inadequate for new developments in synthetic biology the competent authorities would proceed to review and modify them. For example, the regulations in this area include provisions which could serve as a basis for a traceability system for GMOs. However, it is true that it does not contain a definition of the concept or its objectives, nor a complete proposal for implementing such a system. In addition, its applicability to biosynthetic elements is doubtful.

Observing the principles mentioned in this paper should not result in any significant restriction to the development and commercialisation of new synthetic bio-products in the various sectors concerned, such as the agro-food and health industries. This does not exclude conforming to certain procedures relating to human rights, the dual use of technologies, biosecurity, public participation and, in the final analysis, the individual and collective responsibility of scientists.

Synthetic biosecurity and the way in which, from its beginnings, it has raised objections and ethical uncertainties seem to us to be a clear example of the practice of good science and good ethics. We should possibly welcome this development as a promising example of the future relationship between ethics and research and the stimulating (and not discouraging) effect that ethical reflection can have on researchers' inventiveness.

These issues are at the forefront of knowledge and its applications. Even when there are doubts, problems must be presented unambiguously, using open and considered reflection to reach ethical conclusions which are as clear as possible. Only discussion and consideration of the true possibilities of this research will make a clear vision for science and ethics possible. A debate that is both serious and adds clarity will only be possible if those attitudes that intentionally try to distort it are separated out and the real perspectives are evaluated. At the same time, the freedom of the scientist is the greatest risk. It is not possible to maintain the advantages of freedom and independence while trying to escape from the associated responsibilities. Thus, our relationship with scientific freedom above all also means linking it very closely to responsibility.

VIII. RECOMMENDATIONS

Given the considerations discussed in this paper, the Portuguese National Ethics Council for the Life Sciences and the Spanish Bioethics Committee, after their meetings in Lisbon and Barcelona on 8 November 2010 and 24 October 2011 respectively, made the following recommendations:

1. Synthetic biology represents a potentially beneficial development for humankind in a wide variety of sectors, especially the health sector. Its development must therefore be supported though the necessary precautions must always be taken.
2. Synthetic biology does not raise completely new issues, and for this reason its evaluation should be carried out using the same criteria as have been applied to the ethical and legal analysis of other emerging biotechnologies and not in isolation from these. Therefore the science research funding bodies must also finance parallel research into the ethical, legal and social aspects of synthetic biology projects that have been approved.
3. In relation to the safety of synthetic biology, once again the task of risk management has been decided to be the best solution for activities and products that are not expressly prohibited by law, but which require monitoring and follow-up. This should include their potential dual use. This involves subjecting the activity that involves the production or use of organisms to prior authorisation as well as its periodic monitoring and inspection. This should always be subject to the flexible criteria based on the principle of precaution.
4. Activities related to synthetic biology must be carried out gradually, step by step. Progression to the next step will depend on the evaluation of the previous steps in terms of the protection of human health and the environment showing that it is reasonably safe to pass on to the next step. In addition, each activity should be evaluated individually, that is to say, case by case.
5. The public and scientific authorities, companies, entrepreneurs, and media professionals must assume the responsibilities corresponding to their various tasks and duties, in such a way that they direct their actions towards benefiting the community and the general interest.
6. Scientists must provide adequate and precise information so that public authorities, in accordance with their responsibilities, ensure participation by the public and transparency in defining policies relating to the emerging biotechnologies. As a consequence of the responsibility of the scientists, self regulation and transparency, insofar as they serve the general interest, are adequate for achieving an effective and efficient prevention of the risks associated with the use of synthetic biology, and for the protection of consumers' interests through the mechanisms of public participation.
7. The scientific research institutions and the financing bodies must ensure that

research teams have sufficient command of the necessary techniques and sufficient ethical training.

8. The competent authorities should evaluate any new issues that could arise in relation to patenting the processes and products derived from synthetic biology since, due to their potential economic impact, the patenting of these developments could violate the ethical principle of justice.
9. The creation of commissions at a national, autonomous community and/or local level is recommended. These would be responsible for monitoring, supervising and following up activities related to the emerging biotechnologies, including synthetic biology, or for delegating these responsibilities to other suitable bodies already in existence. These professional bodies could also carry out executive functions, issue related reports or authorise or carry out monitoring, supervision and follow-up functions where this has been established by law. Alternatively they could assume merely advisory functions. In all cases, all projects that are approved in this area must have prior consent from the relevant responsible institution.

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