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GM Animals: the quest through science and ethics

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GM animals: the quest through science and ethics

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ABSTRACT: The question of animal welfare in clinical research is particularly fascinating per se, but it acquires a completely different nuance when it is combined with the issue of genetically modified animals and their legitimation. The paper aims to provide a critical, ethical-legal focus on the actual use of GM animals in the field of clinical research, how they are created and whether there is exhaustive legislation covering gene-editing in animals. The legal focal points will be presented through an active synchronization of the regulations at European level and their implementation on Italian soil. Finally, the provocative character of the topic will advance the issue of a further development in the utilization of GM animals in clinical research, providing also an insight on the possible evolution of the protocols which might erase completely the biological component to substitute it for virtual models under the impulse of artificial intelligence.

KEYWORDS: Gene-editing, GM animals, Directive 86/609/EEC, Directive 2010/63/EU, Animals Rights

SUMMARY: 1. Introduction – 2. A powerful duo: the scientific-juridical nuances of GM animals manufacture – 3. The ethical implications of animal welfare: the dichotomy of rights and suffering – 4. New horizons – 5. Conclusions

1. Introduction

The era of genetic engineering officially opened its doors to the scientific world in 1973, when Stanley Cohen and Charles Boyer created the very first "chimeric" DNA molecule *in vitro*, demonstrating it could be efficiently propagated in bacterial cultures. Thus, the prospective of a rapid yet powerful evolution of recombinant DNA technologies sparked as much enthusiasm as doubts with regards to those genetic manipulation experiments which were considered more dangerous. The Asilomar convention of 1975 gave birth to an extremely rigid security protocol[1] on the matter, however, with the passing of time, the more scientists gained knowledge and experience, the more these rules were progressively loosened. It wasn't until the 1980s, however, that the very first human and animal proteins were produced in bacteria, paving the way for the first appearance of a transgenic mammal; in 1980, the so called "super-mouse" (endowed with enormous proportions as a result of the inoculation of rat growth hormone) conquered "Nature" 's cover. A couple of years later, another mouse, the "onco-mouse" (bearer of a mutated oncogene that made it the subject of a model for oncology studies) became the first ever patented transgenic mammal :« The development of microinjection techniques to create transgenic animals stood beside the already established knowledge scientists had of embryology and in vitro fertilization because already implemented in laboratories and farms»[2]. Production and manipulation techniques of animal embryos advanced rapidly and

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[1] P. BREG, D. BALTIMORE, S. BRENNER, R. O ROBLIN III, M.F. SINGER, *Summary Statement of the Asilomar Conference on Recombinant DNA molecules,* Proc. Nat. Aca. Sci. USA, Vol. 72, No. 6, pp. 1981-1984, June 1975.

[2] G. POLI, *Biotecnologie conoscere per scegliere,* Milano, 2001, p. 9.

in the 1990s a wide range of transgenic domestic animals was obtained and was finalized to support human medical therapy. It was then, that animal embryos manipulation started navigating towards cloning. Only a few years later, in 1996, Dolly the sheep was born; the first ever mammal cloned through nuclear transplant[3]. Needless to say, the advent of this practice opened the debate over the scientific, the ethical and the juridical aspects cloning brought about at international level. That is why we now refer to GM animals as:« animals whose genetic material has been deliberately altered in some way by insertion, deletion or substitution of DNA»[4].

But the question we are now faced with is the following: how are transgenic animals made? It is, nowadays, possible to transfer genes of whichever nature (microbial, plant-based, animal) either in plant seeds or in a fertilized animal egg cell so as to create transgenic plants or animals, characterised by new "features" which they would have never acquired through natural techniques: « To insert a new gene in an animal, in order for this trait to show up in its progeny, it is necessary to insert it as early as possible, therefore, when the subject is composed of very few cells or even of the fertilized oocyte»[5]. For obvious reasons, much of what is involved is technical in nature so it will not be discussed in detail here, moreover this not being the main purpose of the paper. Suffice to say that as of today, there are five different consolidated methods to introduce the DNA of interest into zygotes or embryos of the animals to be modified:

1. Integration of retroviral vectors into the embryo at an early stage
2. DNA microinjection into the male pronucleus of a newly fertilized oocyte
3. Incorporation into the embryo at a very early stage of genetically modified totipotent embryonic cells (ES cells)
4. Sperm-mediated gene transfer
5. Transfer of genetically modified nuclei into denucleated oocytes[6]

One important welfare issue for GM animals, aside from the obvious outcome of their genetic modification, is the poor efficiency (on-target efficiency), and associated undesired (off-target) effects, of the process. On-target efficiency has increased and off-target effects have decreased significantly with the relatively recent discovery of new methods especially the RNA-guided *programable nuclease* gene-editing platform, CRISPR (CRISPR/Cas9 system) which is composed of :« a single guide RNA molecule which is specifically designed to seek and bind to precise targets in the genome that are to be modified; and an associated enzyme, Cas9,

[3] G.POLI, *op.cit.,* p. 9.
[4] J. BAILEY, *Genetic Modification of Animals: Scientific and Ethical Issues,* edited by K. HERRMANN and K. JAYNE, *Animal experimentation: Working towards a Paradigm Change,* Boston, 2019, p. 443.
[5] G. POLI, *op. cit.,* p. 63.
[6] This list has as its sole purpose that of informing the reader about the available gene editing techniques and will not be discussed in depth. If interested, consult G. POLI, *op. cit.,* pp. 63-64.

which cuts the DNA at the target site and initiates the genetic modification process»[7]. While this method is generally considered to be much more efficient and specific compared to other approaches, any accurate, definitive, quantitative estimation of the efficiency of CRISPR is difficult to find, as estimates vary considerably and are affected by many factors, including the nature of the target site and the CRISPR molecule used[8]. Regardless, this paper aims to provide a critical viewpoint of the quest for animal wellbeing in clinical research by succinctly yet comprehensively navigating through jurisprudence that has been adopted both at EU level and subsequently implemented into the Italian reality. The author will also analyze the shift in the use of animals in experiments, the purposes for which they have been primarily conceived and then created, and also will move on, without being overly technical, to question herself regarding the ethical issues that animal gene editing carries.

2. A powerful duo: the scientific-juridical nuances of GM animals manufacture

The main declinations of the use of genetically modified animals can be classified under three broad categories:

1. As models for human pathologies
2. For the production of recombinant life-saving drugs
3. As organs and tissues donors for transplantation[9]

With regards to the first category, it is now well established that a vast variety of human diseases lack an equivalent animal model; this not only affects, but also delays research efforts for the development of therapeutic molecules to treat these pathologies: « thanks to recombinant DNA techniques, it was possible to produce transgenic animals carrying genetic lesions identical to those responsible for some human hereditary diseases»[10]. A concrete example of this practice is a mouse of strain "C57BL6-apoEtm.Unc", meaning a "mutant" lacking alipoprotein E, which is able to develop atherosclerotic lesions superimposable on similar human lesions. Nevertheless, one of the most prominent and promising applications of GM animals is the study of oncogenesis; through the use of transgenic mice, it was possible to carry out some investigations which previously were unthinkable of merely through the use of in vitro cultures[11]. A further field in which GM animals have and are being heavily resorted to is that devolved to the production of pharmacological molecules, also known as "gene farming" [12]; the principles on which such a practice is based are seldom but one stands out more than others: such genetically modified animals can be replicated

[7] J. BAILEY, *op. cit.,* pp. 445-446.
[8] J. BAILEY, *op. cit.,* p. 446.
[9] G. POLI, *op. cit.,* p. 94.
[10] *Ibidem.*
[11] D. HANAHAN, E.F. WAGNER, R.D. PALMITER, *The origins of oncomice: a history of the first transgenic mice genetically engineered to develop cancer,* in *Genes & Development,* 2007 http://genesdev.cshlp.org/content/21/18/2258.full.html (last visited: 17.05.20)
[12] G. POLI, *op. cit.,* p. 94.

identically an infinite number of times through cloning: « the main advantage lies in the fact that the transgene is directed to a targeted point of the genome, which therefore allows it to be expressed on the site at the most suitable moment»[13]. With regards to the last category, as presented above, the use of GM animals has landed on the field of transplantation (xenotransplantation to be exact) which sees these creatures as potential organs and tissues donors to use for human medicine[14]. This quest was actually due to the combination of the outstanding lack of human organs availability and the pressing requests many needing patients advanced. With regards to xenotransplantation, researchers have been trying to isolate those species which seem most fit to undergo such a practice and the results are quite fascinating: «the use of non-human primates as organ donors for humans is at high risk: these animals could transmit dangerous viruses such as SIV and STLV, herpes *simiae* (similar to HSV) and, last but not least, the Marburg and Ebola viruses. Xenotransplantation from pigs is instead considered low risk: donors are in fact bred in germ free environments much more easily than primates». [15]

The main questions we are now faced with are the following: considering the pace at which genetic engineering is going, how can the law keep up? Is there any legislation covering gene alteration in animals? And if the question is to be answered in the positive, what are the focal points taken into account? Is it static or dynamic? Does it act in the immediateness of the moment or else, it sponsors a more future oriented approach to the matter? It is worth mentioning how the European Parliament, in its resolution B4-0209, 0213, 0214, 0225, 0242/97 on animal and human cloning confirmed its negative position against the practice as already set forth in its resolutions of 1989 and 1993. Furthermore, more recent jurisprudence on the matter does include, for instance, Art 3 of the EU Charter of Fundamental Rights which advocates for the prohibition of cloning as a reproductive practice[16], *de facto* neither authorising nor prohibiting other forms of cloning; thus, it does not prevent the legislature from disallowing other declinations of the practice. Therefore, considering that cloning invests a new ethical sphere, it represents a serious violation of fundamental human rights since, by allowing a eugenic and racist selection, it invalidates the principle of equality between men, offends their dignity and makes them, necessarily, the object of experimentation[17]. However, with regards to animal cloning, the European Economic and Social Committee advanced a Proposal for a Directive of the European Parliament and of the Council on the cloning of animals of the bovine,

[13] G.POLI, *op. cit.,* p. 95-96.
[14] *Ibidem.*
[15] G.POLI, *op. cit.,* pp. 96-99.
[16] FRA (European Union Agency for Fundamental Rights), European Charter of Fundamental Rights, Art 3 (2) (d) https://fra.europa.eu/en/eu-charter/article/3-right-integrity-person#TabCaseLaw (last visited 17.05.20).
[17] Res. B4-0209, 0213, 0214, 0225 and 0242/97, letter B.

porcine, ovine, caprine and equine species kept and reproduced for farming purposes in 2013[18] where it believes it: « necessary and appropriate to regulate cloning of animals in the EU with the aim of ensuring uniform conditions of production for farmers, while protecting the health and welfare of animals and the expectations of consumers»[19]. The EESC, then, in section 1.1.2 of the Opinion does adhere to the general tendency as set forth by consumer organisations, in accordance with public opposition, to temporarily suspend animal cloning and imports of animal clones for farming purposes in the EU[20]; nevertheless it does not forestall the ban to the area of research-oriented cloning for which, the EESC claims, the use of the technique is justified (sec. 1.1.4)[21].

Now diverting from the above-mentioned reference, in terms of European involvement in the matter of animal welfare, of great relevance is Dir. 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes. Art 1 reads as follows: « The aim of this Directive is to ensure that where animals are used for experimental or other scientific purposes the provisions laid down by law, regulation or administrative provisions in the Member States for their protection are approximated so as to avoid affecting the establishment and functioning of the common market, in particular by distortions of competition or barriers to trade»[22]. As it is clearly portrayed by the text, the directive seeks to set minimum standards for housing and care, and for the training of personnel handling these animals and supervising the experiments; the possibility for states to apply more invasive policies is clearly spelled out in Art 24 which states that the

[18] Opinion of the European Economic and Social Committee on the 'Proposal for a Directive of the European Parliament and of the Council on the cloning of animals of the bovine, porcine, ovine, caprine and equine species kept and reproduced for farming purposes' COM(2013) 892 final — 2013/0433 (COD) 'Proposal for a Council Directive on the placing on the market of food from animal clones' COM(2013) 893 final — 2013/0434 (APP) 'Proposal for a Regulation of the European Parliament and of the Council on novel foods' COM(2013) 894 final — 2013/0435 (COD), EUR-Lex https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52014AE0933 (last visited 17.05.20).

[19] Opinion of the European Economic and Social Committee on the 'Proposal for a Directive of the European Parliament and of the Council on the cloning of animals of the bovine, porcine, ovine, caprine and equine species kept and reproduced for farming purposes' COM(2013) 892 final — 2013/0433 (COD) 'Proposal for a Council Directive on the placing on the market of food from animal clones' COM(2013) 893 final — 2013/0434 (APP) 'Proposal for a Regulation of the European Parliament and of the Council on novel foods' COM(2013) 894 final — 2013/0435 (COD), section 1.1.1, EUR-Lex https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52014AE0933 (last visited 17.05.20).

[20] Opinion of the European Economic and Social Committee on the 'Proposal for a Directive of the European Parliament and of the Council on the cloning of animals of the bovine, porcine, ovine, caprine and equine species kept and reproduced for farming purposes' COM(2013) 892 final — 2013/0433 (COD) 'Proposal for a Council Directive on the placing on the market of food from animal clones' COM(2013) 893 final — 2013/0434 (APP) 'Proposal for a Regulation of the European Parliament and of the Council on novel foods' COM(2013) 894 final — 2013/0435 (COD), section 1.1.2, EUR-Lex https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52014AE0933 (last visited 17.05.20).

[21] Opinion of the European Economic and Social Committee on the 'Proposal for a Directive of the European Parliament and of the Council on the cloning of animals of the bovine, porcine, ovine, caprine and equine species kept and reproduced for farming purposes' COM(2013) 892 final — 2013/0433 (COD) 'Proposal for a Council Directive on the placing on the market of food from animal clones' COM(2013) 893 final — 2013/0434 (APP) 'Proposal for a Regulation of the European Parliament and of the Council on novel foods' COM(2013) 894 final — 2013/0435 (COD), section 1.1.4, EUR-Lex https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52014AE0933 (last visited 17.05.20).

[22] Directive 86/609/EEC of the Council of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86/609/EEC),1986 OJ (L 358), 1 (CE), Art. 1.

Directive in question shall not restrict the right of Member States to apply or adopt stricter measures for the protection of animals used in experiments or for the control and restriction of the use of animals for experiments[23]. Most importantly, it must be highlighted the very nature of the directive which sees animal welfare as strongly valued and its protection emphasised in Art 7 (4): «All experiments shall be designed to avoid distress and unnecessary pain and suffering to the experimental animals. They shall be subject to the provisions laid down in Article 8. The measures set out in Article 9 shall be taken in all »[24] as well as Art 9 (1):« At the end of any experiment, it shall be decided whether the animal shall be kept alive or killed by a humane method, subject to the condition that it shall not be kept alive if, even though it has been restored to normal health in all other respects, it is likely to remain in lasting pain or distress»[25]. Finally Art 3 provides a clear list of the purposes which the use of animals in experiments shall fulfill: «This Directive applies to the use of animals in experiments which are undertaken for one of the following purposes:

(i) the development, manufacture, quality, effectiveness and safety testing of drugs, foodstuffs and other substances or products

(ii) for the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in man, animals or plants

(iii) for the assessment, detection, regulation or modification of physiological Conditions in man, animals or plants

(iv) the protection of the natural environment in the interests of the health or welfare of man or animal»[26].

On a territorial level, it is of quite remarkable interest to introduce the national transposition of the document in question which, with regards to the Italian reality, is depicted by legislative Decree No. 116 of January 27th 1992 on the matter of animal protection in clinical research settings. Overall, the implementing decree does not seem to be adopting any restrictions of a more intrusive nature than the ones already provided for in the original Directive, in fact it does not prescribe any other additional tools than the ones already listed in the European text. However, there are quite a few relevant discrepancies between the Legislative Decree in question and the Legislative Decree No. 26 of March, 4th 2014 which abrogated the former one. Therefore, it

[23] Directive 86/609/EEC of the Council of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86/609/EEC),1986 OJ (L 358), 1 (CE), Art. 24.

[24] Directive 86/609/EEC of the Council of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86/609/EEC),1986 OJ (L 358), 1 (CE), Art 7 (4).

[25] Directive 86/609/EEC of the Council of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86/609/EEC),1986 OJ (L 358), 1 (CE), Art 9 .

[26] Directive 86/609/EEC of the Council of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86/609/EEC),1986 OJ (L 358), 1 (CE), Art. 3.

should not come as a surprise, that with the entry into force of Directive 2010/63/EU on the protection of animals used for scientific purposes, the European Parliament tried to mitigate the ever growing divergences between Member States that had sprung up in the previous years:« Certain Member States have adopted national implementing measures that ensure a high level of protection of animals used for scientific purposes, while others only apply the minimum requirements laid down in Directive 86/609/EEC. These disparities are liable to constitute barriers to trade in products and substances the development of which involves experiments on animals. Accordingly, this Directive should provide for more detailed rules in order to reduce such disparities by approximating the rules applicable in that area and to ensure a proper functioning of the internal market»[27]. The new Directive includes significant improvements from the guidelines provided by the former 1986 text; for instance, the range of animals under the scope of the Directive has been enlarged (Art 3, (a), (i), (ii), b) and furthermore, the core of the text revolves around the 3R's system[28]: a widely accepted ethical framework for conducting scientific experiments using animals humanely. It is interesting to note that: « The 1986 Directive, instead, contained no direct reference to the 3R's, although it requested the use of alternative methodologies if available, the use of the minimum number of animals through which it is possible to obtain the established scientific goals, the housing and the maintenance of the animals at the highest levels and the reduction, where possible, of pain, suffering and anxiety»[29]. As it can be clearly deduced from the wording of the Directive, the main concern presented deals with the measure in which living animals who are bred and conceived for undergoing scientific experiments can experience pain and suffering; it is quite astonishing, to say the least, how the text makes animal distress its focal point. For the first time animal anguish is quantified and is equally revolutionary the extension of the application of the scope of the Directive to GM animals. Replacement is another extremely relevant point of the text and it is defined as ensuring:« wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals shall be used instead of a procedure that involves animals.»[30] ; following this pattern, the term reduction within the meaning of the wording of the Directive, is to be understood as reducing animal numbers to as few as possible without compromising the objective of the project whereas refinement is defined as minimising or eliminating possible harm, distress or lasting pain to the animals. With the entry into force of the new Directive, Legislative Decree No. 116 of January, 27th 1992 is thus abrogated and substituted by Legislative Decree No. 26 of March, 4th 2014 which, contrary to popular belief, is not a piece of legislation concerning the scientific aspects of animal experimentation exclusively,

[27]Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals used for Scientific Purposes, 2009 OJ (C 227), 51 (EU) [Directive for the Protection of Laboratory Animals].
[28]Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals used for Scientific Purposes, 2009 OJ (C 227), 51 (EU) [Directive for the Protection of Laboratory Animals].
[29] I.R. PAVONE, *Animal experimentation and animal welfare in the context of the European Union: reflections on the Directive 2010/63 and its transposition in Italy,* in *BioLaw Journal- Rivista di BioDiritto,* n.3/2015, p. 83.
[30] I.R. PAVONE, *op. cit.,* p. 84.

but more so animal welfare. According to the wording of Art 1 (2) Legislative Decree No. 26 the object and the scope of application of the norm is as follows:« the use of animals for scientific or educational purposes is allowed only when, to obtain the desired result, it is not possible to use another scientifically valid, reasonably and practically applicable method or testing strategy that does not involve the use of live animals»[31]; furthermore, the 3R doctrine here is strongly reiterated within the formulation of Art 1 (1) (a) disciplining the following aspects:« the replacement, the reduction of the use of animals in procedures and the improvement of breeding, housing, care and use of animals in procedures»[32]. Following this line of thought, the application of the concept of improvement is contemplated not only in the field of experimental procedures but also in the sphere of tutelage of animal welfare from birth to death. Speaking of death, the dimension of respect towards animal life is well encapsulated by Art 3 (1) (a) which, for the first time, extends its scope also to the protection of GM animal lives:« procedure [is to be understood as] any use, invasive or non-invasive, of an animal for experimental or other scientific purposes with a known or unknown result, or for educational purposes, which could cause the animal a level of pain, suffering, distress equivalent or greater than that caused by inserting a needle according to good veterinary practices. This includes any action that intends or can determine the birth or hatching of an animal or the creation and maintenance of a line of genetically modified animals with a suffering phenotype under these conditions. Suppression of animals with the sole use of their organs or tissues is excluded from the definition»[33].

GM animal welfare is also envisaged further in to the document, specifically in Art 17 (1) on the termination of the procedure:« A procedure ends when it is not necessary to make further observations or, in the case of new lines of genetically modified animals, the transmission of the genetic alteration has not given rise or is not expected to give rise to a certain level of pain to be experienced by the descendants, equivalent or higher suffering than that caused by inserting a needle.»[34].

Under the light cast by the aforelisted elucidations, this section of the paper had as its sole scope that of confuting the belief that GM animals are not worthy of legal protection because they are seen essentially as non-natural products of human development. Although this conception is peculiar to the author's understanding of the issue, this voluntary lack of anthropomorphism towards genetically altered creatures is fortunately not envisaged in the new Directive 2010/63/UE which, on the contrary, conveys an important message of cohesion and inclusiveness in the scientific world.

[31] Leg. Decree No. 26 of March, 4th 2014, Art 1 (2).
[32] Leg. Decree No. 26 of March, 4th 2014, Art 1 (1) (a).
[33] Leg. Decree No. 26 of March, 4th 2014, Art 3 (1) (a).
[34] Leg. Decree No. 26 of March, 4th 2014, Art 17 (1).

3. The ethical implications of animal welfare: the dichotomy of rights and suffering

Given that biomedical biotechnology is prone to give rise to numerous questions of human bioethics, it is also as vitally important to acknowledge one of the many characteristic traits of the biotechnological process which sees the complex phenomenon of the social integration of biotechnologies into our community as a fundamental pillar. The quite distinctive aspect of the practice entails the emphasising of the various existing links between humans, living creatures and the environment, in the sense that the effectiveness of many biotechnological innovations be evaluated within these three spheres[35]. The biotechnological discourse makes the categorization of bioethics under the above-mentioned heads rather problematic, considering that the most distinctive feature of biotechnology is its pervasiveness[36]. The debate concerning the intervention or not within the context of the ethical discourse is still ongoing: the main argument against lawmaking in the field puts forth the difficulty of unifying rather diverging moral and/or religious conceptions, thus in the very latest years, the urgent issues caused by the absence of codified rules in the bioethical reality have rapidly led national systems to adopt legal regulations regarding some of the most pivotal aspects of bioethics. Moreover, in the European context, an attempt of this magnitude is constituted by the Oviedo convention (April, 4th 1997) aimed at conveying a balanced understanding of bioethics in order to safeguard a common European patrimony of values whilst respecting national sovereignty and states' diversity[37].

As it has been largely discussed already in the previous sections of this paper, animals are fundamental for the purposes of biotechnology; both at international and at European level there exists a neat distinction between laboratory animals and farm animals[38]. This categorization will bring about different legal consequences as according to the group taken into consideration, due to the fact that normative attention will focus on those animals which are subject to greater suffering, namely laboratory ones[39]: « The greatest bioethical concern relating to animals is that of suffering inherent in their living conditions and therefore of the moral limits that human beings must place when abusing other living creatures for their own purposes»[40].

The question of animal anguish can be traced back to the XVIII century, when the British philosopher Jeremy Bentham supported the idea that we should not ask ourselves whether animals can think, reason or perhaps even talk, but more so if they can suffer[41]. The most recent debate on the matter was opened by the philosopher Peter Singer in 1975 with his essay entitled "Animal Liberation" which aims at denouncing the utterly unacceptable moral prerogative which is typical of human beings and which is based on the alleged superiority linked to the mere possession of rational faculties. Alongside Bentham, Singer actually located

[35] G. POLI, *op. cit.*, p. 243.
[36] *Ibidem*.
[37] *Ivi*, p. 244.
[38] *Ivi*, p. 247.
[39] *Ibidem.*
[40] *Ibidem.*
[41] Ivi, p. 248.

the prerequisite for defining morally relevant subjects in the latter's ability of feeling both pleasure and pain[42]. Another philosopher, Tom Regan, continued the fight for the protection of animals by radically affirming that not only do animals have interests, but they are also rights bearers, in particular they have the right to see their lives be respected in a measure not inferior to the value we attribute to human lives: « both are equipped not only with sensitive faculties, but also with cognitive abilities that make them "subjects of a life", that is to say, be able to express preferences with respect to one's own life»[43]. Despite the inevitable differences, there is, among animal rights philosophers, a certain degree of agreement in considering that at least the most human resembling creatures (for both appearance and cognitive skills) should be the recipient for more detailed regulatory reforms.

The main recurring element in animal rights philosophies is the blatant rejection of speciesism[44], understood as discrimination on the basis of one's belonging to a determined species; both Singer and Regan effectively managed to demonstrate how the practice is a mere prejudicial discrimination through the argument of "marginal cases" :« this expression refers to human beings who, due to physical or psychic pathologies, age or trauma, do not possess the cognitive faculties which are normal endowment of the human species. Even in this condition, these subjects continue to enjoy the treatment reserved for all men, precisely for the respect that is due to them as suffering beings. However, their diminished condition makes them, in Singer and Regan's judgment, very similar to animals, who do not reason but suffer. Consequently, if marginal humans have interests or rights that are respected, then animals must also be respected in their interests or rights»[45]. Regardless of the pivotal role animal rights theories have played in the debate over animal welfare, they are still the target of both pragmatic and theoretical objections which have steered the general understanding of the matter away from such an anthropogenic conception, in order to promote a different appreciation of the relationship between human beings and animals; the theory of animal welfare is better seen as a reformist position backed by objective scientific evidence[46]. According to the general wording of the animal welfare thesis, animals' moral relevance does not prevent them from being abused to satisfy human utility, yet it imposes that their fruition take place in the respect of their quality of life; as observed by animal welfare theorists Broom and Johnson[47], the emphasising of the issue of animals' rights has obscured the consideration for their wellbeing, the understanding of the biological meaning of pain, and the investigation on the different modalities of anguish in animal species. Nevertheless, the most advanced

[42] *Ibidem.*
[43] *Ibidem.*
[44] *Ibidem.*
[45] *Ibidem.*
[46] Ivi, p. 249.
[47] D.M. BROOM, K.G. JOHNSON, *Stress and Animal Welfare,* Chapman & Hall, London, 1993.

criticism to animal welfare consists of observing how this theory ends up legitimising any animal practices, provided that an acceptable quality of life is respected; for this reason it is of the utmost importance to cite Art 727 of the Italian penal code which punishes the abuse of animals as a crime: « Anyone who abandons pets or other animals who have acquired captivity habits is punished with arrest for up to one year or a fine raging from 1,000 to 10,000 euros. Anyone who keeps animals in conditions incompatible with their nature and causes them serious suffering is subject to the same penalty».[48]

Needless, to say, the creation and the use of transgenic animals bring afloat new challenges in the reflection on animal mistreatment; first and foremost is the lawfulness of the practices themselves and the question of whether the modification of intrinsic natural characteristics represents an extreme form of human domain over nature, also identifiable by the claim "playing God"[49]. The main counter argument supports the understanding related to the modern biological thesis and its ability to dismantle the fixist and finalistic conceptions which impregnated the sphere of Nature, as well as its affirmation that in the evolution of species, every genetic structure is always temporarily defined, thus the idea of violating species' identity is supposedly part of a pre-modern, ontological vision of natural history[50]. The second ethical issue is pragmatically related to the level of welfare animals must be guaranteed; it is especially tricky in the discussion of GM animals because very little is known about their wellbeing, as opposed to the welfare conditions granted to both laboratory and farm species which are very well known: «Each transgenic animal represents a unique entity, both because the possibilities of genetic modification are endless and affect subjects differently, and also because the standardization of transgenic models is particularly lengthy»[51]. The criterion which, in some bioethicists' opinion, should be followed in the creation of transgenic animals is that of respecting the principle of conservation of wellbeing. The manufacture of transgenic animals can be considered lawful only to the extent that it is possible to guarantee to those animals a quality of life not inferior to that experienced by individuals not genetically modified belonging to the species of origin[52]. This principle has been partially implemented by the provisions on transgenic animals contained in the Protocol of Amendment to the European convention for the protection of animals (Strasbourg, 6.2.1992) as set forth by amended Art 1: «This Convention shall apply to the breeding, keeping, care and housing of animals and in particular to animals in intensive stock-farming systems. For the purposes of this Convention "animals" shall mean animals bred or kept for the production of food, wool, skin or fur, or for other farming purposes, including animals produced as a result of genetic modifications or novel genetic combinations. "Intensive stock farming systems" shall mean husbandry methods in which animals are kept in such numbers or density,

[48] Art 727 Italian Penal Code, 1889
[49] G.POLI, *op. cit.,* p. 249
[50] *Ibidem.*
[51] *Ibidem.*
[52] *Ibidem.*

or in such conditions, or at such production levels, that their health and welfare depend upon frequent human attention.»[53] and amended Art 2:« A new Article 3 shall be inserted in the Convention which reads as follows: "Natural or artificial breeding or breeding procedures which cause or are likely to cause suffering or injury to any of the animals involved shall not be practiced; no animal shall be kept for farming purposes unless it can be reasonably expected, on the basis of its phenotype or genotype, that it can be kept without detrimental effects on its health or welfare."»[54]. Finally, another general ethical doubt concerns the creation of transgenic animals; even if these animals are subject to greater attention than in the past, as regards welfare, their productivity and experimental reliability are likely to give rise to an increase in the number of animals overall employed by science and various industries, thus clashing both with the principle of 3Rs and with the European legislative trend to significantly reduce animals destined for experimentation.

4. New horizons

Science is constantly faced with new questions, with the growing imperatives of an ever changing world, as if we all were in a race against time. To some extent, it is true and some would dare to argue that extreme circumstances call for just as extreme solutions; the need of always feeling one step ahead accompanied by the awareness that we are always going to be one step behind. Science keeps on modernising itself, it becomes more and more advanced each passing day, thus it is only logical to think that its methodologies and convictions must evolve alongside it. This is closely related to animal experimentation especially, for, as it has been highlighted by the previous sections of this paper, animals have always been one of the most fruitful resources in the hands of science; yet, with the advent of the new century, the well-established mentality which saw human beings as the solo players was dismantled in order to favour a fresher, more inclusive mindset which did entail animal welfare. For instance, in tragically up to date terms, laboratory animals are nowadays key players in the Coronavirus saga, for all the reasons that have been heretofore listed; surprisingly, GM animals too have a role to play in the fight against Covid-19:« A different breed of genetically engineered mice are being used to develop drugs. Regeneron, a New York-based pharmaceutical company, is among those racing to roll out an antibody-based treatment for Covid-19. The method relies on a large supply of antibodies produced in response to a viral infection—but those from recovered humans are still in short supply. So the company is harvesting them from mice that have been engineered to produce

[53] Protocol of Amendment to the European Convention for the Protection of Animals kept for Farming Purposes, Strasbourg, 6.II.1192, European Treaty Series – No. 145, Art 1 https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=090000168007bd27 (21.05.20).
[54] Protocol of Amendment to the European Convention for the Protection of Animals kept for Farming Purposes, Strasbourg, 6.II.1192, European Treaty Series – No. 145, Art 2 https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=090000168007bd27 (21.05.20).

human antibodies. The same proprietary strain of mice has been used to produce drugs for autoimmune diseases, cancer, and other infectious diseases, including Ebola»[55]. Once acknowledged how greatly these creatures are contributing to scientific development, it would be also necessary to ask ourselves whether there were no other ways in which to achieve the same, if not even better, results; well, there are certainly good news coming from " The Conversation", an online publication covering the latest research, which on March, 27th 2018, published an essay entitled " Should Computer Simulations Replace Animal Testing for Heart Drugs?" which confidently states that:« While the underlying biology is similar, small differences between animal and human cells are amplified when a patient takes a drug. It means predicting the risk to patients is limited to an accuracy rate of around (75% to 85%), research shows, and it also leads to drug withdrawal from the market because of cardiovascular safety issues. However, it's now possible to test a new heart drug in a "virtual human". Our virtual research at the University of Oxford's Department of Computer Science demonstrates that computational models representing human heart cells show higher accuracy (89-96%) than animal models in predicting an adverse drug effect, such as dangerous arrhythmias– where the heart beat becomes irregular and can stop»[56]. This clearly stands to show that human computational models would not only bring additional advantages by reducing the use of animal experiments in early stages of drug testing, but they would also improve drug safety, thereby lowering the risk for patients during clinical trials as well as speeding up the development of medicines for patients in urgent need of healthcare. It is now evident how Science is devolved to making new steps forward every day in delivering ethically fair treatments which, on the one hand do not endanger human beings, and on the other, do not take advantage of other living creatures at their own expenses; hopefully, the semi complete eradication of the biological component in clinical research will pave the way for a further appreciation of virtual models under the impulse of artificial intelligence, for a more sustainable and accurate way of conducting scientific experimentation.

5. Conclusions

The use of GM animals in the field of clinical research is a reality with which the scientific community has been really coming to terms only in the past decade, since, as it has been highlighted in the previous pages, Directive 86/609/EEC was not exhaustive in terms of classification as well as with regards to the category of genetically altered animals. Fortunately, this gap has promptly been filled by the main source of animal rights legitimation nowadays, namely Directive 2010/63/EU, which does provide for a more inclusive and yet more stringent legislation on animal welfare, now comprising also GM animals. The paper was finalized to an ethical-juridical analysis of the quest for animal rights fairness with a particular, if not preponderant, focus

[55] https://qz.com/1837094/how-lab-animals-are-helping-scientists-fight-covid-19/ (24.04.20).
[56] https://www.scientificamerican.com/article/should-computer-simulations-replace-animal-testing-for-heart-drugs/ (24.04.20).

on the conditions which GM animals have to endure. It is quite refreshing indeed, to witness how both the scientific and the legal world are starting to come together to address the issue of animal mistreatment in clinical research and especially that of the abuse of these man-made creatures which are themselves endowed with rights. Nevertheless, there is still quite a long way to go, however, it is the author's opinion that this new understanding of these living beings, and of the role they play in our society, might be a great starting point for even more revolutionary approaches to animal experimentation.