SECURING ADVANTAGES IN GLOBAL MARKETS: THE EXAMPLE OF STEM CELL TECHNOLOGY

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I. INTRODUCTION

A key mechanism for spurring economic growth is widely regarded as being to encourage technological development and this is overtly apparent in the context of new scientific fields such as stem cell technology. This technology is a cornerstone of regenerative medicine, promising treatments and cures for a host of medical conditions such

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as neurodegenerative diseases (e.g., Alzheimer’s and Parkinson’s) and strokes; repairing spinal cord injuries; growing essential organs and tissue for transplantation; as well as providing disease models for testing new treatments and increasing our understanding of biomedicine. The possibilities for stem cell technology appear limitless in progressing healthcare and this is already translating into economic gains. In 2011 Europe’s market in stem cell innovations was worth $872 million,¹ but the USA is the global leader, estimated to hold 60% of the global market predicted to be worth $88.6 billion by 2014.² Whether Europe or the USA can realize the market potential of this technology is largely determined by how regulation (through formal government laws; ambient regulatory systems such as patenting and market authorization; and by the industry itself through business practices, licenses and the media) shepherds the technology to the market. Effective regulation is also an issue for both Europe and the USA in increasing or retaining their market lead in light of the dynamics in the current global pharmaceutical market, which puts increasing pressure on developed countries to lead medical innovations.

Assessing regulation to determine its impact on encouraging or inhibiting innovatory progress has tended to focus either on regulatory effectiveness (drawn from specialist knowledge in health regulation)³ or innovatory effectiveness (based on specialist knowledge in patent law)⁴. The purpose of this article is to demonstrate that, by cohesively analyzing the regulatory landscape beyond these two perspectives, a new understanding emerges of: (1) how nurturing current regulatory measures/systems are; and (2) what any potential reforms need to take into account if they are to be effective in engendering progress. Stem cell technology is an ideal context for demonstrating the value of an overarching perspective on regulation, because it is part of a cadre of new health technologies⁵ which promise essential medical advancements with vast potential economic gains, making it crucial that these technologies are regulated appropriately. The analysis is undertaken comparatively in Europe⁶ and the USA to allow additional conclusions to be drawn about the scope for market advantage. This focuses on the differences which have the greatest potential impacts, rather than merely iterating all differences.

While collaterally encouraging economic progress and facilitating gains in market share, regulation is primarily about stimulating medical innovation. The regulation of any new technology relies upon balancing the interests of society, which wants novel, ethical technologies to be developed into safe, fairly priced and readily accessible

³ For example Brian Salter & Olivia Harvey, Stem cell innovation in the United States: the benefits of the minimal state, (Future Medicine) 3(4) REGENERATIVE MEDICINE 597-610 (2008).
⁴ For example Sander Rabin, The gatekeepers of hES cell products, 23 NATURE BIOTECHNOLOGY 817-819 (2005).
⁶ Regulation in Europe is a complex amalgam, which comprises: EU regulation (non-EU European countries’ national regulation being beyond the scope of this article); European-wide patent regulation; and the UK as a representative of Member States (relevant for this legally-based analysis, because its permissiveness of embryonic research and stem cell technology development provides a detailed regulatory framework for analysis).
products/processes; with those of innovators, who want a readily navigable, cost-effective regulatory system and to secure profits by ensuring as much market control (and thereby profits) as possible. These interests are often competing (eg. where ethical objections raised during patent proceedings increase the cost of obtaining legal protection to a level which threatens onward technological development), but can be aligned (eg. sharing an interest in getting technology to the widest possible markets). It can be regarded as an abuse of the regulatory system if it is possible for an innovator to market a product which is unsafe, ineffective or unethical. It is equally an abuse of that process if regulation is used to unjustifiably prevent innovations from reaching the market. Even where the effect of regulation on a specific innovation is not unjustifiably restrictive, it is possible that regulation may collateral contribute to an abuse. This occurs, for example, where the effect of patent rights can be used by the patent holder to limit licenses, making it less likely that the patent will be developed into a medical treatment for eventual patients.

While ethics is an integral part of the regulatory process (through ethical review of scientific research and clinical trials; in Europe through patenting; through HTAs; and subsumed within Member States’, the EU’s and the USA’s regulation of specific technology) and the use of embryos is an emotive issue, which is why it dominates current debate, it is not possible to exclude ethics entirely. However, this article adopts a fundamentally legal analysis, which does not extend to a bioethical assessment and makes no ethical judgments. Rather this analysis incorporates ethics principally as a mechanism to contribute to the field an understanding of how the same contentious issue is raised at entirely different points in Europe and the USA’s systems of regulatory oversight and that, while this is a consequence of a minor difference in the law, the impact of ethical objections on new technology is tied to the outlet through which such objections are vented.

The analysis begins with Part II of the article providing brief background information which is essential for understanding the detailed analysis that follows. It provides an overview of the complex regulatory systems that innovation is subject to, which acts as a general landscape for the subsequent analysis of the most contentious regulatory aspects: primarily patenting and licensing, comparatively extending to research funding and specific regulation. Appreciating how effective the regulation of stem cells is requires an understanding of the potential for different types of human stem cells to form the basis for future medical advances, an awareness of how scientific progress is affected by funding constraints and patent rights, and an awareness of relevant current practices in research.

This article uniquely identifies that the impact of regulation is not linear: restrictions on research funding which precede research obviously affect the research undertaken, but this analysis demonstrates how the regulation of property rights (including their impact on the availability of venture capital) which occur after initial research, additionally affect subsequent research. The assessment also shows that there is potential abuse within the existing regulatory system, but whether it translates into adverse effects on continued research and marketing in Europe relies upon the ability to recognize that regulation of technology through patents is limited to what can be taught, rather than what has been done. In the context of the USA, overcoming abuses relies upon the existence of alternative funding

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sources and the prospect of inventing around existing patent rights. In terms of the impact on research, current advances providing alternatives to stem cells argue that there is likely to be only a temporary loss of progress while existing research refocuses.

Part III provides an explanation of the scope of patent protection, which is fundamental to understanding the impact that patents have in progressing medical innovation. Gateway technologies and their relationship to master/foundational patents are also explained, in order to discuss fears that foundational patents can prevent technology from proliferating effectively or restricting on-going research.

This analysis demonstrates that the scope of rights facilitates potential abuses where patenting and licensing can be used to restrict the proliferation of technology, but having this effect arises in very narrow circumstances and is subject to there being no mechanisms to prevent such abuses.

This latter aspect is explored in more detail in Parts IV and V, which assess patenting as a means of regulating hESCs and demonstrates how substantially similar regulatory provisions result in incredibly diverse regulatory approaches. In Europe a restrictive moral stance in assessing patentability threatens the development of stem cell technology; whereas, with no comparable legal basis for assessing innovations for morality, the USA permits patenting (restrictions being imposed only in respect of obviousness). Instead, the contention raised in the USA focuses on the impact of the exclusivity created by patent rights. This establishes that patents have a very limited scope for abuse and on the contrary ‘underwrite’ many of the financial risks inherent in innovating. In Europe, the most pressing needs for change arise from misconceptions about: what the patent system can regulate; the implications of lead cases for future practice; and the tendency to over-challenge competitors’ rights (although this latter is not confined to Europe, it is a particular problem in the context of stem cell patents in Europe). In the USA, the analysis demonstrates that lead innovations (such as those of the Wisconsin Alumni Research Foundation, WARF) have been restricted (arguing that the patent system does not inherently abuse the public interest in innovation) and the analysis demonstrates that the regulatory system provides a diverse range of mechanisms which prevent patent rights per se from unduly limiting subsequent research or marketing (contrary to popular belief).

Part VI considers the wider tranche of government regulation, focusing on the most contentious aspects in order to identify the level of nurturing of innovation by providing:

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10 Primate Embryonic Stem Cells/Wisconsin Alumni Research Foundation (US No 7,029,913 was rejected by the Board of Patent Appeals and Interferences (BPAI) (USPTO Appeal Boards, Foundation for Taxpayer and Consumer Rights v WARF [2010] BPAI No 001854), http://des.uspto.gov/foia/RetrievePdf?system=BPAI&fNIn=fd20100001854-04-28-2010-1 and is currently subject to inter partes re-examination pending before the USPTO (Control No 95/000,154), http://www.pubpat.org/assets/files/warfstemcell/95000154granted.pdf. WARF’s stem cell innovations have become the catalyst for debate and are used in this assessment both as a point of comparison with Europe and as a basis for exploring legislative regulation.

impetus to develop innovation through to the market; as well as providing a global competitive advantage.

This identifies that in Europe the need to provide regulation for Member States with diametrically opposed positions on stem cells has led to seemingly contradictory measures being adopted, which on closer analysis reveal an underlying policy of choice. Conversely in the USA, potential for abuse represented by restrictive policies on public research funding is far less likely to damage long-term marketing prospects, than is the knock-on effect of underlying Government bias. This is because the sympathies of the incumbent administration easily undermines the confidence of private investors and threatens more restrictive stances at every stage of development. In addition, this negative impact of regulation persists even under a permissive regime (such as the current one), if it is perceived as being transient.

Finally, Part VII assesses the scope for proliferating stem cell technology down through the chain of innovation and throughout the eventual market, which begins with the exclusive property rights granted by patents being licensed to third parties for further development.

Far from evidence of widespread abusive licensing practices, this analysis identifies that the self-regulation of the industry has proven to be the most effective means of policing aberrant abusive practices by individual innovators.

II. ESSENTIAL BACKGROUND INFORMATION

A. Regulatory Landscape

Developing medical technology into marketable products and processes is a highly regulated procedure. Before the research phase, peer and ethical reviews are carried out (pre-clinical trials) and these are repeated ahead of clinical trials (Phases I-III trials and including post-marketing pharmacovigilance studies). Pre-clinical trials identify a viable product/process and these innovations are usually regulated through the patent system in preference to trade secrecy, which does not fully prevent copying. This is followed by clinical trials (Phases I-III, commencing with ‘first in man’ studies), which establish the clinical data required to obtain market authorization and, for medicines, to identify dosage. Research is additionally subject to regulation for good clinical practice and EU Member States/the USA generally require institutions to be licensed to conduct medical research. Once commercialized, production of innovations becomes subject to requirements for good manufacturing practice. Take up by the market is increasingly affected by Health Technology Assessments (HTAs), because they incorporate an assessment of the cost-effectiveness of innovatory technology. These remain controversial in Member States, such as the UK, who have been wary of compromising the decision-making of healthcare providers such as Primary Care Trusts and General Practitioners, but which are a key component of the new Health and Social Care Act 2012 and its implementation by the Department of Health.12

Once on the market, pharmacovigilance reportage or Risk Management Plans regulate safe use.

In addition, it is always open to individual Member States/Federal or State Legislatures in the USA to regulate specific technology or innovations. For example, the UK

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originally criminalized the creation of human clones through the Human Reproductive Cloning Act 2001 and in the USA Arizona introduced the Human-Animal Hybrid Prohibition Act preventing the creation of human admixed embryos (these embryos are permitted under the UK Human Fertilisation & Embryology Act 2008, s4 for research purposes). Notably, stem cell innovations have not been specifically prohibited by the legislature in Europe or the USA.

This describes an incredibly complex interweaving of legal, ethical, scientific and political oversight of regulation, some of which will be explored in more detail in the ensuing analysis.

B. Stem Cell Science

Stem cells are medically valuable because, unlike adult (unipotent somatic) cells which are already specialized into heart or liver cells for example, stem cells have not specialized into particular functions. This means that stem cells have the potential to be introduced into the human body and forced to adopt a specific function. This could be to replace malfunctioning cells or be put into a petri dish and grown into specific organs or tissue. This is a nascent field, so medical science has yet to determine precisely how to obtain the entire range of cell types from stem cells, what mankind understands about human biology is constantly changing and it is clear that treatments may not be effective even where specialization can be guaranteed. What is known is that the most effective means of realizing the potential for the development of stem cell technology is to utilize stem cells which have the greatest capacity for developing into the widest array of functions. This requires an understanding of different cell types in terms of this capacity to become other cells: multipotency, pluripotency and totipotency.

Multipotent stem cells have the least potential for development into the entire range of cell types, because they are designed to perform specific ‘repair by replacement’ functions within the human body: for example, neural stem cells in the brain can replace neurons essential to the functioning of the nervous system. On the basis of current biological understanding, such cells are limited in being unable to extend beyond the ‘family’ of cells they are replacing: so neural stem cells are unable to become heart, liver or lung cells. This is significant, because multipotent stem cells are sourced from adult bone marrow, brain and

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13 Repealed having been subsumed within the UK Human Fertilisation and Embryology Act 2008, sec. 3ZA(4)(b) and (6).
14 Human-Animal Hybrid Prohibition Act 2009, S1435 failed to pass Congress in 2010, but Arizona introduced the ban; SB1307 (HB2652) Amending Title 36, Chapter 23, Arizona Revised Statutes, http://www.azleg.gov/legtext/49leg/2rbills/hb2652p.htm and the current NIH Guidelines (infra note 18) include a prohibition on mixing human iPSCs with primate blastocysts.
15 For example Stefano Pluchino et al., Neural stem cells and their use as therapeutic tool in neurological disorders, 48 BRAIN RESEARCH REVIEWS 211-219 (2005).
16 For example general acceptance that stem cells in bone marrow (hematopoietic cells) can replace all of the blood cell types, making them multipotent (meaning a single cell which can specialize into a limited range of different cell-types) has been challenged by identifying that these cells may be a single cellular sac comprising many unipotent stem cells, which are individually capable of renewal but not of specializing into more than one type of cell: C.E. Muller-Sieburg & H.B. Sieburg, THE GOD OF HEMATOPOIETIC STEM CELLS: A CLONAL DIVERSITY MODEL OF THE STEM CELL COMPARTMENT, 5(4) CELL CYCLE 394-398 (2006).
heart tissue, umbilical cord blood or aborted fetal tissue so developments could be limited to these related families for developing new treatments. While the fetal tissue clearly raises moral issues, the point here is that multipotent cells have limited therapeutic potential.

Pluripotent stem cells (hESCs) are obtained at the blastocyst stage of embryonic development; whereas totipotent cells (legally regarded as a human embryo) include the fertilized ova and cells obtained during the morula stage of development. The significance of this is two-fold: (1) it demonstrates the biological progression of cells from totipotent to pluripotent and into either multipotent or unipotent somatic cells; and (2) it identifies that, while pluripotent stem cells are capable of giving rise to every type of cell in the human body (except extra-embryonic tissue), totipotent cells develop into a whole organism (human). The capacity of pluripotent and totipotent cells to specialize into divergent cell types may solve the problem of maximizing potential innovation, but difficulties arise from the moral status of the cells (eg. whether totipotent cells should be accorded legal protection as ‘embryos’ because they can develop into a complete human, given the right circumstances) and their source (eg. obtaining pluripotent/totipotent cells at present generally relies on the destruction of an embryo).

C. Scientific Progress

Global public discussion of recent scientific breakthroughs has caused some reticence to support the development of therapies which are morally questionable, where they are derived from embryos. This has resulted in: (1) funding for human embryonic research being far less available, particularly in the USA; and (2) legal protection through patents being limited. While both of these aspects will be discussed in Parts III-V, their consequences are that scientific research is already developing other alternatives in response. This is important, because it is the effort to circumvent regulation introduced to limit scientific research that is informing the most recent efforts to regulate technological progress. It also evidences the interaction between different aspects of regulation to which innovation is subject: here research aims, research funding and patent regulation intertwine to shape progress.

Most promisingly, scientists have been able to make unipotent somatic and multipotent stem cells display embryonic-type characteristics (iPSCs and maGSCs). This is critical, because it is a means of reversing the biological ‘clock’ and turning adult/multipotent cells into pluripotent cells. Although there are questions over the robustness of scientific claims, the repeatability of results and the therapeutic safety of the cells produced, current

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research is focused on overcoming such concerns by improving safety\textsuperscript{20} and efficient production\textsuperscript{21} in order to encourage the use of iPSCs in preference to embryo-derived cells.

In addition, the Scripps Research Institute reported success in using a cocktail of proteins to stimulate regression of adult skin cells into pluripotency (piPSCs)\textsuperscript{22} which, in common with iPSCs, avoids the use of embryos. In addition, the protein-induction of piPSCs should overcome concerns regarding the propensity of iPSCs to become cancerous, although more recently produced iPSCs have avoided this by changing the transcription factors (meaning the chemicals used to induce the cell to biologically regress). This demonstrates that iPSCs and piPSCs may offer the diverse ‘reprogramming’ normally only possible with pluripotent cells, while avoiding the moral controversy over using embryo-derived cells.

While current trials to treat spinal injury have recently been stopped because the level of medical benefit did not warrant the expense of the trial, other clinical trials of stem cells are expected shortly.\textsuperscript{23} If proven reliably repeatable and safe, this could mean that the restrictions on patenting in Europe (on obtaining stem cells by destroying embryos, discussed in more detail in Part III below) may not be the barrier to progress that is expected.

In addition to seeking cells which circumvent early legal and funding restrictions, researchers sought new methods. A basic understanding of what these methods are is necessary for comprehending and critiquing the legal restrictions that have recently been introduced in response to them.

Preimplantation Genetic Diagnosis (PGD), which is an established fertility technique, can circumvent the need to destroy embryos to obtain embryonic stem cells. PGD enables a single stem cell to be obtained from an embryo because the protective membrane, holding the stem cells together, generally reforms and this allows the embryo to continue growing. The key point here is that the stem cell extracted can form the basis of a rapidly increasing cell population (called a ‘cell line’).\textsuperscript{24} The difficulty is that this technique still presents a risk to the embryo that would not be present without the need for research. As a result it raises both consent and safety issues, without entirely overcoming moral reservations.

Parthenogenesis (stimulating an unfertilized ova to cellular division); embryonic germ cells (obtained by removing the sperm/ova from the embryo whilst it is in the uterus); fusing ova with adult cells without removing the existing genome;\textsuperscript{25} and human admixed embryos (created utilizing animal and human combinations of ova/gametes/genomes) can be distinguished from other cells in the sense of not being ‘human’ (either having the wrong genomic components or including non-human material), enabling them to be subjected to experimentation.\textsuperscript{26} The UK Human Fertilisation and Embryology Authority (HFEA) licensed

\begin{thebibliography}{99}
\bibitem{20} For example Osahiko Tsuji et al., \textit{Therapeutic potential of appropriately evaluated safe-induced pluripotent stem cells for spinal cord injury}, 107 PNAS 12704-09 (2010).
\bibitem{21} Yoshinori Yoshida et al., \textit{Hypoxia Enhances the Generation of Induced Pluripotent Stem Cells}, 5 CELL STEM CELL 237-241 (2009).
\bibitem{22} Hongyan Zhou et al., \textit{Generation of Induced Pluripotent Stem Cells Using Recombinant Proteins}, 4 CELL STEM CELL 1-4 (2009).
\bibitem{24} For example Ian Sample, \textit{Scientists make human stem cells without destroying the embryo}, THE GUARDIAN p3 (August 24, 2006).
\bibitem{25} Scott Noggle et al., \textit{Human oocytes reprogram somatic cells to a pluripotent state}, 478 NATURE 70-75 (2011).
\bibitem{26} For example the UK Human Fertilisation and Embryology Act (HFEAct) 2008, sub-sec.4A(6) and 11(1) define and permit licensing of human admixed embryos (respectively), but other Member States may have more fundamental moral objections to these alternative cells.
\end{thebibliography}
Kings College London, Newcastle and Warwick Universities to use cytoplasmic admixed embryos, but not all EU Member States adopt this practice. The value of this research may be limited (for example, to the production of human cellular test models) where there is potential for the animal component to adversely affect the development or benefits of therapies, or where there are specific moral objections.

Alternative methods for creating stem cells do not entirely avoid the issue of destroying the embryo. Cell Nuclear Replacement (CNR) (also known as therapeutic cloning) involves replacing an unfertilized ova’s nucleus with that of an adult cell: the full genomic complement enabling development to progress as if fertilization had occurred. This may be regarded as an act of intentional creation, because the embryo owes its very existence to the need to conduct research, but its reliance on embryonic destruction continues to be morally contentious.

This demonstrates that research efforts (including funding) previously focused to prompting pluripotent stem cells to specialize into specific adult cells have been redirected into finding non-embryonic sources of stem cells. The ability to compel stem cells to become specific adult cells is crucial to unlocking the health benefits that stem cell technology promises. For example, bone marrow stem cells can be reprogrammed into nervous system cells and embryonic stem cells can be specialized into retinal tissue. Delaying this chain of innovation by requiring researchers to retrace steps represents an abuse, because the law has commandeered research aims. This can only be justified if the interruption of research progress is warranted by the need to safeguard a greater morality. Leaving this issue to Part III, the final aspect of this analysis concerns prevalent research practice to demonstrate the potential impact that recent legal prohibitions may potentially have, to assesses established regulatory provisions as a backdrop to the additions recently introduced and to identify possible limitations on delivering the promise of stem cell technology.

D. Current Scientific Practice and Specific Regulatory Provisions

At present supernumerary embryos/gametes are often used in research (subject to consent), because they are surplus to the requirements of fertility treatments. In Member States/the USA where this occurs, there are strict regulations which must be adhered to. In the UK for example, embryonic research must be licensed by the HFEA and this is conditional upon cell lines being deposited with the UK Stem Cell Bank. Cell lines which involved the destruction of human embryos are also subject to the voluntary Code of Practice of the Medical Research Council (MRC), as well as requiring review by the UK Stem Cell Bank Steering Committee. The USA approach is explored in more detail in Part V(B) below. This type of regulation provides ethical oversight, but does not overcome the morally contentious nature of this practice. In addition, reliance on supernumerary sources often results in poor quality embryos being obtained, because they tend to become available only after the fertility potential has been exhausted. This means that the cell lines created from

28 For example the HFEA in the UK granted two CNR licenses in November 2006 and currently has 21 active embryonic research licenses, http://www.hfea.gov.uk/166.html.
such embryos will be less likely to provide the research results hoped for, collaterally raising issues about the cost-effectiveness of research/trials where materials preclude success.

The current raft of research and innovation that has already emerged is dominated by pluripotent stem cells (obtained from human embryos) which are used to establish a self-perpetuating cell line. This means that, while the original pluripotent stem cells are obtained by destroying an embryo, there is no need to continue destroying embryos in order to obtain more stem cells. The effect of this should reduce the overall necessity to destroy embryos on an on-going basis by individual research teams, but will only have this effect collectively across research if the cell lines are licensed on reasonable terms. Fundamentally, licenses rely on patent rights. This does not overcome all moral objections, but represents prevailing research practices and must be recognized as a means of at least minimizing immorality by consigning it to the past (analogous to the science which informed space exploration, but emerged from immoral practices carried out under Nazism).

In Europe patenting is generally regarded as unavailable where embryonic destruction has occurred, but this perception is challenged in Part III below. Under the prevailing view, researchers will need to find alternative sources of cells (eg. iPSCs or piPSCs) as the starting point for subsequent innovation and this could have enormous implications for the stem cell industry in Europe: licensing of existing cell lines becoming redundant and demand for alternatives to pluripotent cells soaring. This exemplifies the potentially detrimental effects that can ensue where the scientific and legal community misinterprets judicial decisions. In the USA, no such ambiguities exist and patents can restrict the ability of researchers to produce their own cells lines (by destroying new embryos), requiring them to obtain a license to gain access to approved stem cell lines. Before discussing the current legal situation, it is necessary to understand why the impacts identified occur and what impact risks arise. This relies on an appreciation of how patent rights are used by the medicines industry to ‘reserve’ market entry, risking inhibiting further research by competitors.

III. SCOPE AND EFFECT OF RIGHTS: EUROPE AND THE USA

The strength of the patent right granted is a key factor in determining the prospects of innovations getting to market, and this is predominantly dictated by the scope of the patent. This is determined by the patent’s form (eg. product per se, ‘method of use’ patents, product-by-process, or process patents); and the description of the invention in the application claim, which describes the specific innovation. Collectively, these factors define the ‘scope of protection’, because they determine how much and precisely what is owned. Scope is relevant because stem cell technology can only be exploited effectively if it is granted an optimal amount of protection and deviation from this optimal level represents an abuse of the patent right. This requires an understanding of how scope relates to legal exclusivity and how this can result in restricting the potential for further research and/or market competition. While it is not possible to discuss this exhaustively, this section focuses on specific pressure points which could slow/stop the flow of innovation reaching the market.

A. Over-Broad Patents and Narrow Patents

Product per se patent protection means that the product identified in the patent claim is legally protected no matter how it is produced or what it is used for. This represents the broadest scope of protection and enables legal protection to include uses of an innovation not
yet thought of. Product per se rights are construed this way because existing products are often found to have diverse new uses by other innovators who are entirely unconnected with the original innovation. This represents a potential social benefit (known products being used in new contexts), so the law allows that the subsequent innovator can protect that product limited to the context of the new use, by a new ‘method of use’ claim (a form of process patent). This does not rely upon the original product being outside of its patent protection, but if the patent is still active the subsequent innovator must indemnify the existing product patent holder. This appears to reserve innovation to the original patent owner, because they obtain financial benefits from uses which did not exist at the time the right was granted, and were not thought of by the right holder. Yet it cannot be regarded as being unjustified, because the subsequent innovation inherently relies upon the original contribution for its existence. It would only be an abuse of the patent system if the product per se has the effect of limiting how the innovation is exploited: for example, this could occur if the innovation is not exploited to its fullest because the indemnification of the existing patent owner proves too costly for the subsequent innovator, resulting in the innovation never being marketed. Beyond these unjustifiable circumstances, the law enables the product to be marketed before every use has been fully identified so that others can help push the innovation forward: the product needs to be publicly accessible for new uses to be independently identified by third parties. Conversely, if the scope of protection is narrowed down from product per se protection, it would have the effect of slowing the pace of innovation. This is because innovators would not put their inventions into the public domain (either published through patenting, or by marketing if protected by trade secrecy) until they were sure they had exhausted all possible uses for their innovation.

If an innovation can only be described in terms of how it is produced, it is limited to a product-by-process patent. This represents far weaker protection than product per se protection, because it is only infringed by a product which is produced by the precise method relied on for the claim. Process patents are explored in II(B) below. Product per se protection, product-by-process patents and process patents are infringed by products/processes falling within the doctrine of equivalents (eg. an equivalent technology and here including product variants). In Member States such as the UK, the test for

31 (EU) generally European Patent Convention 2010 (EPC), Article 54(1) most famously utilized in G2/88 MOBIL/Friction Reducing Additive, EPOR 73 (1990), requiring only a new technical effect for novelty to exist and in the context of medicines EPC. Articles 53(c), 54(4) & (5), including where the only novel feature is the dosage regime (G2/08 Dosage Regime/ABBOTT RESPIRATORY, OJ EPO 10 (2010); comparatively more restrictive in the USA, requiring a new use which has resulted from a new technical effect: 35 USC §101; In re May, 574 F.2d 1082, 1090; 197 USPQ 601, 607 (CCPA 1978).

32 In Europe there is no specific law protecting trade secrets and it is down to individual Member States to protect this as they wish (eg. in this context the UK protects trade secrets through the common law on confidentiality (see: Coco v AN Clark (Engineers) Ltd, RPC 41 (1969); Facenda Chicken Ltd v Fowler, Ch 117 (1987)) and restraint of trade clauses in employment contracts (Mason v The Provident Supply and Clothing Co., AC 724 (1913), Lindner v Murdock’s Garage, 83 CLR 629 (1950), and on the Springboard Doctrine restricting the use of proprietary know-how: classically Terrapin Ltd v Builders’ Supply Co., RPC 375 (1967), but see Vestergaard Frandsen v Bestnet Europe Ltd., FSR 2 (2010); comparatively the USA has incorporated it within their legislative code: 18 USC §1839(3).


34 (Europe) as an infringement issue, this is down to Member States (the EPO is confined to the grant of patents until the unitary patent is implemented, which looks to be some way off given the discussion on 10 July 2012 of the European Parliament Committee on Legal Affairs (JURI) on the European Council’s
equivalents is designed to remove improvements (which are sufficiently different to the originator to attract separate patent rights); innocent infringers; and prevent the patent scope from being increased post-patenting, to unfairly ensnare infringers. In the USA, the doctrine of equivalents performs essentially the same function by recognizing that a patent right is infringed where products/processes have the same basic function, are undertaken in the same way and have the same result (the ‘triple identity test’).\(^{35}\)

Legal protection affixes to the patent claims in the application and in infringement proceedings the court purposively construe the claims with recourse to collateral documents (the specification: description, drawings, etc.).\(^{36}\) Purposive construction defines protection to include what the claims literally mean, as well as a measure of what the applicant intended based on the supporting documents.\(^{37}\) Consequently the claims are crucial in determining how broad the right is, as well as identifying to third parties how not to infringe. It is essential to achieve an appropriate balance in order to successfully shepherd a technology to market. Where patent rights are interpreted too widely, the right holder is gifted an unwarranted degree of control over the technology inherent in the innovation, preventing the proliferation of the technology. Conversely, where protection is too narrow the right becomes worthless, or a ‘patent thicket’ is created. Thickets refer to narrow patent rights over innovations within the same generation (eg. DNA patents), each of which is held by different owners. This jeopardizes the development of the technology: the innovation can be priced out of the market (the licensing fees being larger than returns on development), or researchers cannot penetrate the sheer volume of rights (tracking down so many parties).\(^{38}\)

An overly generous scope of protection is guarded against within the legislation itself. ‘Sufficiency’ requires that the innovation be described clearly enough to enable someone ordinarily skilled in that specialty to recreate the invention in the best way.\(^{39}\) This ensures that the statements made in the claims are substantiated by the description in the supporting documents. This is not a perfect safeguard, because right holders want to construe their rights at their widest to ward off competitors and purposive construction allows for a degree of mismatch (eg. courts can generously interpret what was intended by the patent holder as being within the scope of the right). However, it provides a bastion against a significant mismatch, because the claim must be clear enough to enable third parties to avoid infringing.

Even patents which are construed effectively can cause problems with the impact of the right, rather than its scope. Foundational patents refer to legal rights which are extensive

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\(^{36}\) (Europe) EPC, Article 69 and the Protocol to Article 69; comparatively (USA), 35 USC §154(4) (as renumbered after infra note 92).

\(^{37}\) (Europe) For example in Member States such as the UK, supra note 34 (in particular Kirin-Angen ); comparatively (USA) Whirlpool Corp. v Camco Inc., 9 CPR (4th) 129 (2001).

\(^{38}\) Trilateral Project B3b identified that general patent practice is to restrict the potential for ‘reach-through claims’, which widen the scope of protection: TRILATERAL PROJECT B3b, TRILATERAL PROJECTS, REPORT ON COMPARATIVE STUDY ON BIOTECHNOLOGY PATENT PRACTICES: COMPARATIVE STUDY ON “REACH-THROUGH CLAIMS” (2001), http://www.trilateral.net/projects/biotechnology/patentability.pdf.

\(^{39}\) (Europe) EPC, Article 83; comparatively (USA), 35 USC §112
because of the significance of the technological breakthrough that they represent. Consequently, they provide a broad scope of protection which is warranted by the contribution to knowledge, but this scope of protection also means that a succession of ensuing patent rights and licenses will inevitably flow from a single originating patent right. This provides the potential for control over future developments in the field and this can be considerable.

It is these foundational/master patents upon which it is claimed that the development of stem cells is being monopolized, principally by WARF and its licensee (Geron, discussed in section 3 below). The concern is that the concentration of control in the hands of a select number of right holders is an abuse if it permits control over a ‘gateway’ technology. These arise where a single development represents the only means by which subsequent innovatory steps may be made. This gateway technology may go on to be the first in a new field of innovation (eg. monoclonal antibody technology or recombination), or it may simply be the beginning of a broad/long chain of innovation (‘broad’ referring to parallel technologies which derive from a single originator and have many purposes; ‘long’ referring to innovations which rely upon the previous step for development and progress towards a single purpose). A gateway technology, if patented, gives rise to foundational patents which inherently allows the right holder to control successive development of that specific technology. This could create the potential for a bottleneck, because access (and therefore progress) relies upon the right holder.

This is an impact which affects not only commercial organizations, preventing them from competing in the market, but it is feared that it is preventing research generally. Monoclonal antibody technology and recombination both began with a single breakthrough development and subsequently gave rise to entirely new scientific specialties, notwithstanding that only the initial innovation in recombination was patented. Therefore, the problem may not be as simple as patents preventing technological development: it may be that the impact of patent rights is that they temporarily slow the pace of innovation by restricting access, but in the long-term represent no numerical loss of development.

In the context of stem cell technology, without access to human stem cells or cell lines, a whole raft of researchers in disparate fields of medicine would be unable to identify new treatments for medically recognized conditions such as heart disease, cancer, or spinal injuries. At the risk of hugely over-simplifying, this is because there is a developmental pattern in the chain of innovation: first come the isolated stem cells; then the creation of the cell lines. From this point the sequence relies upon research priorities and rests upon the

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41 For example Mike Clark, Empowering the inventor – the case of monoclonal antibodies, 23 NATURE BIOTECHNOLOGY1047-1049 (2005).

42 For example Geron have already secured Food and Drug Administration (FDA) approval to conduct clinical trials using stem cell-based medicines to treat spinal damage: Geron, Geron Receives FDA Clearance to Begin World’s First Human Clinical Trial of Embryonic Stem Cell-Based Therapy (January 23, 2009) New Release http://www.geron.com/investors/factsheet/pressview.aspx?id=863.
availability of funding, which means that any (or all) of the following links in the chain may ensue, but not necessarily in this order: the method of converting stem cells into cells with specific biological functions, facilitating the supply of specialized ‘factory’/disease model cells (including toxicity testing for new medicines), and the supply of stem cells for therapeutic treatments (including transplants, etc.); methods of treating specific conditions with those specialized cells; and methods of efficiently creating cells which are tailor-made to specific patients/patient groups.  

Irrespective of how that chain diverges as it nears the point of application to patient-users, without access to stem cells the best prospect for developing effective and non-toxic medical treatments may never exist. So this is a very high-stakes issue.

**B. Ring-Fencing Restrictions**

Process patents are just as susceptible to abuse where ring-fencing occurs, which can be impossible to invent around. This arises where a gateway product (such as hESCs) is not claimed, but claims to every possible method of creating it result in preventing others from gaining rights over the product. Although the product of a patented process falls within the legal protection granted, the monopoly comes from preventing any alternative means of creating the product. Ring-fencing can occur even where alternatives exist, but cannot be found. Geron were exclusively licensed to use WARF’s cell lines (which they provided funding to the inventor to develop, highlighting the interaction between licensing, marketing and funding) to produce their own innovations, which predominantly relate to process patents (with tools and follow-on products making up the rest of their USA patents). While this lends cogency to fears of ring-fencing, there is ample scope for inventing around Geron’s rights, as the development of iPSCs/piPSCs discussed in section 1demonstrates. Indeed, the development of iPSCs caused Geron’s stock value to plummet by an incredible 40% within three months.

The propensity for abuse of the patent system is limited (even with gateway technologies) because, in the absence of ring-fencing or impenetrable product claims, it is possible to simply invent around bottle-necks. There is no potential for abuse if there is no concentration of control of key technology. Outside of this, the only difficulty is how long rival and replacement innovations take to create. The effect of one research organization obtaining a foundational patent is that all of the competitors in that field, who were racing to the patent office, become potential customers in the ensuing race to develop the next generation of innovation. It is almost inevitable that, in protection of their own investment in research, rival researchers/companies will litigate where they have available resources to do so, but this in itself represents a significant abuse of the public interest in obtaining cost-effective medicines.

The analysis in this section demonstrates that the exclusivity which is the crux of a patent right, together with the potential for commercialization which can derive from it, are the reason for the focus on patents and licenses as the causes for concern. This requires a

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43 Although this may be more difficult than first thought, because iPSCs can trigger an adverse immune response: See Zhao et al., supra note 19.
44 (Europe) in Member States such as the UK, Patents Act 1977 (as amended) [hereinafter UKPA], sec. 60(1)(b) and (c); comparatively (USA), 35 USC §271(2)(g) and §295.
46 See Salter and Harvey, supra note 3.
47 35 USC §271.
distinction to be drawn between the appropriate use of patents to provide a lead over competitors (which cannot be regarded as abusive, but is the focus of most objections), and genuine abuse which prevents/inhibits development. Abuse of patent rights occurs when the exclusivity granted is not used to progress the innovation to market in a timely fashion, making it an abuse of the public interest.\(^\text{48}\) For example, ‘patent trolls’ which sit on their rights in the hope of either selling them at an exorbitant market value, or to develop themselves although they have woefully inadequate resources. To substantiate criticisms, the regulation of patents must prove to be inadequate and/or innovators such as WARF must be shown to be unnecessarily preventing or delaying the progress of stem cell technology. This necessitates an examination of patenting.

IV. POTENTIAL FOR ABUSE OF PATENTS – EUROPE

European-wide patents are granted through the European Patent Office (EPO) under the European Patent Convention 2010 (EPC) (as amended by the Biotech Directive)\(^\text{49}\) and all Member States’ domestic patent legislation must conform to its provisions.\(^\text{50}\) While the courts of Member States are not bound to follow the case law of the EPO and the Appeal Boards, it is generally accepted that they are highly persuasive. There is no expectation of complete uniformity in applying legal rules, but there is an expectation that decisions of Appeal Boards should only be departed from in exceptional circumstances.\(^\text{51}\) Conversely, Member States are required to follow the judgments of the CJEU.

At the EPO, it is accepted practice that cellular material is patentable and, relatively recently this was extended to include genetic innovations which have been synthesized (isolated and purified) or made available outside of the human body for the first time.\(^\text{52}\) This is confirmed in the Biotech Directive, which distinguishes between ‘the human body, at the various stages of its formation and development’ and its constituent parts, which are not patentable if they have merely been discovered; as opposed to parts of the human which rely on technical processes for their existence, making them patentable.\(^\text{53}\) In addition to complying with the general qualification criteria which require innovations to be new, sufficiently different from the existing field and capable of commerciality,\(^\text{54}\) stem cell technology is morally controversial and this

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\(^{48}\) For more on the ‘public interest’ see for example: Lok-Sang Ho, Health Policy and the Public Interest (Routledge, in press 2012); Mark J. Taylor, Health Research, Data Protection, and the Public Interest in Notification, 19 MED. L. REV. 267-303 (2011); Mike Feintuck, ‘The Public Interest’ in Regulation (Oxford, OUP, 2004).


\(^{50}\) UKPA, sec. 130(7).

\(^{51}\) For example in the UK Supreme Court case Human Genome Sciences v Eli Lilly [hereinafter HGS] UKSC 51 (2011), point 87.

\(^{52}\) T272/95 Howard Florey/RELAXIN, 6 OJ EPO 388 (1995).

\(^{53}\) Biotech Directive, Articles 5(1) and 5(2) respectively.

\(^{54}\) EPC, Articles 54-57, the latter aspect of which is currently highly contentious in the UK following the judgment of the Supreme Court in the HGS case, supra note 51.
means that it becomes subject to both a general morality provision (known as the core morality provision), as well as a specific provision aimed at protecting human embryos.

There is a trilogy of stem cell cases decided by the European Appeal Boards, of which the most authoritative is the WARF case. More recently, these have been supplemented by the decision of the CJEU in the Brüstle patent case, which informs the case law of Member States directly and only indirectly affects the European Appeal Boards by defining the meaning of the Biotech Directive.

The WARF case centered upon patenting primate embryonic stem cells, cell lines and methods of producing the cell lines. Notably human stem cells, or methods of obtaining human stem cells from their embryonic source, were absent from the application. This was an effort to avoid the pitfalls that had been encountered by the earlier Edinburgh patent case, refused protection to human stem cells derived from embryonic destruction. WARF’s drafting efforts were unsuccessful because the Examining Division decided that because: (1) the documents supporting the application identified that the same procedures would be effective on human stem cells which could be sourced from IVF surplus; and (2) the application identified that human stem cells had been banked in America, the application necessarily relied upon embryonic destruction and, as such, the patent was rejected. The fact that embryonic destruction did not need to be repeated made no difference to this judgment.

Similarly after the Edinburgh patent case, CIT’s application excluded any reference to destruction of embryos as the method of obtaining stem cells and, on appeal, amended the application to include statements that the stem cells did not come from an embryo and can be obtained from adult cells. Nevertheless, the application fell to be considered in tandem with that of WARF. The subsequent Brüstle patent before the CJEU is distinguished by the fact that the stem cells were derived from an established cell line, meaning that they did not owe their existence directly to embryonic destruction. Following the decision, the European (German) patent can only be maintained with the addition of a disclaimer to exclude stem cells derived from human embryos, and circumventing the presumption of destroying human embryos where the methods of obtaining stem cells derive from non-embryonic sources (such as iPSCs or piPSCs). It is to be hoped that this will be confirmed by the final consideration of the German court following remittance from the CJEU, but this relies upon describing an appropriate non-embryonic stem cell source which can result in the invention.

This legislative and judicial law defines the key aspects of the European and EU approach to the commerciality of stem cells, with which Member States’ patent office must adhere in order to resolve the hundreds of applications stacking up whilst these issues have awaited resolution. It is notable that the UK Intellectual Property Office (UKIPO) already

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55 EPC, Article 53(a), EPC; replicated in Article 6(1), Biotech Directive.
56 Biotech Directive, Article 6(2)(c).
57 T1079/03 Stem Cells/University of Edinburgh (EP 94913174.2, unreported); T522/04 Stem Cells/California Institute of Technology (EP 93921175.1, unreported), EPOR 45 (2009); and supra note 8.
58 See supra note 8.
59 Although it is to be noted that the EPO have accepted the decision of the CJEU in the Brüstlé case evidenced in the revised EPO Guidelines (2012) G:II:5.3(iii).
61 This relies upon ‘enablement’, which is the requirement to describe the invention clearly and completely enough that someone ordinarily skilled in the field of expertise could re-create it. In this context it means proving that the use of iPSCs or piPSCs could be used as materials which would result in the invention claimed: EPC, Article 83, and as ‘sufficiency’ (a ground for infringement) Article 100(b), EPC.
reflects the law in Europe,\textsuperscript{62} represented by the \textit{WARF} case and the CJEU decision in \textit{Brüstle}. Indeed, the bulk of the \textit{Brüstle} decision merely confirmed and clarified the decision in the \textit{WARF} case, and the only additions were to: (1) extend the prohibition (to patenting pluripotent stem cells created by using human embryos as starting materials) to include any inventions derived from destruction, no matter how remotely connected; and (2) to prevent methods from circumventing the prohibition on destroying embryos. Before exploring the specifics of the exclusion on human embryos in relation to stem cells, it is necessary to understand how the core morality provision applies.

\textbf{A. The Core Morality Provision}

The core morality provision precludes patenting if the ‘commercial exploitation’ of an innovation breaches moral standards identified from more than just a Member States’ regulation (which may be out-dated).\textsuperscript{63} What precisely is regarded as being immoral is within the discretion of Member States, but this must be gauged by a European understanding of fundamental legal principles and established moral values.\textsuperscript{64} The difficulties of being able to identify such a common set of principles, let alone ensure their uniform compliance throughout Europe, has been the subject of much debate.\textsuperscript{65} In terms of stem cells, the Enlarged Board of Appeal (which is the highest appeal body within the European patent system) in the \textit{WARF} case decided that destroying embryos contravenes the core morality provision (but provided no definition of an embryo). Conversely, the CJEU decided that this destruction contravened specific legal restrictions (discussed in detail below) aimed at protecting against the commercial use of human embryos (which it defined).

Individual Member States are able to decide to prevent patenting where the commercial operation of the invention requires that embryonic destruction is continually repeated, on the grounds that this is an immorality which breaches the core morality provision (quite apart from any specific provisions which may capture this act). Extending this to preventing patenting of innovations which only destroy embryos in their development, and which is never repeated once the invention is commercialized, is arguably an unjustified extension of the law. This is because the Technical Board of Appeal in the Oncomouse II case stated that the ‘making of [creating] an invention (which by definition must occur in private if there is to be any chance of a patent)\textsuperscript{66} cannot be deemed immoral under the core morality provision, which is aimed at public morality. On this point it would appear that the Oncomouse II case has been implicitly overruled by the higher Enlarged Board of Appeal in the \textit{WARF} case. It is similarly difficult to agree that this immorality, in the initial development of the invention, can be caught by a provision that is aimed at commercial uses (which is the CJEU’s approach), where the use does not repeat the

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{62} Sean Dennehey, Director of Patents (UKIPO), Practice Notice \textit{Inventions involving human embryonic cells} (2009) \textit{BUSINESS LAW REVIEW} 627.
\item \textsuperscript{63} EPC, Article 53(a), and Biotech Directive, Article 6(1).
\item \textsuperscript{64} See T1372/04, \textit{supra} note 8, point 29; G2/06 Opinion of the President of the EPO on the \textit{WARF} case (2006), 51-55; G2/06, \textit{supra} note 8, point 28-31; T356/93 Plant Cells/PLANT GENETIC SYSTEMS, 8 OJ EPO 545, 561 (1995).
\item \textsuperscript{66} T315/03 Oncomouse II, EPOR 31 (2005), para 4.2.
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destruction. Regarding the destruction of embryos as a breach of a European-wide ethical norm is also problematic, because embryonic research is an accepted practice in Member States such as the UK and Germany. Both the Enlarged Board of Appeal and the CJEU considered embryonic destruction as breaking fundamental human rights principles which protect human dignity. Yet, the factual operation of this principle is not universally accepted and this is evident in the actions of Member States, who obviously do not consider themselves to be compromising their compliance with such entrenched legal principles. None of these arguments have affected the current legal position. Analysis, therefore, needs to focus on the specific prohibition relevant to stem cells.

B. Specific Prohibition to commercial ‘uses of human embryos’

In addition to the core morality provision, stem cells are subject to the specific legal prohibition on ‘uses of human embryos for industrial or commercial purposes,’ and this includes post-patenting research, but does not extend to treatments or diagnostic products/processes which are beneficial to the embryo. The Appeal Boards stipulated that getting through the specific provision does not exempt an innovation from being considered under the core morality provision. To facilitate these requirements for ethical analysis, Recital 44 of the Biotech Directive provides that the European Group on Ethics and New Technologies (EGE) should be consulted, but only on basic ethical principles. Anomalously, the CJEU, the Advocate General, the European Appeal Boards and the President of the EPO have been at pains to resolve the patentability of stem cells on legal principles rather than moral ones, even rejecting the opinion of the EGE in reaching decisions.

While there is ambiguity about how Member States will apply the core morality provision to stem cell technology, it is still possible to draw conclusions about limitations. This is because the effect of the dual system, represented by the core morality provision (which is decided by the individual Member State on the basis of shared European legal and ethical standards) and the specific exclusion to commercial uses of human embryos, is that Member States can be more restrictive than the specific exclusion but they cannot be more permissive. This means that they can refuse to patent any types of stem cells on the grounds of immorality (even though it is not excluded by the specific exclusion to commercial uses of human embryos) but they cannot decide to patent cells which are excluded under the specific exclusion. This enables conclusions to be reached about what cannot be patented.

This also means that there is little purpose in trying to patent human stem cells through national patent offices in Europe where the EPO would not permit patenting. This is because national patent offices are constrained to follow the legal principles identified by the European patent system, making it unlikely that their application of the law to individual facts will result in a more permissive decision. There is some benefit in omitting Member States known to be morally restrictive of such innovations in the European patent application, as these are likely to be removed prior to grant.

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67 See supra note 8, points 44-46.
68 Contained in Biotech Directive, Article 6(2)(c) and Recital 42 (respectively).
69 Biotech Directive, Article 6(1), and in supra note 66, para 7.4.
How do these legal principles, prohibiting discoveries and commercial uses of human embryos, apply to stem cells?

C. Multipotent Stem Cells

Multipotent stem cells, although not embryonic stem cells (because they cannot be regarded as a whole organism at any stage of its biological lifespan) owe their independent existence to technological processes that have removed them and given them an in vitro (outside of the body) existence. This brings them within the definition of an invention, rather than a discovery. In addition, these stem cells can be readily distinguished from pluripotent stem and totipotent cells, because there is no suggestion that multipotent stem cells fall within the definition of a human embryo, either in terms of their nature or where they come from. This means that fetal material is considered a morally appropriate source for stem cells, which is contentious but has been confirmed by the Appeal Boards.71 Multipotent stem cells may have the least scientific potential but they are the least morally contentious form of stem cells and, therefore, the most likely to be patentable (and consequently funded). This is evidenced by the Edinburgh patent, which had all claims to hESCs and methods for obtaining them removed, leaving a patent valid principally for animals and including humans only in respect of multipotent stem cells from adult sources.

D. Totipotent Cells

According to the Advocate General’s legal approach in Brüstle, totipotent cells have the capacity to develop into a whole organism which brings them within the definition in Article 5(1) of the Biotech Directive: they are part of the ‘human body, at the various stages of its formation and development’, preventing patenting. In order to exclude patent rights totipotent cells are accorded a special status under the aegis of the principle of human dignity. This is the same approach adopted in Recital 38 of the Biotech Directive to the production of human/animal hybrids (for example complete gestation of admixed embryos), irrespective of whether they are produced by the fusion of germ cells (ova and sperm), mosaicing (fusing totipotent cells within a single embryo), or genetically.

It may be argued that equating totipotent cells with a human is flawed because it rests on the expectation that the cells will necessarily develop into whole organisms. On the contrary, it is incredibly difficult to create a human from totipotent cells artificially. If human reproduction relied only on totipotent cells and a sufficiently sized petri dish, there would be no requirement for: surrogacy;72 adoption; Fertility treatments such as IVF; or artificial uteruses.73 Conversely, the Opinion of the Advocate General was that legal protection as a human cannot be reliant upon the degree of risk involved in achieving viability: instead status is triggered by fertilization, and reflects the recognition of all Member States that human embryos require protection. For example, this is true in the UK where embryos can be subject to experimentation, because the degree of protection is relative to the development of the embryo: the more progressed the embryo, the more legal protection is provided.

In the context of both the judgments of the Enlarged Board in the WARF case, and more explicitly by the CJEU in Brüstle, this status limits patenting embryonic research which

71 Confirmed by the Opposition Division’s decision in (T1079/03) supra note 57, p28.
72 UK Surrogacy Arrangements Act 1985 (as amended by the HFEActs 1990 and 2008).
73 Robin McKie, Men Redundant? Now we don’t need women either, THE OBSERVER (February 10, 2002).
is regarded as a commercial activity. This must be distinguished from a prohibition on embryonic research as being immoral. Consequently, this is an interpretation of an embryo which can be shared amongst all Member States and which can accommodate individual nations, thereby permitting embryonic research and funding. This is important, because the CJEU were keen to prevent forum-shopping (the selection of countries for patent protection) based on whether the definition of an embryo accommodates the embryonic research undertaken. In addition, the CJEU stipulated that:

[t]he fact that destruction may occur at a stage long before the implementation of the invention, as in the case of the production of embryonic stem cells from a lineage of stem cells the mere production of which implied the destruction of human embryos, is...irrelevant.\footnote{See supra note 8, point 49.}

This is clearly an attempt to restrict the scope for framing claims around the specific prohibition to ‘uses of embryos’: patents cannot be obtained by simply omitting reference to embryonic destruction in the application (as was seen in the WARF case and CIT). Patent law in Europe only requires an application to describe a method for obtaining the invention: it does not have to be the best method or even the method actually used. This means that it is possible to obtain stem cells by destroying embryos, provided the patent application identifies how the stem cells can be created by methods which do not use human embryos (describing the production and use of iPSCs or piPSCs). In the Brüstle application, a simple disclaimer has been added, but whether this will be sufficient in all cases is likely to be determined by the degree to which existing methods for inducing pluripotency in multipotent (adult) stem cells can support the stem cells being patented. In other words, it is a matter of how much existing methods can explain the existence of the products claimed to be producible from them. The approach of the CJEU revolves around whether embryonic destruction is necessarily a part of the process of development: so stem cells which can only be produced by use of human embryos, or which cannot prove that they can be produced without embryonic use, will be excluded from patenting (eg. actual/presumptive use of embryos).

It is inevitable that patents will be challenged by forcing disclosure of methods actually used in order to attempt to invalidate/oppose grant of competitor’s rights (even where they rely on claims through iPSCs and piPSCs), but this should not succeed for two reasons. Firstly, the patent is not granted to a tangible product, but to the knowledge of how to create it and therefore the law is not an assessment of what was actually done, but of what is claimed. This is most clearly illustrated by the fact that a product need never have been physically created for a patent right to be granted. Logically, how can the innovator’s actions have any effect on an intangible property right, unless a tangibility requirement is construed as having been imposed by the CJEU? Secondly, most researchers working in the field of embryo research/stem cells have destroyed embryos at some point in the past, so disclosure will inevitably enable destruction and current innovations to be linked. The only constraints will be how reliable the research records are and how far back the records date: this means that no innovations will be patentable while disclosure can track back.

This analysis demonstrates the futility of attempting to impose moral obligations on researchers through patents. If the EU wishes to stop embryonic destruction, it must be done by specific legislative prohibition, because the CJEU decision does not have this effect. Of perhaps greater concern is the potential for Brüstle to be misconstrued by practitioners and examiners alike as imposing a positive requirement to prove that no destruction occurred (requiring disclosure of actual method at the point of filing the patent application). This is
not specified in the post-Brüstle 2012 revision of the EPO Guidelines of Examination and there is good evidence that imposing any disclosure requirement was not intended by the CJEU. The Brüstle decision demonstrated that the CJEU are already sensitive to the attempts of the legal profession to side-step legal restrictions and there is a danger that litigation on this issue could persuade the court that a positive disclosure of the actual method used is warranted. This would be catastrophic. At present the position is that patenting relies upon describing a method in the application which does not involve embryonic destruction or products produced (however far up the chain of innovation) by such methods. Litigating in an effort to prevent competitors getting rights runs the risk of raising the legal requirements for all researchers.

E. Research methods circumventing early legal restrictions

The CJEU stated that ‘the removal of a stem cell from a human embryo at the blastocyst stage entails the destruction of that embryo’ but this was based on the evidence before the court, which did not extend to obtaining a single pluripotent stem cell by PGD. Yet, the exclusion to embryos was stated by the CJEU to include destruction and embryonic use as starting materials and this would include obtaining stem cells from an embryo by PGD even though the embryo could remain intact and viable.

In addition, the definition of a human embryo was extended by the CJEU to include embryos produced by CNR and parthenogenesis, which is anomalous for a definition triggered by fertilization because no fertilization occurs: this creates a definition which rests upon fertilization or the equivalent. This is because the CJEU regarded the products of both processes as developing toward a human, bringing them within the definition of an embryo. This is indicative of the broad interpretation that the CJEU and Appeal Boards have adopted, making it more likely that this will extend to embryos created by other methods such as fusing the existing nucleus of ova with a somatic cell to create a triploidy embryo (which has too many chromosomes). The CJEU definition of an embryo is not supported by science, because (irrespective of whether the embryo is ‘fertilized’) triploidy embryos cannot develop into a human and the key factor justifying the legal definition adopted for patenting is whether the development of a human is interfered with.

The UKIPO Practice Notice states that processes for obtaining stem cells from human embryos are not patentable but it is debatable whether this includes the production of stem cells from human admixed embryos (clearly they are not considered immoral if the HFEA license their use, but their potential to develop into a whole organism can be equivalent to totipotent cells). The general approaches of the EPO and CJEU argue that processes to create admixed embryos are likely to be prohibited under Recital 38 of the Biotech Directive, even though the provision is aimed at processes to create a chimera (human/animal hybrid), which is a whole organism and no whole human is produced where an admixed embryo is used in stem cell research. In addition, whether or not processes for creating stem cells from admixed embryos are prohibited from patenting is likely to rest upon whether the embryo is regarded as human. The broad definition of a human embryo as relying on fertilization or the

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75 Id. at point 48.
76 Id. at point 52.
77 Id. at point 36.
78 Evidenced by the CJEU leaving it to the referring German court to determine if the specific pluripotent cells which fell within the claim would be able to develop to full maturity (discussed further in III(F)): id. at point 37.
equivalent, adopted by the CJEU, argues that admixed embryos will fall within this definition. However, humanity will invariably rest on what has been mixed (e.g., use of animal cytoplasm may be regarded as fundamentally a human embryo, given the whole genome is human, but genomic animal-human mixtures are less clearly defined). Whether the stem cells resulting from these embryos will be regarded as not patentable may be a matter for individual Member States to decide (discussed in III(F) below).

Overall, the European approach to defining a human embryo and the processes available for patenting, have a restrictive effect. It removes the potential to gain legal rights based on destroying or commercially using embryos (or adopting methods which attempt to invent around this prohibition). It falls short of actually preventing these practices, because the prohibition is aimed at preventing patents. Increasingly patent applications will need to rely upon the existing methods for producing embryonic stem cells which are focused to inducing biological regression. Of greater concern, is that these are limitations that are not applied in the USA, which means that the flow of stem cells innovations will not be interrupted by the need for research to back-track in search of suitable methods and materials.

F. Pluripotent Stem Cells

Scientifically, drawing a distinction between totipotent and pluripotent cells, is problematic: it is almost impossible to ensure that a population of pluripotent cells, obtained from an early-stage blastocyst, does not additionally incorporate a few stray totipotent cells. The prohibition will not ensure that the development of stem cell technology is free of embryonic destruction or that it will protect totipotent cells. Therefore, these decisions cannot be critiqued purely for their protection of embryos based on ethical values. This is because it is only patenting which is limited by this definition of embryos. This also has the effect of diluting the need for complete parity with regulatory standards applied to stem cells through funding or specific regulation (discussed in section 4 below).

Pluripotent stem cells in the lab are clearly the result of technical processes, making them inventions. In addition, because pluripotent stem cells are incapable of becoming whole organisms, they do not come within the CJEU’s central definition of human embryos as fertilized/unfertilized ova. Whether or not they fall within a broader definition of an embryo is left to individual Member States to determine based on ‘whether they are capable of commencing the process of development of a human.’ This does not include the blastocysts used in fertility treatments (which are not patentable), because the definition is aimed at pluripotent stem cells which have been removed from the blastocyst. Consequently, this means that whether or not pluripotent stem cells are prohibited from being patented relies upon the context of their use and the progress of science. This is not a definition which relies solely upon the discretion of Member States to decide, but rather a requirement that the nature of pluripotent stem cells will change with scientific advances. This concept must be applied by Member States using the capacity for human development as the benchmark of assessment. At present, pluripotent stem cells cannot develop into a human unless they are either induced to regress totipotency or fused with ova. Similarly, admixed embryos have not been expressly identified as within the scope of ‘human embryo’ defined by the CJEU in Brüstle, either by oversight or because they comprise an amalgamation of human and animal materials. This suggests that stem cells produced from admixed embryos should not be caught by the prohibition. Otherwise,

79 Id. at point 37.
provided pluripotent stem cells are capable of being produced without embryonic destruction or use as a starting material, they are patentable.

**G. Derivatives of Pluripotent Stem Cells**

Another key issue is whether the products and processes developed from pluripotent stem cells can be patented. For example, does the immorality of destroying an embryo, or using it to obtain starting materials, mean that the therapeutic products developed from it are tainted, thereby preventing patenting? Does this also extend to the products and processes developed from use of embryos as disease/toxicity models or as organs/tissue for transplantation? How many generations of innovation must elapse or are all subsequent innovations tainted? The answers are not about whether such limitations can be enforced by tracking actual stem cells (which is not currently accommodated across Europe). The CJEU approach is that stem cell derivatives will be excluded from patenting where their existence can only be attributed to either embryonic destruction or commercialization, no matter how removed the product is from this event. This places an additional burden (albeit short of actual disclosure) on applicants to prove that their products/processes can be achieved by other methods and it will have the effect of excluding protection to any that cannot do this. At present it means that patent protection is limited to innovations which can rely on describing reproducible through regression to iPSCs or piPSCs.

**H. Impacts of Patents**

Limitations should not be overstated and, in terms of the potential for progress in stem cell technology, it is this first wave of innovations which is bearing the brunt of the WARF and Brüstle decisions in Europe. The successful innovations of iPSCs/piPSCs and follow-on products/processes (the next generation of innovation) look to be robust candidates for patentability from a morality perspective in Member States which permit embryonic research. This may seem small comfort to those applicants who were hoping to become patent holders in the first developmental wave (such as Edinburgh University, WARF, CIT, and Brüstle), but the reality paints a far from despondent picture. While clearly patent regulation narrows the potential to obtain broad rights over pluripotent stem cells, some innovators have already channeled their research into the next generation of innovation (giving them a lead in the field) or are pursuing different research paths. For the rest, progress depends upon which description of regressed pluripotent cells (eg. iPSCs or piPSCs) applies to their innovation.

The types of abuses within the patent system which this analysis identifies are limited. The current approach to patenting stem cells does not create overly narrow patents (causing thickets), because there are still relatively few right holders in this field and there is plenty of scope for securing non-infringing stem cells without necessarily jeopardizing subsequent patent rights. Granting too narrow rights and subsequently retracting them is a situation which is only now being dealt with by DNA-based patents\(^80\) and should be avoided with stem cell technology.

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\(^80\) See 23andMe patent to ‘Polymorphisms associated with Parkinson’s disease’ (US patent number 8,187,811) [http://www.genomicslawreport.com/wp-content/uploads/2012/05/01-pdf-23andMe-Issued-Patent1.pdf](http://www.genomicslawreport.com/wp-content/uploads/2012/05/01-pdf-23andMe-Issued-Patent1.pdf), which is confined to claims to diagnostic methods rather than the DNA (polymorphisms); see also the Leahy-Smith America Invents Act 2011, sec. 27 ([infra note 92](#)) and HR2276, [http://www.govtrack.us/congress/bills/112/hr1249](http://www.govtrack.us/congress/bills/112/hr1249).
In addition, rights to multipotent and non-embryonic pluripotent stem cells do not appear to be overly broad. This is because there are numerous legal provisions within the EPC and Member States’ domestic patent law which ensure that the legal right granted is as fair as possible in balancing the interests of society with those of the innovator (eg. sufficiency requiring that the invention can be proven to be reproducible;81 and pre- and post-grant objections by innovators and third parties, narrow the scope of the right).82 The research exemption83 is intended to enable researchers to continue to innovate around existing patents, but this must not undermine the value of the patent right, thereby deterring investment in research. This is an incredibly difficult balance to achieve, because it involves trading the rights of one group of innovators with those of the rest of the research community. This is exacerbated where funding increasingly encourages otherwise competitive research communities to co-operate globally. In Europe, the cross-border nature of research is dealt with by an EU-wide definition of the exemption. This permits patent infringement to be exempted where protected products/processes are used in pre-clinical and/or clinical trials undertaken to obtain market authorization.84

Market authorization is principally governed through Directive 2001/83/EC85 enabling generic medicines (copies of patented chemical-based originator medicines) to fast-track the regulatory procedure to expedite marketing once the patent term has expired.86 This is done by ‘piggybacking’ the generic medicine’s market authorization procedure on the safety and efficacy data originally submitted to the European Medicines Agency (EMA) for the patented originator medicine. To ensure that safety is not compromised for speed, authorization relies upon proven therapeutic equivalence (meaning that both medicines perform in the same way, because they have the same active ingredients). This is far more difficult for biologics (DNA-based medicines) than traditional pharmaceuticals (synthetic chemical-based medicines), because the biosimilar (copy of a biologic) does not always perform in the same way as the original medicine. This is because the normal operation of the biologic medicine in the patient relies upon cellular transcription (reading the DNA), which randomly includes errors. In practice, this means that while generics are reliable copies of chemical-based pharmaceuticals, are less reliable copies of biologics. The reliance of stem cells on transcription and site-specific take up for effectiveness, make them liable to encounter similar difficulties with proving therapeutic equivalence to biosimilars.87 Given that the most recent

81 Discussed in II(A) above,
82 EPC, Articles 115, 99-101, and 105.
83 Also known as the ‘experimental use’ exemption.
85 Directive 2001/83/EC (as amended); supported by Regulation 726/2004/EC establishing the EMA (as amended); Regulation 658/2007/EC providing penalties for failure to comply with authorization conditions; Regulation 507/2006/EC detailing conditional market authorization; and Regulation 2049/2005/EC reducing the fee burden on Small and Medium-Sized Enterprises (SMEs)
86 Although data exclusivity granted under Directive 2004/27/EC (id.) may additionally delay market entry of generics/biosimilars, it does not prevent the use of the medicine.
EMA initiative on this is focused on introducing regulation of potential implications of ‘cocktail’ effects of medicines and interaction with food,\(^8\) exploring the implications of stem cell-based medicines for bioequivalence remains unaddressed. In the context of this analysis, the point is that the research exemption preventing patent infringement is construed widely enough to permit competitor generics/biosimilars to get onto the market as quickly as possible once the patent expires. In addition, using patented products/processes in trials to test originator medicines (chemical or DNA-based), combination medicines, new therapeutic value for existing medicines, or to obtain information for public health reasons\(^9\) are all within the research exemption.\(^{10}\)

Beyond the EU-wide understanding of the exemption, some Member States have considered the exemption in more detail, providing further insight into how the research exemption will be applied in practice. For example, in the UK the exemption has been considered as potentially excluding research tools (defined as the use of protected products/processes ‘on another invention’).\(^{11}\) In the context of stem cells, the limitations on patenting stem cells \textit{per se} (distinguished by their non-embryonic method of production) means that future patents are likely to be claimed by reference to the cells into which stem cells can be specialized. This brings stem cells within the definition of a research tool where they are not being used directly on patients for therapeutic purposes: research tool status taking stem cells outside of the research exemption. This interpretation is supported by the need to construe the exemption so that it does not impinge upon marketability: for research tools the interim research market is their end market, so an exemption which includes such tools would have the effect of stopping research tools being developed or traded.

The overall impact of patents in protecting stem cells is that the reduction of patent holders with rights to stem cells has been restricted (following the \textit{WARF} case and \textit{Brüstle}), in consequence of moral restrictions and not because of abuses arising from patent rights. Even within the moral restrictions imposed by the CJEU, stem cell technology development is likely to experience only a minor ‘hiccup’ in maintaining an effective pace of innovation. This is because iPSCs/piPSCs should enable compliance with requirements for a moral developmental chain of innovation and technological progress is likely to expand significantly once the procedures for getting stem cells to specialize are explored further. Since these specialized cells will invariably align closely with eventual therapeutic and test model applications, the potential for either too broad or too narrow rights should be minimized.

This analysis demonstrates that the perception that Europe’s approach is legally restrictive and will inherently impede future stem cell research is a misconception. Right holders such as \textit{WARF} are already being invented around and this illustrates that there is no abusive impact of patents, either in bottle-necking or ring-fencing to obtain an unwarranted

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\(^10\) See supra note 84, importing a new Article 10(6) into Directive 2001/83/EC.

degree of market control. Whether the same is equally true in the USA, where morality is not a consideration, requires assessment.

V. POTENTIAL FOR ABUSE OF PATENTS - USA

The introduction of the Leahy-Smith America Invents Act 2011 (AIA)\(^{92}\) amending the USA patent legislation, pursuant to the need to introduce parity with the EPC-based Chinese Patent Law,\(^{93}\) means that the patent criteria in the USA and Europe have become almost indistinguishable. Negligible differences remain, but this analysis is limited to identifying differences which affect practical application of the law, rather than to comprehensively analyze the law in the USA compared with Europe. For example, a key point of difference prior to the 2011 amendment of the USA patent law was the requirement for disclosure of the ‘best mode’ of recreating an invention,\(^{94}\) whereas Europe only requires disclosure of a means of recreating the invention, not necessarily the best one.\(^{95}\) While the ‘best mode’ remains in the USA, non-disclosure no longer forms a ground for challenging the validity of a patent.\(^{96}\) This turns the requirement into a preference, which represents no practical difference in comparison with the application of the EPC. Innovators in Europe inevitably disclose one version of the method they know to work (one embodiment)\(^{97}\) with scope for variance from test results and examiners must be able to extrapolate the rest of the claim if it is to succeed.

A difference of minor note is that the USA retains the year’s grace period before disclosure destroys novelty,\(^{98}\) compared to the European 6 month period with additional restrictions.\(^{99}\) This means that some inventions which cannot be patented in Europe could be protected in the USA, but this is unlikely to have a significant impact on the number of inventions worked in the USA and certainly it will have no impact on particular technological fields. Indeed, the only significant difference in the context of this analysis is that the USA has no legal requirement to assess patentability on the grounds of morality.\(^{100}\) As has been seen above, in Europe this is the key factor in determining protection of stem cells. Consequently, the question is whether this necessarily leads to a more permissive approach to

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\(^{93}\) People’s Republic of China Patent Law 1984 (as amended), Chapter 11.

\(^{94}\) 35 USC §112; Eli Lilly v Barr Labs., 251 F.3d 955 (Fed. Cir. 2001); Benger Labs. v RK Laros Co., 209 F. Supp. 639 (ED. Pa. 1962); Union Carbide v Borg-Warner 550 F.2d 555 (6th Cir. 1977); Consolidated Aluminum Corp. v Foseco Inc., 910 F.2d 804 (Fed. Cir. 1990).


\(^{96}\) See supra note 92, section 15 amending the existing 35 USC §282 to insert a new §282(3)(A).

\(^{97}\) EPC, Article 83 and Implementing Regulations of the Convention on the Grant of European Patents 1973 (as amended), r42(1)(e).

\(^{98}\) See supra note 92, Amended §102(b)(1).

\(^{99}\) EPC Article 55, relying on an ‘abuse’ (eg. breach of confidence) or disclosure at an international exhibition.

\(^{100}\) Albeit that case law occasionally regards moral considerations are part of the utility of the invention: Lowell v Lewis 15 F.Cas. 1018, 1019 (CCD Mass. 1817); Juicy Whip v Orange Bang 51 USPQ 2d (BNA) 1700, this is in the nature of judicial reliance on public policy grounds rather than a recognition that there is a moral criteria for patentability.
granting patent protection over stem cell technology in the USA and it is to this that the analysis now turns.

Patents are granted under Title 35 of the United States Code (USC)\(^\text{101}\) by the United States Patent and Trademark Office (USPTO) for a term of 20 years from the date of filing for a patent.\(^\text{102}\) In the case of stem cells, this can be extended where Food & Drug Administration (FDA) approval delays market entry.\(^\text{103}\) The right granted is often referred to as being monopolistic, but it has limitations. It is not a right to market, or a right not to be prohibited by regulation, and it is territorially limited (only protecting inventions within the USA).

WARF were assigned US patents to: (1) purified primate embryonic stem cells (including pluripotent cells) and their method of production;\(^\text{104}\) (2) those cells specific to humans (hESCs);\(^\text{105}\) and (3) the cell line created by culturing hESCs.\(^\text{106}\) In 2008 the USPTO limited the cell line patent to pluripotent hESCs obtained from pre-implantation embryos,\(^\text{107}\) and in early 2010 the Board of Patent Appeals and Interferences (BPAI) invalidated the patent. WARF have related patents,\(^\text{108}\) which are shored up by a raft of collateral, follow-on patents.\(^\text{109}\) The relevance of this is that, although WARF must appeal the decision to reinstitute existing licenses, it has already made sufficient further developments to enable those licenses to be replaced by licensing the next generation of innovations following on from the original invention.

The salient point for this analysis is that the patents predominantly relate to products: notably hESCs in a form suitable for use as a starting material; and potentially cell lines, which enable those stem cells to be reproduced on a manufacturing scale. The WARF patents have been the focus of contention because the control of the science principally comes from owning product per se patents. The product claims in WARF’s foundational patents are defined relative to the biological characteristics of the stem cells, so the claims are not diminished by being construed as product-by-process claims. This supports general fears about the potential for abuse, because the patent rights are strong. In context, purposive construction means that stem cells which do not comply with any of the defining characteristics identified in the WARF claims cannot infringe the patents granted from them. WARF’s patents can be invented around by innovations that do not entail using pluripotent stem cells,\(^\text{110}\) such as the iPSCs/piPSCs discussed in section 1. However, this relies upon WARF’s patents being limited to deriving from an embryo, which effectively excludes

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\(^{\text{101}}\) Parts I-IV (Fed. Cir. 1999).

\(^{\text{102}}\) 35 USC §154(2) protection is back-dated to the date of filing notwithstanding that the decision to grant occurs much later, or back-dated to the priority date where a related invention was already filed (35 USC §120), unless it relates to a foreign application which only qualifies for parity and not back-dating (35 USC §119 and §154(3) respectively) (and as renumbered by supra note 92).

\(^{\text{103}}\) 35 USC §155 (extension) and §155A (restoration). Similarly, delays with interferences and appeals can be ‘grabbed back’ to ensure a fair term of protection (35 USC §154(C)) (and as renumbered by supra note 92).

\(^{\text{104}}\) US patent number 5,843,780 (December 1998).

\(^{\text{105}}\) US patent number 6,200,806 (April 2006).

\(^{\text{106}}\) US patent number 7029913 (March 2001).

\(^{\text{107}}\) See Shyntum and Kalkreuter, supra note 40.

\(^{\text{108}}\) James A Thomson (the inventor) assigned a raft of additional patents specific to his research, eg. US patent number 6,534,052 granted in March 2003 relating to a method of treating heart attack patients with hESCs; or US patent number 7,176,023 granted in February 2007 relating to a method of making primate (including human) embryonic stem cells specialize into blood vessels cells.


\(^{\text{110}}\) See Bahadur and Morrison, supra note 10.
iPSCs/piPSCs because they come from multipotent (adult) cells. Patent law and research practice enable WARF’s competitors to legitimately circumvent WARF’s rights by inventing around them. The only problem is that, for every innovator inventing around WARF’s rights, new right owners are created who are ready to robustly litigate to protect their patents. This is supported by the recent litigation activities of companies such as Stem Cell Inc and Pharmastem Therapeutics. Circumventing WARF’s patents suggests there is no long-term abuse by WARF, but any initial abuse could cause a ripple effect: each new innovation replicating the initial abuse until it is invented around in turn and so on.

As soon as WARF obtained legitimate patents to the hESCs, its competitors had three choices: (1) find an alternative research direction; (2) invent around the patent; or (3) take a license and begin racing to develop the next generation of innovation, such as products/processes making stem cells specialize. Indeed this is already happening with innovations to induce cellular development into liver cells and into retinal structures. Alternatively where a bottle neck does occur, there are additional options.

A. Bottle-Neck Patents

Mechanisms for circumventing patent rights which block progress are found within the patent system and wider regulation. The potential markets in biomedicine, combined with the usual market rivalry of commercial enterprises, and the financial impact of patent rights (both in securing exclusivity which could result in market advantage, and in promoting investment) encourage organizations to adopt an aggressive approach to any rights granted in their technological field, whether they bottle-neck or merely inconvenience. However, the potential for an abuse of rights is reduced the more effective and greater the number of ways there are to circumvent patents: the potential for abuse of patents is marginalized if there is a robust system of regulation both within the patent system and outside of it.

B. Circumvention by challenge

The most commonly used means of getting around restrictive patent rights is to challenge them. This can be done by lodging a protest in which anyone can make a formal objection or simply submit documents to be considered where a patent is pending before examination. Post-examination, it is equally open to anyone to instigate re-examination on the grounds that the previous examination(s) did not take account of documents (representing knowledge already known) which cast doubt on patentability (eg. challenging whether it is new or sufficiently different). Arguably recent decisions make it easier to challenge on this ground, because they require courts to adopt a flexible approach to determining whether an innovation is obvious in comparison with existing knowledge. This replaces the

111 See Vrtovec and Scott, supra note 40.
112 See Van, supra note 29.
114 See Eiraku, supra note 30.
115 37 Code of Federal Regulations (CFR) 1.291 and 35 USC §122(2)(c) requiring written consent of the applicant if it is after publication.
117 35 USC §301-307 inclusive (as renumbered, supra note 92).
previously accepted formulaic TSM test (where the ‘teaching, suggestion, or motivation’ in the knowledge already known/the inventor/the problem being solved, identify that the invention was obvious to try). The consequence of the new approach is that the Supreme Court decision permits courts to take account of a wider range of factors. This makes it less predictable, but should make it easier to validate. This challenge can be undertaken either ex parte (without the continued involvement of the third party) or inter partes (with continued involvement). Despite commentary to the contrary, there is no limit to how many times an individual can instigate re-examination provided that it relates to new evidence. Third parties who are still dissatisfied can appeal to the BPAI (after the AIA is implemented, appeals being heard within the USPTO by the Patent Trial and Appeal Board), and actions can be referred to the Court of Appeals for the Federal Circuit or to the Supreme Court if permitted. While the cost of fees may not deter objectors at the protest or review stages, as actions progress into appeals, the legal costs can become prohibitively high for all but the most committed competitor. This represents a huge disadvantage for small and medium-sized (SMEs) companies.

Assertions that re-examinations are instigated by patent applicants tactically in “buttressing their claims” and that this results in the patent being more difficult to challenge, because third parties “must present more persuasive evidence to a court to invalidate patents that have survived re-examination” are highly misleading. The reason that patent holders instigate re-examination is to ensure that the patent granted is in its strongest form, but re-examination frequently includes having the claim more narrowly worded, so it presents a risk. However, it is a form of good practice which puts the patent holder in a better position to attract licensee and in subsequent infringement proceedings the patent holder may bring. Expensive counter-claims to revoke a patent can be reduced if the patent has been re-examined or challenged by protests, but this does not rely upon the patent holder doing this themselves. Any re-examination can demonstrate due diligence, because it identifies that the claim is appropriately worded to cover the innovation that it genuinely warrants. Re-examination is not undertaken with the intention of staving off attacks by competitors when the patent is initially granted, because competitors only have to present new evidence in order to bring their own challenge (no examination involves an exhaustive picture of the knowledge already known in a specialist field). This means that, no matter how many re-examinations a patent has undergone, there is no guarantee that another one will be unsuccessful. On the contrary, an applicant who triggers re-examination of their own patent can inadvertently alert competitors to weaknesses in their claims.

120 See supra note 92, §321-329 applying to patents submitted after March 16, 2013.
121 35 USC §311-318 inclusive, (amended under supra note 92 §311-319 and applying retrospectively) notable introductions in the new law are: (1) inter partes review cannot be instituted earlier than 9 month post-grant (§311(c): replacing inter partes re-examination with inter partes review); (2) review cannot be run in tandem with a claim for revocation (§315); and (3) the threshold of review is that there is a ‘reasonable likelihood’ of success.
122 Aurora Plomer et al., *Challenges to Human Embryonic Stem Cell Patents*, CELL STEM CELL 13-17 (January 2008).
123 35 USC §317 (supra note 92, §319).
124 35 USC §134(c) (supra note 92, §316(c)).
125 35 USC §141-144 inclusive (as renumbered, supra note 92).
126 As per Plomer et al., supra note 122, 14.
There have been numerous challenges to WARF’s patents directly and indirectly\textsuperscript{127} and, in order to retain licensing fees (generated from their foundational patents), it will be necessary to keep fighting. This is irrespective of the fact that the follow-on innovations (eg. processes for differentiating stem cells into germ layer cells)\textsuperscript{128} have diminished the relevance of the foundational patents; they have done their job in giving WARF a head start in stem cell innovation and in creating the basis for the next generation of product patents. The existence of checking mechanisms such as protests, re-examinations, reviews and appeals, which are available to be instigated by any third party, suggest that the potential for abusive patent rights is minimal. The fact that WARF/Geron’s rights continue to be tested by these mechanisms indicates that the hESCs patents are not unwarranted, because they have been invalidated where they grant too great a degree of control over the field of technology, but central rights remain.

\textit{C. ‘Safe Harbor’ and Experimental Use}

Beyond core mechanisms (such as re-examination and protest) for limiting the potential for abuse of patent rights, there are collateral mechanisms which can have the same limiting effect. Concerns that the impact of the hESCs patents will inhibit continuing research are addressed by the ‘safe harbor’ created under 35 USC §271(e)(1). This defines the ability of a non-patent holder engaged in research to use patented innovations which involve fusing cells or genetic manipulation, and this includes stem cell technology. The problem is that the harbor is reasonably narrow\textsuperscript{129} and in this context generally refers to uses attendant to obtaining FDA approval of medicines. The Drug Price Competition & Patent Term Restoration Act (Hatch-Waxman Act)\textsuperscript{130} governs market authorization procedures and the Biologics Price Competition and Innovation Act 2009 enables fast-tracking under the guidance of the Biosimilar Implementation Committee on the same general basis as those discussed in the context of Europe in III(H) above.

The restrictive wording of the ‘safe harbor’ provision under §271(e)(1) is wide enough to prevent future research being restricted by existing patent rights. The harbor exempts infringement for activities undertaken as part of the process of proving the FDA benchmarks for market authorization, no matter what stage of the investigatory process the use occurs\textsuperscript{131} in developing new medicines or devices.\textsuperscript{132} Within this it does not matter if the use of the


\textsuperscript{128} US patent number 7,585,672 B2.

\textsuperscript{129} For example Roche Product v Bolar Pharmaceuticals 733 F.2d 858 (Fed.Cir. 1984), prompting the introduction of the Hatch-Waxman Act permitting generics to use patented products/processes without infringing.

\textsuperscript{130} specifically 21 USC §355(j).


\textsuperscript{132} Eli Lilly v Medtronic 496 US 661 (S. Ct. 1990) including earlier District Court opinion rejecting application of the harbor to devices.
patented product/process is not part of the eventual FDA submission,\textsuperscript{133} just as long as its use is not collateral to it.\textsuperscript{134} The ‘harbor’ is wide enough to include use of patented products/processes in developing generics, as well as identifying new medicines.\textsuperscript{135} However, the harbor is not broad enough to capture the development of products/processes which do not have to comply with market authorization requirements\textsuperscript{136} and it does not include research tools,\textsuperscript{137} which expressly refers to ‘cell lines’. For stem cell technology and some of the follow-on innovations that come from them, this means that the ‘harbor’ is not wide enough to prevent licenses having to be obtained. This is a closely analogous approach to Europe,\textsuperscript{138} the USA being more explicit about excluding research tools from the exemption. After the introduction of the AIA, this provision will be extended by §273 permitting commercial use of patented products/processes where use occurs in good faith during market authorization review, which is more appropriately framed to encapsulate past case law.\textsuperscript{139}

The existing ‘safe harbor’ is supplemented\textsuperscript{140} by a common law defense to patent infringement based on an experimental use.\textsuperscript{141} This does not rely on any link with FDA approval, but any suggestion that research has a commercial aspect to it, takes it outside of the exemption\textsuperscript{142} and this includes use for educational purposes which may only be indirectly linked to tuition revenue.\textsuperscript{143} Clearly this is unlikely to provide researchers with much scope for avoiding licensing fees. Instead this defense must be considered as an aberrant judicial policy-based decision-making which has been amply accommodated by the imminent introduction of the much broader ‘commercial use in good faith in non-profit lab’ defense (under §273 as amended).

The safe harbor is more generously applied to State Universities and non-profit research labs, because they are immune from liability for breaching patent rights.\textsuperscript{144} However, immunity requires the research to be akin to pure science, because 35 USC 273(2)\textsuperscript{145} states that innovating in the public interest does not extend to actually performing the invention on the public. This is a critical limitation, because stem cell therapies are applied to the public both experimentally and as healthcare delivery. This blurs the distinction between commercial and non-commercial uses, as well as those between pure and applied science.

Non-State Universities do not enjoy the same government-related status, making their research activities part of their commercial presence and excluding them from immunity at present.\textsuperscript{146} Although research is not totally inhibited, there is an obvious inequity in the way

\textsuperscript{133} See Integra case, supra note 131.

\textsuperscript{134} Third Wave Technologies v Stratagene Corp. 381 F. Supp. 2d 891 (2005).

\textsuperscript{135} See Integra case, supra note 131.

\textsuperscript{136} Proveris Scientific Corp. v Innovasystems No 2007-1428 (Fed. Cir. 2008).

\textsuperscript{137} NIH definition of a ‘unique research resource’: 64 Fed. Reg. 72090, 72092, footnote 1 (23.1299) adopted as the definition of research tools by the Supreme Court in the Integra case, supra note 131.

\textsuperscript{138} Discussed at III(H) above.

\textsuperscript{139} Specifically sub-sections (c)(1).

\textsuperscript{140} See Integra case, supra note 131 in which the Supreme Court clarified that the ‘safe harbor’ and experimental use exemption are mutually exclusive.

\textsuperscript{141} Whittemore v Cutter, 29 F. Cas. 1120 (C.C.D. Mass. 1813).

\textsuperscript{142} Embrex v. Service Engineering Corp., 216 F. 3d 1343 (Fed. Cir. 2000).

\textsuperscript{143} Madey v Duke University, 307 F. 3d 1351 (Fed. Cir. 2002).

\textsuperscript{144} 35 USC §273(2) (§273(c)(2) as renumbered post-n91); Florida Prepaid Postsecondary Education Expense Board v College Savings Bank, 527 US 627 (1999).

\textsuperscript{145} As renumbered after supra note 92.

\textsuperscript{146} Supra note 143.
that the law operates between government and non-governmental institutions. Arguably this redresses the imbalance between federally-funded organizations (which have traditionally been unable to compete in developing innovations through to market), and commercial businesses or well-funded non-State Universities with commercial links (which have enjoyed greater success in pushing forward new technologies). While there is ambiguity about the precise stage of product development that can be reached by commercial organizations before falling outside of the safe harbor, this is not the focus of the criticisms aimed at stem cell innovators such as WARF.

There is room to argue that the safe harbor should be cast far wider if it is intended to create a comprehensive research exemption, but this would result in diluting the exclusivity of the patent right and creating a knock-on effect which deters subsequent innovation. In its current form, the provision at least allows that some experimental use and federally-funded research is non-infringing. By 2006, WARF had licensed their stem cells to 365 academic organizations, so it is difficult to agree they are responsible for inhibiting continuing research or that patents inherently have this effect.

D. March-In Rights

The 1980 Bayh-Dole Act enables State Universities to license their patentable research to commercial organizations. The purpose of the Act is to better equip federally-funded institutions to progress their innovations to market, by enabling them to tap into the existing product development resources of commercial enterprises. The interests of the Government are secured by provisions ensuring access to the innovations, as well as a default provision requiring any ownership rights not taken up to revert to the Federal Government. The interests of society are secured by the requirement that the innovation be predominantly manufactured in the United States, unless this is not possible, at which point the focus shifts to getting the technology onto the market and manufacture abroad suffices.

The introduction of the Act immediately prompted fears that federally-funded research would be co-opted by commercial interests, taking it away from its traditionally altruistic pursuit of research in the public interest. This is of particular relevance, because WARF are a non-profit organization set up by the State University of Wisconsin-Madison specifically to take advantage of the interface with industry created by the Bayh-Dole Act. A 2007 survey of the top 125 Universities (ironically conducted by Wisconsin-Madison University) identified that such fears were without foundation and only 8% of researchers had received

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147 This accords with the Bayh-Dole Act.
150 See Shyntum and Kalkreuter, supra note 40.
152 35 USC §204.
So there is little risk of a general trend towards academic researchers being seduced into following the agendas of ‘moneybag’ companies. This places WARF’s hESC patents in a context in which public research is encouraged to become commercial. Additionally, even if proven to be an instance of abuse, WARF are an isolated instance and not the beginning of a mass stampede which justifies radical/strict regulation.

The patent law also provides march-in rights for federal funding bodies (eg. the California Institute of Regenerative Medicine, CIRM) where innovations they have paid for are sat on by commercial organizations. This means that, if the commercial organization refuses to license-on the innovation, the federal funding body can circumvent them and grant licenses to third parties, free of the normal constraints of contract law. This is a classic example of flexible legislative drafting, which hinges upon concepts of ‘responsible applicants’ and ‘reasonable’ terms. Yet the fundamental limitations of the provision relate to the behavior by the commercial organization which instigates the march-in by the funding body. This is constrained to fall within one of four possible scenarios: (1) the commercial organization has not taken ‘effective steps’ towards proliferating the technology within a ‘reasonable time’; (2) requirements of health and safety; (3) Federal regulations specifying ‘public use’ are not being met; or (4) there is no agreement to manufacture the innovation either in the USA, or abroad.

This is a form of compulsory licensing which severely limits the scope for abuse of patents. This is because it ensures that, as a minimum, the Government can step in to ensure that federally-funded innovations will be proliferated. Criticisms are that: there is a great deal of flexibility in how the provision is construed; it is only as strong as the willingness of the Government to enforce it; and it cannot be used where the research is privately funded. However, the Government’s track record ably demonstrates that they are very willing to impose compulsory licenses and this is not the only form of compulsory licensing available.

### E. Compulsory Licensing

Compulsory licensing is automatically granted for Government use of any innovation patented by the USPTO. While the patent owner is entitled to reasonable compensation, they are not able to prevent its continued use. This was a point which was underscored by the National Institute of Health’s (NIH) Working Group Report on Research Tools. Compulsory licensing is also used by US competition authorities to remedy anti-competitive practices, such as paying competitors not to enter the market and can be brought as a private action against anyone abusing patent rights to gain market advantage. Finally, it is also open to the courts to impose a compulsory license, with or without a royalty fee, where they believe that it is necessary.

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155 Specifically the Contract Disputes Act (41 USC §601).
156 For example Crater Corp. v Lucent Technologies 255 F.3d 1361 (Fed.Cir. 2001).
157 28 USC §1498(a).
160 For example re Dell Computer Corp.121 FTC 616, FTC LEXIS 291 (1996).
161 For example Innogenetics v Abbott Labs. 512 F. 3d 1363 (Fed.Cir. 2008).
All of the various avenues for imposing compulsory licenses support the contention that there is little scope for abuse. Key criticisms tend to revolve around the interpretation of the events that trigger the compulsory license, or the need to delay proceedings in order to provide time for the abuse to become established. These are countered by the need to distinguish between enforcing abuse, and not using the law to prevent any market advantage. Where an abuse does occur, it cannot validate allowing the Government to claim back rights to gateway technology, or mandate devising new systems beyond patenting that are specific to pivotal innovations. This is because it teaches innovators to either fail to be ambitious in their achievements, or not to bother innovating at all.

Overall, the patent system presents a range of mechanisms which, in concert, are effective at preventing abuses which can result from rights which are too broad, too narrow, not worked or are simply too fundamental. Development is achieved by balancing the innovator’s need to exclude third parties, with the rights of researchers to continue exploring. Expanding research exemptions means that there is less scope for innovators to exclude competitors, and this is likely to prevent innovations being marketed. In essence, the expense of R&D and trials are ‘underwritten’ by the patent, which is critical in medicine because even large companies struggle to fund expensive extended human clinical trials. An altruistic research community is impossible to maintain, but patents are not the problem. This is demonstrated by WARF’s patents (along with the legal decisions in WARF and Brüstle) doing no more than contributing to the temporary redirection of research in Europe. The patent system imposes limits on unwarranted rights, but this cannot mean merely inconvenient. Ultimately, it is WARF which suffers the loss of license fees that ensues, but even this is ameliorated by the innovation lead that they have achieved. By far the biggest danger is that the diverse opinions of commentary obscure the fact that legally restricting the form of patent claims cannot have the moral effect predicted. All that is excluded in Europe are claims which either expressly or impliedly rely on embryonic destruction (or morally equivalent methods, irrespective of what the physically process of invention). Scientific research has already developed means of inducing pluripotency without recourse to embryos, but still offering a generous scope for subsequent specialization into a wide range of potential cells. Crucially, this represents no disadvantage in Europe competing with the USA.

Freed of moral consideration at the patenting stage of development, the USA faces difficulties in balancing the needs of researchers who reach the patent office first and those who do not want to load development costs with additional licenses. The existence of rights is about reaching compromises, but they must ensure progress above all else. Patent law provides plenty of mechanisms to address potential abuses, but there is no evidence of abuses in progressing stem cell technology. While there are arguments that the pace of innovation could be improved by extending the research exemption and reconsidering compulsory licensing mechanisms, exploration of these issues requires analysis beyond the scope of this contribution.

This section demonstrates that, either side of the Atlantic, nurturing technology as complex as stem cells requires rolling amendments, and reconsideration as more is learnt about the technology and how it fits into existing R&D practices. Fundamentally, progress relies upon achieving a complex mix between broad terms (which can accommodate a wide range of future prospects), specific terms (which can provide legal certainty) and having varied checking mechanisms which can be tweaked as needed. Having established that patents have not proven a significant problem in the development of stem cells, an analysis of specific regulatory measures is required. This will determine whether wider regulation threatens progress (representing potential abuse of the public interest) and the nature of the relationship of patents to this overarching regulation.

VI. GENERAL REGULATIONS: EUROPE AND THE USA

Irrespective of whether technology is patented, in the context of stem cell technology there are additional requirements to obtain ethical approval, conduct clinical trials and to obtain market authorization before any innovation can enter the market. The focus of assessment for Research Ethics Committees (RECs, EU) or Institutional Review Boards (IRBs, USA) is generally upon safety, the protection of participants and runs in tandem with robust peer review. As such these bodies are not generally regarded as being open to abuse because it relies upon an ability to play the system which is not realistic. The requirements of clinical trials are concerned with safety, repeatability and reliability and as such rely upon technical standards.165 This is similarly true of the regulation of market entry, governed trans-nationally by the EMA (EU) or nationally by the FDA (USA), where standards revolve around specific interpretations relating to the general requirements for safety, efficacy and security. Although a comprehensive discussion is not possible, analysis in the foregoing subsections identified that these regulations do not represent any unnecessary restrictions for the development of stem cell technology than is presented to other forms of technology. This is because the purpose of review, trials and market authorization is to ensure that the public are not subject to any unnecessary risk, and this is also true of post-marketing reportage, health technology assessments and pharmacovigilance measures.166 Consequently all of these forms of oversight are intended to provide equivalent benchmarks which must be overcome in order for any technology to enter the market and, where there are risks specific to a particular technology, the general framework is supplemented by technology-specific requirements. These aspects of the innovation process represent potential abuses which arise from factors outside of the regulatory provisions.


In terms of the potential for abuse, there are none apparent in REC/IRB oversight, clinical trials regulation or market authorization procedures because these systems are not reliant on specific characteristics or individual companies. Instead, regulation is reliant upon scientifically proven standards, and this plays no favorites.

A. Broader Regulation: EU

As previously stated, funding and EU regulation do not have to adopt the same approach to regulation as the approach to patenting hESCs. This is because moral reservations which impinge upon funding research may not necessarily extend to the prospect of patenting the innovations developed. The Technical Board of Appeal in the Oncomouse II case stated that patenting in itself does not raise any issues of morality. This is because patenting and commercialization are very distinct concepts. This indicates that a cohesive system of regulation can accommodate disparate approaches, provided appropriate justifications underpin the need for such disparity. In the context of Europe, it is possible to provide a system of regulation for a technology which is morally disapproved of because regulation applies to so many jurisdictions. In the context of stem cells, this means that an assessment of the broader regulation should represent a cohesive system which either adopts the same approach to regulation or underpins divergences with appropriate reasons. In addition, if stem cell technology is going to be promoted efficiently towards marketable products and processes, this broader approach to regulation should be no more restrictive than the approach to patenting identified above.

Article 18(2) of the Convention on Human Rights and Biomedicine 1997 prohibits the creation of human embryos for research purposes and this is a key reason why Member States, such as the UK, have not signed the Convention. The consequence is that Europe is divided between those countries with a moratorium on embryonic research and those who permit it. It is against this background that the FP6 (2002/6) EU Funding Programme and the current FP7 (2007/13) programme were created. Under the FP6 programme, the EU Commission implemented what became known as a ‘procedural modality’ in order to circumvent the moratorium on embryonic research within limited parameters. This permitted funding for hESC research provided the research involved banked or previously isolated hESCs. This suggests that the EU are prepared to actively encourage embryonic research, evidenced by the inclusion of an innovative medicines initiative within the FP6 programme as one of the technology platforms designed to encourage public/private partnerships in research. The list of projects funded by this programme is a matter of public record. The introduction of the FP7 programme, following vociferous debate, and eventual compromise in the European Parliament, continues the same broad approach to funding embryonic stem cell research as does the FP6 programme. Under the FP7 programme initiatives, such as ESNATS, which uses EU funding to develop hESCs to create toxicity tests, have been created.

167 See Oncomouse II case, supra note 66, para 4.2.
168 CETS No 164 (1997).
Beyond this, the EU introduced protective measures which regulate the procurement, testing, processing, storage and distribution, as well as the import and export, of cells for human application. In addition, the Advanced Therapy Regulation 1394/2007/EC identifies that the industrial-scale production of tissue engineered products, which are subject to the market authorization benchmarks laid down by the Regulation, include hESCs. Recital 7 makes it clear that it is open to individual Member States to introduce domestic legislation which can prevent marketing within that particular country. The provision of this type of regulation, which, of necessity, is permissive of embryonic research and the products and processes derived from it, is not the hallmark of an institution which is determined to prevent such research for moral reasons.

What appears to be an active encouragement of embryonic research, by the provision of funding and regulatory measures, is arguably the complete reversal of the highly restrictive attitude which prohibits patenting innovations which are reliant upon the destruction or use of human embryos (or the equivalent) for their existence. In many respects the current approach to patenting continues the artificial construction of the ‘procedural modality’, which enables the EU to accommodate the needs of Member States, such as the UK, (which rank highly in the global biomedicine industry) and Italy (which completely bans embryonic research). Consequently, this strengthens the understanding outlined above of the CJEU (and in some respects also of the European Appeal Boards) to prohibiting patenting hESCs only to the extent that Europe needs to avoid being seen to operate a policy which actively encourages the destruction of human embryos. The fact that the prohibition on patenting is unlikely to prevent the destruction of embryos is beside the point: the point is that the EU is providing Member States with the choice of conducting embryonic research and it is down to the individual Member State to take the moral responsibility for doing so. Providing a choice can be justified to those Member States which are horrified by such research, because this is not the same as endorsing or actively encouraging. Consequently the funding and specific regulatory approach of the EU and Europe’s approach to patenting align. Researchers can: take the funding money; undertake the research; develop the innovations that will result in increasing Europe’s economy; and market them with the permission of the Member State, but protecting that research through patents relies upon being able to demonstrate that the innovation could have been developed without destroying embryos and, even then, it is subject to the morality of individual Member States. This represents a cohesive system with individual choice built in at all points which, given the fact that regulation in any form needs to accommodate diametrically-opposed views to the morality of embryonic research, is no mean feat. The degree to which it will result in stem cell technology progressing to marketable products/processes, even in the most permissive Member State, is likely to be temporarily adversely affected by the recent decisions on patenting. This will be magnified beyond all measure if the legal decisions are wrongly interpreted as being a carpet prohibition on patenting pluripotent stem cells.

B. Broader Regulation: USA

This analysis focuses upon the aspects of regulation which have the greatest impact on the progress of stem cell technology emanating from the wider regulatory landscape created

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by the government. It is not possible to provide a fully comprehensive review, but an overview can identify specific measures which have positive/negative effects on the progress of stem cell technology.

In 1974 Congress voluntarily imposed a moratorium on federal-funding of embryonic research (including pluripotent stem and totipotent cells), until moral issues could be resolved. The Department of Health and Human Services (DHHS) adopted regulations for embryonic research and lifted the ban on funding. Yet, over the course of the next fifteen years, the DHHS refused to authorize any funding and the moratorium was re-imposed. In 1990 Congress’ attempt to remove the ban was prevented by President George Bush and successive attempts to reverse it were staved off.

The Clinton administration lifted the moratorium in 1993 on the advice of the Human Embryo Research Panel, which the NIH had recently created. Congress attached the Dickey-Wicker Amendment to a 1996 Appropriations Act, which prohibited federal-funding for research involving damage/destruction to embryos, but the Clinton administration interpreted the Amendment as permitting federal-funding of hESC research where the destruction of the embryos is privately funded. This relied upon an understanding of the Amendment which rests upon the publicly-funded ‘research’ not including the act of embryonic destruction. However, the position was effectively reversed following a public outburst against embryonic research: the Clinton administration did not withdraw its interpretation of the Amendment, but did not grant funding for hESC research either.

In 2001 President George W Bush introduced a new ban, which excluded hESC research from federal-funding, unless the cell lines already existed. This was not a tangible relaxation of a prescriptive policy, but a means of re-instigating a restrictive approach overturing the foregoing liberal approach which had stalled in the face of converse public opinion. The scarcity and poor quality of the existing cell lines prompted the introduction of the Stem Cell Research Enhancement Act 2005, which was vetoed the following year by President Bush. There was some minor leakage to the economy where companies which were heavily invested in hESC research, and had limited market portfolios (inhibiting their ability to diversify), migrated to countries such as the UK and Singapore. Anomalously, additional protection was added in the form of §3504 of the Fetal Farming Prohibition Act 2006. This prevents the intentional creation of fetal tissue for research purposes and was introduced despite the Act’s recognition that fetal farming is not even contemplated by the scientific community. Consequently, this must be seen as a symbol of a pro-life commitment, rather than as a realistic form of specific regulation excluding a particular form of technological development.

While this represents a brief review of the federal situation and there is a patchwork of mixed approaches on a State-by-State basis, it has been suggested that additional measures were undertaken on a federal level during the Bush administration to stack decision-making

172 See Termini, supra note 11, 267.
175 For more on the global approaches to regulating stem cells see MBBNet’s WORLD STEM CELL MAP http://www.mbbnet.umn.edu/scmap.html.
bodies with members who were overtly anti-hESC research. This is a typically political approach to dominating a specific regulatory landscape which enables the incumbent administration to ensure that its agenda is pursued effectively. As such, it demonstrates how specific regulatory legal measures are shaped by political science as much as by public opinion, the media or informed debate. In this particular context, it is clear that the overall effect of such a restrictive stance has been to deter venture capitalists from investing in hESC research and driven funding towards competitor innovations such as iPSCs. However, polls identified that during 2001 to 2004 73% of the public in the USA were in favor of hESC research, making it debatable whether the overall effect of the restrictive Bush administration had the long-term consequence intended.

In 2009, President Obama signed the Executive Order which lifted some of the previous limitations on hESC research and charged the Secretary of the DHHS to review NIH regulations. These Guidelines permit federal-funding to be granted for research in which the source of the hESCs (in addition to the pre-2001 cell lines), also include surplus embryos from IVF treatment which have been donated, and embryos from Pre-implantation Genetic Diagnosis (PGD) (subject to proper consent). These embryos are either ‘left over’ or not viable for implantation, so lie at the less contentious end of the possible sources. Commentators are already quite rightly bemoaning this compromise, which will hamper the ability to obtain disease-specific cell lines. Given the fact that the greatest value of stem cell research at present is in the creation of disease models (providing greater insight into disease processes) and in utilizing the cell lines as factories for the production of biopharmaceuticals (rather than in the provision of therapies treating conditions such as Alzheimers), it is a shame that much of this value is restricted by the NIH. However, the ability of the NIH to make far-reaching policy is doubted where its sphere of influence is limited to public research and so it has been suggested that the Guidelines represent little more than an “incremental, rather than sweeping, change...[enabling] new, better-quality lines to receive funding”. This overlooks the possibility that the Guidelines may become an industry standard where other regulatory bodies and oversight committees adopt the same or similar approaches. The Guidelines also make it explicit that embryos cannot be donated for either self-therapy or for therapeutic value to named recipients. This is clearly an issue which must be revisited as the chain of innovation progresses and stem cell treatments are marketed: it is inescapable that personalized medicine is the direction in which innovation is moving. As they stand, the Guidelines should have the effect of reversing reticence to invest in hESC innovation, putting the USA in a strong economic position as the technology develops. This is already evidenced by stem cells from the two largest stem cell banks being twice as likely

178 See supra note 3.
179 See Termini, supra note 11, 274.
183 id., 303.
to go to the USA, than anywhere else.\textsuperscript{184} In 2010 the National Stem Cell Bank’s contract with the NIH expired, and its closure led to supply fees doubling.\textsuperscript{185} It is difficult to argue that the taking up of this role by the Wisconsin International Stem Cell (WISC) Bank\textsuperscript{186} has adversely affected the competitive market in stem cell supply, given that there are stocks available at other Cell Banks around the world.

The changing political administrations in the USA have intermittently promoted and opposed stem cell technology. It is inescapable that the Obama administration is attempting to reverse the anti-stem cell technology approach which preceded it. Venture capitalists looking to the permissiveness of the regulatory regime to determine where to invest with the greatest security for long-term benefits, as well as providing a steady stream of start-up companies to invest in, are likely to view such variable funding availability as cause for a cautious approach. So too for stem cell researchers reliant upon brief spells of NIH funding, the lack of long-term security is undoubtedly going to adversely affect the continued development of hESCs.

The current administration has gone some way towards ameliorating this with the introduction of Executive Order 13563, which is designed to cushion the introduction of new technologies which “protect public health, welfare, safety”.\textsuperscript{187} This is a regulatory approach which is reliant upon innovatory progress where it is based on firm scientific knowledge, gains legitimacy from public consultation, and gains efficiency from better “coordination, simplification and harmonization”.\textsuperscript{188} This prizes non-interventionism and cost-effective, but beneficial\textsuperscript{189} outputs, arguably above competing requirements to secure against as much risk as practicable.\textsuperscript{190} It is doubtful that this general permissiveness in regulating a broad range of technologies will allay concerns that future administrations will return to restrictive policies on hESCs. The best hope for long-term security rests on two Bills currently progressing through the 112\textsuperscript{th} Congress entitled the Stem Cell Research Enhancement Act. The primary aim of both is to ensure that embryonic research (even in a limited form) is a legally protected activity. While this would certainly be more difficult for ensuing administrations to overturn than moveable interpretations of the Dickey-Wicker Amendment and Executive Orders, it is not proofed against revocation. It is also to be wondered if either Enhancement Act will eventually be implemented, given that both are re-introductions of Bills that failed to make it out of the previous Congress.

One of the key reasons hESC research has encountered such variable regulation is because it is rooted in a far deeper division in the USA regarding the sanctity of human life.\textsuperscript{191} Most notably, the Supreme Court in \textit{Roe v Wade}\textsuperscript{192} permitted abortion on the basis that the unborn have no legal rights. More recent challenges to stem cells through the courts have

\begin{footnotesize}
\begin{enumerate}
\item id.
\item Executive Order 13563 (January 18, 2011) 76(14) Federal Register 3821-382.
\item id.
\item HR 873 and S487, reintroduced after failing to complete under the 111\textsuperscript{th} Congress, but being considered by the House Committee on Energy and Commerce (notably Congressman Waxman, who sponsored the Hatch-Waxman Act, is the ranking member on the Committee).
\item id., evidenced in particular in Section 1(b).
\item See supra note 119.
\item Roe v Wade, 410 US 113 (1973).
\end{enumerate}
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come from a cryopreserved embryo (Mary Doe), which lead the court to state that embryos are not legal persons under the law because they do not have legally protectable interests. In Doe v Obama another cryopreserved embryo was found to have insufficient standing to bring an action, because embryos do not warrant protection under relevant Amendments of the US Constitution (one of which guarantees citizenship, due process, the right to equal treatment under the law, and the right to life, liberty and property).

The NIH Guidelines have already been challenged in Sherley v Sebelius, in which various pro-life groups and individual researchers sought to re-impose limits on federal-funding of hESC research. Administrative Law reviews public decision-making to prevent it being "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law". Most of the initial litigants were excluded, because they did not have a sufficient interest in the outcome. This is a limitation on the public’s ability to change wider regulation not imposed when challenging patent decisions. The initial decision of the District Court of Columbia held that the Dickey-Wicker Amendment was still in force and unambiguously identified that federal-funding of hESC research extends to the entire research process; in other words, the Amendment cannot be simply circumvented by adopting an artificial construction of ‘research’ which permits the destruction of human embryos to be hived off from the rest of the investigatory process. This had the effect of collaterally making the Executive Order issued by the Obama administration redundant. On appeal, the decision was reversed on a 2:1 vote and Circuit Judge Ginsburg’s lead judgment identified that the meaning of ‘research’ is open to interpretation. In Administrative Law this means that such ambiguity in legislation must be left to the decision-making body to determine the meaning reasonably. The converse opinion, expressed in Circuit Judge Henderson’s dissenting judgment, hinged on the fact that the first research act is the destruction of a human embryo, tainting every subsequent step in the composite research process. While this is a justifiable approach to legal construction, it overlooks the obvious issues with enforcing the law: there are no reliable means of distinguishing the source of the stem cells being considered unless the information is volunteered. Clearly despite the passage of time and the shift in political agendas, the issue of hESC research continues to polarize opinion seemingly without thought to the broader implications. This notwithstanding, on remittance to Chief Judge Lamberth the decision of the Court of Appeals was given effect, although it must be doubted that this is the end of the issue.

A fundamental reason why funding has become such a pivotal issue in hESC research is that it makes the link between the public purse and a form of technology which elicits

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197 See for example Short, supra note 11.
198 Sherley v Sebelius, supra note 195, 16.
200 See Lujan v Defenders of Wildlife, supra note 196, 4.
strong opinions. Should the public be expected to fund research which a significant proportion (even though a minority) vehemently oppose? It is generally accepted that taxpayers are expected to fund technologies irrespective of moral abhorrence (eg. nuclear weapons). Similarly, funding does not equate to results: innovation cannot be guaranteed even with unlimited funding.

Commentators have tended to over-rely on funding as the key to development. Winickoff suggested that public trust can only be secured where funding priorities and timescales for beneficial outputs are openly agreed, resting on the fallacy that innovation can be organized. What should have become clear from this analysis is that innovation is unpredictable, cannot be guaranteed and relies on lots of factors. It can be maximized by competition for resources and rights (undertaken in a supportive regulatory environment which at least ensures no favorites), but more than this cannot be realistically expected.

Eisenberg and Rai recommended that funding agencies (such as the NIH) be given more control of the patent rights and licensing behaviors of those they fund. They pointed to the genomics industry as an example of a technology that progressed by both private and public funding despite the release of otherwise proprietary information (capable of being patented) into the public domain. In the alternative, the option to limit patent protection on gateway technologies was rejected on the grounds that “it is difficult to fine-tune the patent statute to achieve just the right balance” and the risk to the economy of getting it wrong is too great. This overlooks the impact on public research: research institutions very often rely upon the prestige of the patents they generate to attract income. These institutions already experience difficulties in keeping top researchers, because private companies offer superior employment and remuneration packages. For many researchers, career development plans include having one foot in academia and one in a startup company created on the back of patentable innovation. While there is no evidence of a mass exodus to the private sector in stem cell development, there is the potential.

Borlongan et al. regarded the public funding of stem cell technology as necessitating public accountability. They proposed the creation of a multi-disciplinary Ethics Research Consortium which would serve as a consultation group, public educator and trainer to all affected parties in the regulation of stem cell technology. Conversely, Sage pointed to the travesty of concentrating limited social resources on expensive stem cell therapies, while the existing demands of public health in the USA are more likely to be met by concentrating upon “health behaviors and chronic diseases so multi-factorial in origin that no stem cell treatment is likely to cure them.”

The move from the protectionist, pro-life policies which dominated both Bush administrations and dogged the Clinton years, into the pro-research Obama administration has not represented a vast difference in the overarching regulation of stem cell technology. Neither administrative approach unequivocally banned stem cell technology per se, instead the difference is in the underlying intention and the overt posturing: restrictive under both

202 David E. Winickoff, Governing stem cell research in California and the USA: towards a social infrastructure, 24(9) TRENDS IN BIOTECHNOLOGY 390-394, 391 (2006).
204 id., 175.
205 Cesar V. Borlongan et al., The care for an Ethics Research Consortium for emerging technologies: public perception of stem cell research and development, 12 TECHNOLINNOV 1-11 (2010).
Bush administrations and more permissive under the Clinton and Obama regimes. While the current context of permissiveness suggests that the USA looks set to herald a renaissance for hESC technology, the details identify a far more limited prospect. The constantly changing policies is likely to result in a more tentative attitude to funding research by both public and private funders and this is highly likely to slow the pace of stem cell innovation. This is because, although innovation cannot be guaranteed simply by access to funding, funding does improve the prospects for progress. Without security in the future permissiveness in the regulation of stem cell technology, funders are less likely to consider hESC research a prudent investment. This is because there is a greater risk that restrictive regimes in the future will impose a complete ban, or stack key decision-making bodies with sympathizers. However, both restrictive Bush regimes have stopped short of imposing an outright prohibition and this gives hope that emerging products/processes can be marketed well into the future. This indicates that the wider regulatory environment has a far greater power to encourage or deter innovation towards marketing than does patenting. This is an important consideration in determining how to promote innovation.

Government-led regulation is open to abuse, because it is: too fragmented; too open to change with different administrations; and too susceptible to agendas being secured that are not in the public interest or representative of public opinion. The approaches of both Republican and Democratic administrations rest upon unfounded prejudices which restrict the scope for exploring disease processes. Therefore, there is reason to support a reconsideration of the existing Guidelines to provide a much better template as a possible industry standard in reflecting a full range of sources for stem cells, which could easily be limited to particular research activities. For example, human admixed embryos (human/animal hybrids) or embryos obtained by parthenogenesis may be suitable sources for the investigation of disease processes as disease models, or even potentially as factories in the production of biopharmaceuticals, but not for the development of therapies.

VII. INDUSTRY REGULATION (LICENSING)

A. Europe

The failure to patent existing pluripotent stem cells which have been derived by embryonic destruction/use means that there is less incentive to obtain stem cells from existing lines. This is because there is no patent to prevent researchers destroying embryos to create their own lines. The net result is that those who have already created stem cells will be unable to charge more than nominal access fees (much less than license fees), which will prevent them from recovering the costs of development. It is also likely to mean that potential customers will be from overseas (eg. from the newly, post-generic originator producing countries such as India and China, or the USA, with the commonality of wishing to explore stem cell technology, but with few limits on stem cell sources). In the short- to medium-term it could mean that researchers will avoid developing stem cells which cannot be obtained without utilizing embryos and this is likely to slow the pace of innovation. This is because there may be no evidence that the pluripotent stem cells produced/used could be created by either transcription or protein induction methods (producing iPSCs and piPSCs). This means that innovation may rely on researchers either developing specific pluripotent cells (such as those having genetic propensities to develop particular conditions or to correct particular biological processes) without utilizing embryos, or wait until this is done by others and use trade secrecy to protect innovations developed using embryo-reliant stem cells in the
meantime. The effect is likely to push back current research initiatives which focus upon the subsequent therapeutic and clinical value of stem cells at least to some degree.

For those who have already banked iPSC or piPSC lines, there could be a significant increase in revenue from licensing if the existing law is misinterpreted as a blanket prohibition on using embryo-derived stem cells (rather than as a restriction on patenting where stem cell production is solely reliant on embryonic destruction/use), pushing up demand. In the long-term, once research overcomes this initial hurdle and re-focuses on follow-on products and processes (such as specialization and subsequent therapies), the amount of embryonic use will only be reduced where production of iPSCs or piPSCs (and any other non-embryonic pluripotent stem cells available at the time) is cheaper than obtaining pluripotent stem cells from embryos.

In terms of the potential to abuse patent rights in order to restrictively license, this is minimized by international and domestic patent measures and by collateral European regulation aimed at permitting compulsory licenses or licenses as of right to be granted.\(^{207}\) In the context of stem cells, the most effective mechanism for ensuring that innovators cannot offer licenses subject to restrictive or onerous conditions has been the industry itself. This is evidenced by the criticisms which followed the conditions attached to WARF’s American stem cell patents, which prompted them to change their licensing conditions\(^ {208}\) and to which this analysis now turns.

**B. USA**

The final criticism of WARF is its prohibitively restrictive licensing practices and this is a recurring factor generally identified as being a main reason why innovations such as stem cell technology are prevented from realizing their full potential. In the context of WARF, this revolves around four problems: (1) the initial high cost of license fees;\(^ {209}\) (2) the memorandum of understanding (MOU) granting researchers royalty-free access to cell lines but not extending to research funded outside of the NIH (setting the NIH up as a guardian of the technology);\(^ {210}\) (3) the fact that WARF’s approach makes it difficult for small companies to innovate where they cannot afford access to cell lines;\(^ {211}\) and (4) that any commercialization which results from licensed commercial/non-commercial organizations requires a separate license to be agreed with WARF (reach-through).\(^ {212}\) Had WARF been a commercial organization, the licenses would have extended to grant back clauses, which provide the licensor rights to follow-on innovations that the licensee subsequently develops. The WARF patents were challenged by competitors and public interest organizations and, in response to criticisms in the press and the low take-up of licenses, WARF lowered its fees and introduced three policy changes: (1) making it easier for small companies to gain access to the cell lines

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\(^{207}\) eg. Agreement on Trade-Related aspects of Intellectual Property Rights (TRIPs Agreement) 1994 (as amended), Article 31, UKPA, sub-sec. 46, 48-54 and incorporating The Patents (Compulsory Licensing and Supplementary Protection Certificates) Regulation 2007; Regulation 816/2006/EC on compulsory licensing of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems.


\(^{209}\) See Bahadur and Morrison, *supra* note 10.


\(^{211}\) *id.*

\(^{212}\) *id.*; See Chapman, *supra* note 40.
in order to innovate independently; (2) facilitating cell transfers between researchers; and (3) clarifying that CIRM-funded research is not subject to licenses or fees. However, not everyone appears pacified by this shift. The fact that much of the focus of criticism has been aimed at WARF presents a distorted picture of the development of this technology: this is an international endeavor undertaken by a reasonably diverse field of specialists. Indeed, far from attempting to dominate stem cell technology, a 2007 study stated that WARF has legitimized the technology by acting as a “protector, propagator and influencer”.

Aggressive licensing and reach-through provisions that result in license stacking (which occurs where licenses affix at every stage of the chain of innovation, making delivery to end-users less likely) are a problem, but are merely speculative in WARF’s case. Any innovator who beats their competitors to patents or exclusive licensing rights will derive an advantage. Commercial reality dictates that gaining an advantage cannot mean pricing yourself out of the market. This is a lesson that WARF have learnt the hard way, but it is clear that the long-term and on-going abuse that is feared has not reached the level at which the public interest is adversely affected. What is being affected is free access to innovation, but this is what the patent system is designed to create: a short-term restriction, in order to secure a long-term social gain.

Licensing is regulated to some extent within the broader framework of patent rights (and collaterally by commercial contract and anti-trust legislation), but there have been many suggestions for radically changing the regulation of licensing. Benefit sharing (which enables access to resources in exchange for other assets such as money, training, or manpower); patent pools (which enable a vastly reduced fee or free access to a limited range of patented innovation in the ‘pool’, with those outside paying full fees); clearinghouses (mediating fees between subscribers); modeling open source proliferation (free access to originating innovation, but which is reliant upon adding to the innovation and then re-offering it for free to others who will also add-on); or liability regimes (which rest upon paying reduced fees for use rather than a license which grants rights to exclude). These proposals have the benefit of moving the debate away from using licensing as a means of demonizing patents. However, they are unlikely to be as effective at regulating access to legally protected innovations as is self-regulation within the industry and general commercial practice. This has been ably demonstrated by the quick response of WARF to the lack of parties willing to take up their licenses long before any measures could be undertaken through legislative protection of: licensing patents; compulsory licensing; march-in; contract mediation; or anti-trust measures regulating anti-competitive practices.

VIII. CONCLUSION

It is clear from this analysis that there is a strong interaction between the general regulatory landscape, the specific agendas of political administrations and existing commercial practice. It is this interaction which describes how easily stem cell technology

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213 See supra note 208.
214 eg. See supra note 122; and Bahadur and Morrison, supra note 10.
216 35 USC, Chapter 23, §261 and Chapter 18.
217 See for example Geertrui Van Overwalle (ed.), GENE PATENTS AND COLLABORATIVE LICENSING MODELS (Cambridge CUP, 2009).
can reach its market. It is notable that the moral agendas of Europe and the USA have taken effect at entirely different points in the regulation of innovation: for Europe patenting has provided the moral testing ground, but in the USA (deprived of moral review of patents) the broader sphere of government-led regulation has proven the sticking point of morality. On a legal basis, the greatest scope for either Europe/the USA gaining a competitive advantage relies upon the perception of the impact of the hESCs patents in Europe taking effect.

The patenting system in both Europe and the USA has proven to be the most open to individual abuses and academic criticism, but it also contains the most comprehensive mechanisms to deal with such abuses. Anomalously, emerging from closely similar forms of regulatory systems, a single difference (morality provision) has resulted in entirely different pressure points emerging for Europe and the USA. In the USA consideration of ethics is limited to discussion on wider regulation, principally because ethics has become synonymous with political affiliation (for example, pro-life with the Republican Party and pro-choice with Democrats) directly affecting wider regulation because it is Government-led. Conversely, in a European context much of the law and judicial dicta is centered upon ethics at the patenting stage and this is only indirectly affected by political affiliations. This demonstrates that, without access to ethical objections overtly through the patenting system in the USA, such objections find their voice in the politics which drive Government-led regulation and this has the potential to be far more damaging to progressing innovations such as stem cell technology. Venting ethical objections during patenting, on the other hand, have an incredibly limited effect because it is intangible innovation which are being regulated.

In Europe potential problems arise from the likelihood that scientific researchers in stem cell development and the legal community, as well as academic commentators, will turn the prevailing perception that the recent cases in the EBA and the CJEU are prohibitive of patenting pluripotent stem cells (no matter how they are derived) into a reality. In addition, legal challenges risk making the approach even more restrictive by requiring disclosure of actual methods of development. Ambiguity over the bioequivalence of stem cells and whether they are incorporated within the research exemption are far more likely to have a detrimental impact on progress than the actual ruling in the patenting cases in Europe, provided that current perceptions do not threaten to overtake them. Consequently, the biggest threat to achieving a timely page of innovating stem cell technology in Europe is not the patent system, but the potential for overreaction of its effects.

In the USA, challenges to patent rights through protests, re-examinations or appeals are available where bottlenecks arise. Purposive construction limits the scope of patent rights granted and opportunities to invent around the rights of competitors diminish the opportunities for abuse, as do the interaction of patent law (eg. through sufficiency) with contract and anti-trust measures. Federally-funded research is additionally protected and encouraged by the provision of safe harbors and march-in rights and there are a range of compulsory licensing mechanisms beyond this to restrict inequities. While this indicates that there is plenty of good practice which leaves little scope for long-term abuse of patents, there is clearly scope for improvements (such as expanding the research exemption and narrowing time delays before march-in, which either side of the Atlantic appear to reflect archaic business practices for securing funding for either start-up, capital investment or venture capital). However, implementing changes must be approached from an understanding that minor tweaking of many factors produces a more effective system of regulation than can major alterations to a few isolated aspects. There is no evidence of an apparent trend in patent rights over stem cell technology preventing research generally: at most there are anecdotal incidents of abuse, which are either unfounded or quickly curtailed, as demonstrated through
WARF. However, it is apparent that patenting encourages private funding, venture capital and provides security in undertaking costs for clinical trials and marketing. These are clearly factors which enhance the pace of innovation, rather than diminish it. Similarly, ethical review, regulation of trials and market authorization procedures facilitate development on a level basis with other technologies.

While broader regulation of stem cell technology within the EU identifies an accommodation of choice (which supports the interpretation advanced here of the EBA and CJEU’s approach to patenting), it does not represent a specific pressure point in this analysis. However, the EU risks being perceived as sending ‘mixed messages’ in its attitude to stem cell technology. Crucial in the development of any technology is the need for clear evidence of unequivocal support in the broader regulatory landscape. This is crucial for ensuring investor confidence, which is difficult to earn (demanding concrete evidence of affirmation), but incredibly easy to lose and which can be subsequently impossible to ‘earn back’ (ably demonstrated by the analysis of the USA system). This cautions Europe to be clear that both patenting and regulation in Europe is fully supported by those Member States who are/wish to pursue it.

Comparatively, stem cells are tightly regulated by the USA Federal government, but this snapshot demonstrates that the effect of the recent permissiveness is much less about the form of the regulation and more about the ambient attitude of the incumbent administration. This is because it is the overall regulatory regime (stacked with sympathetic decision-makers or not) which determines whether stem cell technology will be able to develop right through to the market. Restrictions upon funding to contain the development of a nascent field can easily develop into outright prohibitions or technology-specific limitations on market authorization. If the intention of a permissive administration is to promote stem cell technology, then a more nuanced approach to regulation must occur. It is suggested that this include a wider cadre of sources of stem cells, which arguably can be justified if they are use-specific. The impending Stem Cell Research Enhancement Act, in overtly approving of hESC research, will go a long way towards allaying the fears of investors and funders even in ensuing restrictive administrations (as will its successor should it fail). The ability of the USA to dominate the global development of stem cell technology is fundamentally reliant upon a permissive regulatory regime (both in the general system of regulation and in the prevailing administration), because it is this which has the greatest impact upon the regulation (e.g. affecting the availability of private/or public funds, not bringing in restrictive regulation, etc.). Patent rights are a secondary consideration: they are a necessary means of protecting financial investment throughout the process of innovating, but they cannot substitute for a regulatory regime which prevents development.

This combination of robustly policing patents to ensure that they warrant the market they will attract and permissive wider regulation which is quick, clear and supportive in formulating its regulation represents a good model for dominating global markets and leading medical innovation. Yet, it is self-regulation by the medicines industry which has proven the most effective at preventing abuse. Challenges by competitors and public interest organizations, together with adverse press from the research community, precipitated a change in approach by WARF: there is every reason to expect that other maverick organizations will be similarly constrained. Chapman stated that had WARF “more of a public interest orientation, it might have avoided challenges to its claims”, but what was missing was an accurate understanding of what the market would bear. Whether the current

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218 See Chapman, supra note 40.
licensing fees result in future license stacking that choke off stem cell technology, before it is
developed to the patient-user, is a matter that only time can tell. In the meantime, it forms a
pressure point for change in both Europe and the USA. What is certain is that, if the promise
of better medicine is to be realized, it is in the medicines industry’s interests to keep self-
regulating; it is in everyone’s interests to have an effective patent system; and it is always
open to the government to step in to correct abuses if all else has failed.