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Opening the gateways to market and adoption of regenerative medicine?

The UK case in context

Regenerative medicine is a site for opposing forces of gatekeeping and innovation. This applies both to regulation of market entry and to clinical adoption. Key gateways include the EU's Advanced Therapy Medicinal Products Regulation, technology assessment body NICE and commissioning/service contractor National Health Service England. The paper maps recent gatekeeping flexibilities, describing the range of gateways to market and healthcare adoption seen as alternatives to mainstream routes. The initiatives range from exemptions in pharmaceutical and ATMP regulations, through 'adaptive pathways' and 'risk-based' approaches, to special designation for promising innovation, value-based assessment and commissioner developments. Future developments are considered in the UK's 'accelerated access review'. Caution is urged in assessing the impact of these gateway flexibilities and their market and public health implications.

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Major international policy developments in pharmaceuticals are aimed at accelerating the innovation and patient access process for new drugs. One important development is the New Drugs Paradigms (NEWDIGs) initiative, started in 2010 and moderated by the MIT Center for Biomedical Innovation (MA, USA). This is a forum for co-ordinating and exploring a shift from the dominant binary yes/no market approval decision-making system to a more flexible, stratified, conditional approach. Recent developments of both in the US FDA and EMA are linked partly to the NEWDIGs initiative, which also involves the UK Medicines and Healthcare products Regulatory Authority (MHRA), Health Canada and the Singapore Health Services Authority as well as sponsors, health technology assessment organizations, reimbursers/payers, patient

associations and academics. It is aimed "on enhancing the capacity of the global biomedical innovation system to reliably and sustainably deliver new, better, affordable therapeutics to the right patients faster" [1], a ringing endorsement of current governments' political 'innovation' agendas. The pharmaceuticals policy arena is also shaped by massive policy actions such as the Innovative Medicines Initiative (IMI) which is Europe's largest public-private enterprise, aimed at accelerating the development of safer and improved medicines. IMI is a joint undertaking between the EU and the pharmaceutical industry association EFPIA and supports collaborative research projects and networks across industry and academia (funded at GB£3.3 billion in the period 2014–2024 [2]).

In this context, the last few years have seen a major set of policy initiatives and actions to

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boost the UK's regenerative medicine activity for both 'health' and 'wealth' objectives, including the 2011 Life Sciences Strategy and the 2013 House of Lords report on regenerative medicine [3] which proposed a wide range of investments and infrastructural developments specifically to promote regenerative medicine as a sector in which the UK would excel on the world stage. In the UK, a research report following on from the House of Lords' recommendations examined perceived requirements to facilitate commercialization, funding and reimbursement [4]. The UK's 'Innovate UK' and Knowledge Transfer Network are also highly active in promoting innovation partnerships in the regenerative medicine field. Furthermore, at the time of writing the UK government is sponsoring a wide-ranging, consultation-based review of 'accelerated access' to medicines, devices and diagnostics [5] – this is discussed in the concluding section of this article, but it is worth noting at this point that regulatory and reimbursement 'flexibilities' are one of the key concepts of the review.

In considering the emergence into the marketplace and healthcare practice of regenerative medicine products, a complex and sometimes baffling range of pathways, routes, hurdles and so on present themselves, so there is a need to understand and keep abreast of these policy-related developments, which continually evolve. Broadly speaking, two types of 'gateways' present themselves, and each of these types has a range of different and evolving features, which must be understood and negotiated in order for products to have a chance of clinical translation to reach the bedside. In other words, in order to reach and pass through these evolving gateways, a number of different routes might in theory be taken and these routes recently show signs of increasing flexibility under pressure from the powerful biomedical innovation agendas. It is important to describe and assess the impact of the gateway flexibilities, which is what this discussion sets out to do.

First, the UK's legal regulatory activity in the field of regenerative medicine is conditioned by its position in the EU and especially, though not exclusively, the Advanced Therapy Medicinal Products Regulation of 2007. Second, the UK's (England's) public healthcare adoption activity is undertaken notably by technology assessment-based policy body NICE and commissioning/service contractor NHS England. Both gatekeeping arenas are the site of a range of contests about whether, and if so, how, regenerative medical technologies might be accorded special treatment, and might fall under any of the range of regulatory and reimbursement flexibilities that are currently being developed.

Gateways to regenerative medicine marketplaces

The last decade has seen the development in Europe of a number of regulatory policy initiatives, including some novel gateways for biomedical innovation, that can be seen as relaxations by gatekeeping actors, under specific conditions, of the basic regulatory frameworks, infrastructures and dominant technology assessment gatekeeping regimes. This trend appears to be increasing as different regimes and their gatekeepers struggle with the dilemmas of innovation and potential health benefit that regenerative medicine and its proponents raise. There are signs that developers and producers of regenerative medicine products are seeking and choosing nonmainstream gateways to market in preference to central pathways. This leads us to ask: in what sense might regenerative medicine or cell therapy be framed and defined in market regulation and healthcare system innovation as a special sector or zone deserving of its own gatekeeping conventions, its own gateways to markets and routes to health system/clinical adoption and support systems?

This article analyses current and recent trends in terms of the tension between existing, inherited regulatory domains and standards on the one hand [6], set against counter movements of 'exceptionalism' and 'exemptionalism' on the other. It is argued that there is a trend in formal regulation to create exceptions to the rules of entry to the regenerative medicine marketplace and healthcare systems through various exemptions, exceptions and conditional alternative gateways to established paradigms, noting that this flexibility varies across different jurisdictions. Some of these apparent relaxations are enshrined in pharmaceutical law and thus apply to products more broadly than regenerative medicines, and some are more specifically tailored. But it is further argued that, although the overall effect is one of somewhat hybrid, imbalanced frameworks, it would be easy to overestimate the extent of these developments. In concluding reasons are offered why this is so.

Market access gateways for regenerative medicine products in the UK are institutionalized mainly via EU pharmaceutical or 'advanced therapy' regimes and their implementation in national authorities.

Pharmaceutical legislation in the EU already contains some notable gateways to market, aside from the mainstream centralized market authorization routes. Applicable to pharmaceutical products, three main 'licensing flexibilities' intended to improve developers' incentives have already been introduced, and have been summarized by Mittra *et al.* [7]. First, is conditional approval – essentially a leap frogging of Phase III trials and launching a Phase IV study once a product

has been placed on the market. Proponents argue that this might speed up bench to bedside translation by approving technologies with less than complete safety and efficacy data. The procedure is allowable when there is a complete pharmaceutical and preclinical data package and an almost complete set of clinical data, if it is considered reasonably likely that the remaining data will be collected in a short time frame. To qualify, a product must be intended for treatment, prevention or diagnosis of a seriously debilitating or life-threatening disease; have designated orphan status or be intended for use in emergency situations, responding to European Community or WHO recognized unmet medical needs. Immediate availability is likely to outweigh the product's risks. Conditional marketing authorizations (MAs) must be renewed annually. It is notable that 10–20% of all drug approvals are now conditional MAs. Second, exceptional circumstances licensing is available when comprehensive data could never be provided, for example because the disease is too rare, the scientific knowledge is too limited or because of ethical issues such as constraint on submitting seriously ill patients to extensive tests. Third, accelerated assessment is designed in principle to meet the expectations of patients and to take account of the rapid progress of scientific innovative and new therapies. It applies to products where there exists a strong case from public health benefit and therapeutic innovation perspectives. Application for an accelerated assessment procedure must justify itself on these grounds. The EMA's Committee for Medicinal Products for Human Use makes a decision based on the justifications presented and recommendations of independent rapporteurs, and the normal criteria of quality, safety and efficacy apply.

Where regenerative products are deemed to be pharmaceuticals or advanced therapy medicinal products (ATMPs – see below), these alternative gateways to market may apply. These licensing flexibilities, which are drafted within the pharmaceutical legislation, are now being recast in terms of a broader movement toward so-called 'adaptive' approaches. In March 2014 the EMA launched an 'adaptive licensing' program, inviting companies to participate in a pilot project [8]. However, in 2013 the European Commission had stated that it was not convinced that adaptive licensing *per se* was the best way forward [8]. The European Commission's IMI initiative is currently attempting to clarify and consolidate these and other apparent regulatory easings under the umbrella concept of medicines adaptive pathways to patients (MAPPS). EMA's Eichler has preferred to redefine this initiative as 'adaptive pathways', indicating a less legally based and softer, provisional approach to flexible gatekeeping that arguably lessens the financial risk for producers [9]. Thus

EMA's intended approach does not create new regulatory tools, but aims at: "increasing awareness and optimizing the use of all tools and flexibilities within the existing regulatory framework" [10]. Notably, it may integrate a number of elements such as adaptive clinical trial design, patient-centric benefit/risk assessments and the continuous evaluation of a therapy as new evidence 'including real-world evidence' (e.g., data from a registry) becomes available [10]. Interestingly in the context of debate about the role of consumer/patient demand for therapies, the initiative includes an acknowledgment of patient access issues as part of a life cycle approach to the innovation process. The expected impact would be: "a comprehensive plan of development and exploitation of tools, methodologies, infrastructures that will allow changes in R&D, regulatory and medical practice to enable early patient access to innovative prevention and treatment options" [11].

It is notable that many of the initiatives noted above, including adaptive pathways and conditional approval, apply to medicines for rare diseases and are seen as part of 'compassionate use' programs, the drugs in question being accorded 'orphan' status in practice [12]. It is clear that the 'orphan' route is applicable to, and indeed sought by, many of the regenerative medicine drug products currently under development for relatively small numbers of patients. Alongside these developments in pharmaceutical regulation, on 13 November 2007, the EU had adopted the new regulation for medicinal products based on genes, cells and tissues: Regulation (EC) No 1394/2007 on 'ATMP' (the 'ATMP Regulation'). This was a new category of medicinal product established by the law, which covers many, though not all products deemed to be regenerative medicine products. The regulation established an EU-wide centralized system for market approval applicable to products either 'prepared industrially' or 'manufactured by a method involving an industrial process'. The safety standards differ somewhat from the accepted pharmaceutical regime, partly because of the novel modes of action of regenerative products and the need to take account of aspects such as potency; the regulators continually emphasize that producers should consult them at an early stage. The 'industrial' definition implied that some therapies would be allowed to be produced outside the conventional pharmaceutical batch production, and thus the famous, if not by now infamous, 'hospital exemption' was created. This exemption means that medicinal products not falling under centralized EU regulation are not to be regulated as part of the harmonized regime across the EU marketplace, though they have to respect national laws [13] and should maintain the same level of technical and safety standards.

The industrial/nonindustrial distinction is crucial to defining the status and responsibilities of producers of regenerative products, whether in hospitals or in the commercial sector. Here we see an attempt to define a borderline between commodity market and nonmarket forms of the production of tissue and cell therapy, typically, though not straightforwardly, institutionalized in the distinction between hospitals and commercial enterprises (and leaving aside such difficult issues as the fact that there is no legal definition of a ‘hospital’ in EU law, and that the legal entities which constitute healthcare providers vary greatly across the EU). Thus the hospital exemption has emerged as an alternative, national-level gateway to clinical application, requiring in the UK the regulator MHRA approval of a manufacturing license, but is widely acknowledged to be one of the most controversial features of the regulation and its implementation in different EU member states. The guidance provided by national authorities on application of the hospital exemption varies greatly across different member states, particularly revolving around the number of individual therapeutic applications of the ‘same’ procedure that are regarded as breaking the ‘nonindustrial’ rule and amounting to a ‘routine’ service. In the UK, the hospital exemption has only been granted to a minimal number of manufacturing sites (data from a current research project indicate that the exact number is not clear, due to some producers possibly confusing the hospital exemption with the ‘specials’ scheme [15] (and see below)). It is possible that the low uptake in the UK is because most clinical applications to date involve transport of materials across national borders, which is not allowed under that scheme – unlike the ‘specials’ scheme. It is clear that some developers/producers see this exemption as an attractive option, and the EMA has expressed concern that the exemption not be overused in terms of numbers of individual patient applications – thus distorting the marketplace for commercialized products – nor that member states fail to apply analogous safety criteria to the production processes and resulting therapies. EMA’s concern includes both market distortion and the safety regarding, especially, stem cell products [15].

Alongside the hospital exemption, the UK had previously created a pharmaceuticals ‘specials’ scheme under 2001 EU pharmaceuticals legislation which provides: “a member state may, in accordance with legislation in force and to fulfill special needs, exclude from the provisions of this (medicines) Directive medicinal products supplied in response to a *bona fide* unsolicited order, formulated in accordance with the specifications of an authorized healthcare professional and for use by an individual patient under his direct personal responsibility.”

For such products, no product license or marketing authorization is required, but a manufacturer’s (GMP standards) license is required. Under this scheme, doctors and certain other prescribers can commission an unlicensed relevant medicinal product to meet the special needs of individual patients [13]. It is known in the UK that this gateway is favored by producers, compared with the ATMP hospital exemption.

Another alternative to the obligatory gateway of centralized pharmaceutical/ATMP gatekeeping is, arguably, designation of a new cell technology as a medical device. This is generally seen by developers as a less stringent route in Europe for RM products, compared with the pharmaceutical route and a number of products under development and a few on the market are regulated in this way. In the EU, medical device market assessment is made by devolved ‘notified bodies’ which are specialist centers with particular expertise in different types of devices, mandated under the EU Medical Device Directives. Products are given a classification according to the deemed level of physical health risk. Device status can be a realistic and crucial consideration for developers, because the ‘primary mode of action’ of given technologies is by no means always clear-cut, and indeed is one of the aspects that regulators such as the EMA’s Committee for Advanced Therapies regularly adjudicates on. Thus for example the rise of ‘closed system’ centrifuge technologies in which a patient’s cells are processed within a single operative procedure to isolate ‘regenerative cells’ (e.g., producers Cytori; Regeneus), which may include adult/mesenchymal stem cells, are regulated as medical devices, and the resultant therapy is not subject to regulation because it is assessed as not involving ‘substantial manipulation’, one of the key criteria for defining an ATMP product.

So there are a range of developments in gatekeeping policy designed to allow potentially beneficial innovative technologies to pass through one or other gateway to market, to a greater or lesser degree, under various conditions and in some cases prior to full marketing authorization. As has been noted, some of these are mandated within legal/regulatory frameworks, while others are not.

Gateways to healthcare system & clinical adoption

This section considers the policy development and activity of recent discussions and developments in the MHRA, NICE and NHS England and high-level Regenerative Medicine Expert Group (RMEG) meetings during 2014 (in which the author participated), which was formed on the recommendation of a 2013 House of Lords Science and Technology Committee

report on RM. The RMEG was a multistakeholder group charged with producing recommendations on the sector for the UK government to consider. Again, the focus in this section is on the relaxative exceptions and exemptions that appear to be being debated and created in and around gateways through which producers and their products must pass. These apparent relaxations are under negotiation and debate, so points of expert disagreement, contested positions, interests and methodologies are highlighted.

In the UK, one of the schemes now being embraced under the holistic lifespan Medicines Adaptive Pathways to Patients (MAPPS) concept referred to above is the 'Early Access to Medicines Scheme' [16], which was instigated in the UK government's 2011 new strategy for life sciences. This scheme "aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorization when there is a clear unmet medical need," and allows for designation as a promising innovative medicine (PIM). A PIM will: "...give an indication that a product may be eligible for the Early Access to Medicines Scheme (based on early clinical data). The PIM designation will be issued after an MHRA scientific meeting and could be given several years before the product is licensed" [16].

Regenerative medicine products are within the scope of the scheme: as the MHRA website proclaimed in November 2014: "MHRA awarded the first PIM designation for a cell therapy product for the treatment of cancer on 8 September 2014." The scheme is distinct from the legal licensing flexibilities discussed above which operate within existing market authorization law, and mandates the producer to provide the therapy outside the marketplace, at no cost until licensing is achieved. The EAM scheme has been supported by the British government in consultation with trade associations and other interested parties during 2014, in response to earlier stakeholder consultations by MHRA and the Department of Health [17]. The scheme explicitly addresses "the landscape for early access to medicines which reflects the UK Life Sciences Strategy and NHS Innovation Health and Wealth reforms," and "reflects the profound changes driven by Genomics, Data, and the rise of stratified and personalized medicines" [17]. Notably also, patient group involvement is explicitly recognized in the early adoption process, as it is in the MAPPS philosophy: "encourages startups, patient groups and charities to collaborate within the extensive infrastructure via the National Institute for Health Research funded Clinical Research Facilities and Biomedical Research Centres and Units in leading NHS Trust/university partnerships" [17]. The government response also mandates

for "a newly coordinated NICE technology appraisal and NHS England Commissioning process."

The first product to be accorded full EAM status via positive scientific opinion was announced in early 2015: pembrolizumab, a monoclonal antibody produced by US company Merck (NJ, USA). The data requirements for the Early Access to Medicines Scheme are less onerous than the full marketing authorization application dossier which would otherwise be required: "the trigger for an Early Access to Medicines scientific opinion does not necessarily have to be the submission of a dossier for marketing authorization application, but the availability of a sufficiently compelling case based on the total data and evidence collected to date as assessed by the MHRA" [16].

While the Early Access Scheme is operated by the market-entry gatekeeper the MHRA, it requires coordination with NICE and NHS England as the commissioner of health services, including especially 'specialized services' [18]. NHSE's Specialized Services' strategy is to have a "clear focus on a range of rare conditions and low volume treatments ranging from medical genetics, kidney disorders and uncommon cancers to complex cardiac interventions, burn care and some specialized services for children" [18]. The rationale for this set of services is thus to provide services for relatively rare medical conditions with severe effects, and thus does apply in principle to some regenerative products. Likewise, the NHSE has to produce a policy for a new technology if five or more mandated 'Individual Patient Funding Requests' are received from NHS clinicians, so this also may apply to regenerative medicine products.

Alongside NICE, as national commissioner of health services NHS England undertakes some technology assessments that NICE does not undertake, and contracts with providers in order to secure services for the population, including the aforementioned 'specialized services'. The RMEG report to the UK government discusses pros and cons of risk-sharing schemes between NHSE and local commissioners and commercial technology providers, noting their drawbacks and refers more positively to NHSE's recent 'Commissioning through Evaluation' scheme, which is applied to a limited number of therapies, and which enables health technology assessment (HTA) assessment to be undertaken while a technology is introduced in a limited number of sites. The RMEG concludes on this issue with a very general, flexible recommendation, simply that 'an innovative business model' should be developed [19].

NHSE had set up a working group on regenerative medicine in response to the House of Lords report. The following recommendation also is made in the RMEG

report, to strengthen this cross-cutting initiative: “the cross Clinical Reference Group (CRG) working group for regenerative medicine set up by NHS England to support RMEG should be further developed into a formal ‘CRG for regenerative medicine’. It should include clinicians covering a wide range of specialisms and experience in regenerative medicine to provide specific insight and advice on regenerative medicine products to other CRGs and NHS England” [19].

Another possible relaxation, arguably, could be achieved via ‘value-based pricing’ and ‘value-based assessment’ (VbA). Several countries have been developing frameworks under these names to try to define the health and health system value of drugs in broader ways than hitherto. In the UK this is a methodological HTA/NICE development. The concept arguably extends the possibilities for RM products becoming adopted in the NHS, especially because many of these products promise long-term benefits, that may not easily be captured by existing methodologies. VbA has been partially developed by NICE following extensive consultation, highlighting a high degree of uncertainty around the definition of the concept. It is currently unclear if and how this might be incorporated into NICE’s assessment methodologies and organizational infrastructure, and how closely it will be tied to, or equated to, the long-established QALY methodology [20]. In a former incarnation, the intention was to develop value-based pricing, whose three dimensions for methodological development were defined as: ‘burden of illness’, ‘therapeutic improvement’ and ‘wider societal benefits’: “...we intend to consider the wider impact of a disease on people’s ability to be part of society. We refer to this as the ‘wider societal impact’ and define it as the loss (or shortfall) in a person’s capacity to engage with society as a result of living with the disease or condition, compared with their capacity to engage with society without the condition. We propose calculating wider societal impact by measuring the absolute shortfall in QALYs” [20].

The tension between existing methodology and the new proposals is evident here (in the proposal to retain the QALY method as the basis for wider societal impact assessment rather than population health status and longevity). Attempting to reinforce the extension of QALYs, later in the document we see: “since loss of good health affects a person’s ability to engage in society, societal shortfall can be assessed by measuring the absolute QALY loss” [20]. Nevertheless, if this methodological innovation is implemented, it will imply a widening of the goal-posts or oiling of the hinges of the gateway controlling products’ entry into the UK healthcare marketplace, by extending the criteria of assessment. In principle VbA thus means that

a broader, social-good-oriented approach to valuing technologies could be used, an example, crudely speaking, being the inclusion in gatekeeping evaluations of potential knock-on effects of a technology on return to work of previously incapacitated patients, with its consequent calculable impact on the economy. An early analysis comparing extended US data that included some societal ‘value’ elements with existing standards of care, produced positive conclusions for a value-based approach for a number of conditions [21]. However, the development of VbA has stalled on this point at the time of writing, under criticism that it would operate in an ageist way, favoring for example, formal economic activity over informal caring for example, and lack of public support for an ‘innovation premium’ [22].

Negotiating the gateways

The potential for tensions and potential nonalignment between the two forms of gatekeeping described above is high, and some recent initiatives are hybrids, straddling the boundary between gateways to market and gateways to reimbursement, attempting to bridge between these two gatekeeping arenas. The range of potential gateways is outlined in **Box 1**.

When it comes to the pathway taken by specific regenerative medical products, there is often likely to be iteration between the market and HTA/reimbursement parts of the translational journey. There are examples of market-authorized products with regenerative claims that have not been authorized by national HTA bodies, and, short of HTA-negative opinions, there are examples of national HTA processes resulting in requests to a manufacturer of a cell therapy product to undertake more research to address particular information deficits. An example of this decisional route in NICE’s deliberations is ‘ReCell®’, a spray form cell-based product for burn injuries: “The medical technology guidance on the ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury recommends further research. This recommendation is not intended to preclude the use of the technology in the NHS but to identify further evidence” [23]. Such policy positions clearly attempt to find a balance between commercial interests, clinician decision-making and national system-level evidence appraisal, attempting to find a ‘third way’ through the market and HTA gateways.

Likewise, there are escalating calls for increasing dialogue between market regulators and HTA/reimbursement assessors and payers more widely in regenerative medicine communities. In the UK, there are currently moves to create closer coordination between NICE and the MHRA and between NICE and NHS England. Links between the two gatekeep-

ing arenas that are discussed here may be increasing more in some jurisdictions than others. In fact the EMA since 2010 has offered parallel scientific advice with HTA bodies to attempt to allow medicine developers to establish the required evidence base. A draft best practice guidance for EMA–HTA parallel scientific advice was published for public consultation in May 2014 [24].

In considering the fundamental tension between the gateway requirements for market approval and reimbursement decisions, we can note that the ‘adaptive pathways’ pilot project of EMA explicitly involves early negotiation between EMA and HTA bodies in attempting to engineer a life cycle approach. It thus aligns, in spirit at least with the ‘early access’ scheme in the UK. Clearly, the shared aim is to achieve conditional forms of availability of innovative medicines in the two gatekeeping arenas. The different gateways discussed here are categorized and listed in Box 1.

Discussion

Many of the pressures apparent in the UK case are echoed currently in the global context in which regenerative medicine is being developed. The tension seen in cases of disjunction between market authorization gatekeeping and healthcare adoption gatekeeping is starkly exemplified by the South Korean case. This nation has been progressive with RM approval, having approved 16 therapies to 2014 – said to be the most of any country in the world – but has not supported these same technologies through reimbursement decisions. Not one has been reimbursed or exported out of the country [25]. On the other hand, a precedent in attempts to ease this alignment and reduce the tension can now be found with Japan’s well-known recent regulatory innovation, where the government has implemented a conditional approval system. Cell therapy developers are only required to have a single, albeit larger than conventional, Phase I study, sufficient to demonstrate stringently a product’s safety, to achieve initial marketing approval. Notably, although few in number, all the cell therapies currently approved in Japan, have been approved for reimbursement, the converse of South Korea. However, although Japan’s new system may stimulate private investment, this may not accelerate the rate of products reaching the marketplace and clinical practice, because only products with more or less guaranteed reimbursement will be proposed and receive this approval.

Governments worldwide are gripped by an innovation fever when it comes to bioscience and biotechnology, and the UK government’s current ‘Accelerated Access Review’ (AAR) [26] is a good example of this.

Box 1. Gateways to market and clinic applicable to regenerative medicine in the UK.

Mainstream gatekeeping regimes: central, legal

- EU Pharmaceutical directives
- EU Advanced Therapy Medicinal Products Regulation; UK Medicines and Healthcare products Regulatory Authority implementation and guidance;
- National Health Technology Assessment/NICE

Exceptions & exemptions: multiple; flexible; alternative

- Market and individual patient gateways:
 - Adaptive licensing
 - Exceptional circumstances
 - Advanced therapy medicinal products hospital exemption
 - Accelerated assessment
 - ‘Specials’ license (UK only)
 - Orphan designation
 - Medical device
- Hybrids: integration/legal easing/broadening criteria:
 - Adaptive pathways (lifespan approach)
 - Early Access Scheme/promising innovative medicine assessment
 - Conditional approval
 - Risk-sharing reimbursement
 - Value-based pricing/assessment (if implemented)
- Adoption gateways:
 - Commissioning through Evaluation – National Health Service Executive
 - National Health Service Executive special commissioning schemes
 - Local devolved commissioning
 - Multiple individual patient funding requests

While the discussion in this perspective has focused on existing gatekeeping flexibilities, the AAR interim report affords a glimpse of what direction future policy developments, many applicable to regenerative medicine, might take. While some coordinative developments between the different gateways of approval are already under way, the AAR consultation emphasizes that this issue remains at the forefront of stakeholder concerns, reflected in its ‘key messages’: “ensuring consistency of requirements across regulatory and commissioning components of the pathway;” and “aligning regulatory and reimbursement requirements and the data requirements between agencies internationally and nationally” [26]. The interim AAR report also highlights stakeholders’ perception that the reimbursement process can be improved through greater flexibility and conditional adoption, echoing the flexible adoption gateway features discussed above. The interim report highlights stakeholders concerns of “assessing value based on factors other than cost–effectiveness; Having a more flexible and speedy appraisals process

that allows for different types of evidence, conditional approvals and varying criteria for different categories of products” [26].

As part of the AAR, RAND Europe was commissioned to produce a study focusing on leading exemplars internationally of speeding up adoption, which reported in mid-2015 [27]. Although concluding that one-size-fits-all examples do not exist, this study produced ‘four conceptual approaches’ categorizing key interventions to speed up adoption, namely: “process improvement, risk sharing, process linkage and addressing market failure/pricing” [27]. In turn, these approaches typically would involve: reducing the time taken in a stage of the process by extra funding among others; ‘blurring decision points’ by spreading risk; reducing duplication; and addressing pricing for example by broadening cost–effectiveness or value proposition criteria. As the RAND report points out, different approaches to the gateways to market and clinic may be combined. For example, the concept of value-based pricing in principle may combine elements of risk-sharing (conditional, performance-related reimbursement) and broadened socioeconomic/health value criteria (pricing), along with ongoing data collection and evidence feedback. An evaluation from Sweden suggests that such a multipronged scheme may well speed up the adoption of innovative medicines [28].

The AAR report can be read as supporting the development in the UK of market access and adoption flexibilities along the lines of the embryonic schemes discussed above, and some of which are already introduced to some extent elsewhere in the world. A number of examples of other such gateway innovations, not available in the UK/EU (and not listed in Box 1), could be mentioned as possible future developments. These include ‘parallel review’, similar in principle to the scheme of EMA’s adaptive pathways pilot, overlapping HTA assessment for reimbursement with the market authorization process, which has already been introduced by Health Canada and the Canadian Agency for Drugs and Technologies in Health for all new drugs in late 2012.

Are the developments considered in this paper really about gatekeeping after the cattle have already broken down the fences? In other words, are there now so many schemes for exceptions and exemptions or alternative gateways to the dominant gatekeeping institutions and methodologies – in principle at least, or in terms of visionary scenarios of medical futures – that the slowly growing tide of novel RM technologies is clearly going to be well supported, strongly evidence-based and sustainable long term? This survey of current flexibilities suggests that this is not the case. Although, as this paper shows, there are a number of apparent easings and relaxations of the prevailing regimes, vari-

ous exceptions and exemptions and alternate gateways, their scope (in the UK at least) is somewhat limited, in spite of the examples of early conditional authorization and the like. This limited scope of exceptions and exemptions is defined by narrow criteria of rare disease, orphan designation, compassionate use, critical disease applications such as cancer, emergency or unmet need and individual medical prescription. Although there is a case for compassionate use aligning with the ‘enlightened self-interest’ of pharmaceutical developers, and that human rights and disability legislation should require reimbursement of orphan medicine costs, it remains the case that they present a number of challenges, not least in the UK’s case where there is no formal compassionate use program [12].

Furthermore, more than one outcome analysis suggests that with conditional approval, actual approval times are not necessarily shortened. Thus accelerated approval systems may not actually result in incentivization and faster approval times [29]. Likewise, evidence-based doubt has been cast on the maintenance of efficacy standards for pharmaceuticals under both the European conditional marketing and the US (FDA) accelerated approval in the case of cancer drugs [30]. Hence, at the very least, the effects of these exceptions and conditional contracts on producers’ innovation pathways and approved/adopted product volumes and timescales, and the implications for safety and efficacy standards, requires further, thorough and systematic evaluation.

A current social science research project [14] is assessing the dynamics of regenerative medicine adoption in detail in the UK case, assessing business models and the ‘readiness’ of the UK health system as a set of economic, biomedical and healthcare infrastructures. Such disciplines have a role to play here, and this project builds on novel approaches that are required to understand the broader social and economic environment into which regenerative medicine products will be more, or less, adopted. Surrounding the more or less formal gateways of access to new products is a web of perceived values and attributes of new health products, which gradually evolves, is promoted and contested by stakeholders, and percolates through to the world view of policymakers and decision makers. ‘Technology identities’ are built up through these processes [31] and influence the passage of products through the market and health system gateways described here. Such research also enables us to see the many ways in which regenerative medicine products share characteristics, as innovations-in-context, with other medical technology innovations [32].

Conclusion

In summary, a range of alternative gateways to the marketplace and to healthcare adoption of regenera-

tive medicine products appear, slowly and with a high degree of gatekeeper attention, to be proliferating.

Future perspective

It is likely that the trends noted here in alternative gateways will increase, both in the volume of products and in the range of different schemes at the borderline between market authorization and reimbursement gateways (that is, the 'Hybrids' section in Box 1). Serious questions about the market incentivization and the overall public health benefit of these developments remain, with the few already published outcome evaluations being inconsistent in their support for gatekeeping flexibilities. Policy perspectives focused narrowly on supply-side innovation and acceleration, albeit in the name of 'patient access' run a risk of side-lining system-level analysis of the true value, social consequences and public health effects of these developments. It is also unclear as yet whether highly innovative, possibly game-changing products will be facilitated by the emerging gateways and

their flexibilities. These evolving measures therefore require rigorous systematic evaluation of their implications for the advancement of regenerative medicine and also for population-level access to its potential benefits.

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Executive summary

- A range of regulatory and reimbursement flexibilities are developing that are important for regenerative medicine translation and for certain groups of patients.
- Developments in the UK are mirroring and in some cases leading broader international trends.

Gateways to market

- A range of exception-based licensing routes are available in the EU pharmaceutical regime, many of which are linked to orphan drug designation and compassionate use frameworks:
 - The UK has not adopted a formal compassionate use framework.
- The 'hospital exemption', within the advanced therapy medicinal product regime in the EU, is controversial and currently little used in the UK.

Gateways to clinic & healthcare system

- A range of conditional, risk-sharing and criteria-expanding approaches are being debated and experimented with.
- Notable developments are underway in the UK and EU to close the gap between market access regulation and adoption/reimbursement data requirements and Health Technology Assessment gatekeeping regimes.

Conclusion

- The current impact on speed of authorization and clinical translation of the available gateway flexibilities and measures to accelerate access should not be overestimated.
- Social science approaches are needed to set innovative medicines translational issues in context.
- The emerging gateway flexibilities should be evaluated for their effects on regenerative medicine development, safety and impact on population-level healthcare delivery.

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