Closing the Regulatory Regress: GMP Accreditation in Stem Cell Laboratories

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Introduction

The development of contemporary biomedical research has led, *inter alia*, to a proliferation of regulatory regimes and protocols, in addition to major transformations in its knowledge-base and management (Clarke et al 2010). The configuration of theories, technologies and techniques include complex systems of regulation. When biomedical research is developed specifically for application to human subjects for medical treatment, the regulatory imperatives become especially stringent. These regulatory regimes are not merely external or contextual features of biomedical work. They are also integral to the work of the scientists and clinicians themselves. In essence, the work of the laboratory is geared not only towards the production of scientific knowledge, but also the demonstration that regulatory protocols have been adhered to (Lewis and Atkinson 2011, Stephens, Atkinson and Glasner 2011[i]).

We examine some key aspects of the dialectic between innovative bioscience and the regulatory frameworks in which it operates. Basing our discussion on two case-studies, we detail the tensions faced by scientists working to establish a particular level of laboratory sterility deemed suitable for handling cell therapies for clinical use. If the laboratories are successful, they would be recognised as meeting the requirements of Good Manufacturing Practice (GMP): an essential criterion for using biological materials intended for clinical application. We use the two cases to introduce our analysis of *regulatory regress*. Regulatory regress reflects the potential

for uncertainty in scientists' attempts to achieve regulatory compliance, and regulators' uncertainty in recognising when such compliance has been attained.

Our two ethnographic case-studies are of laboratories dealing with human cellular material. The first ethnography, conducted by Stephens, is a three-year project exploring the UK Stem Cell Bank, which acts as a central storage hub and distribution centre for human embryonic stem cells (as the UK Stem Cell Bank is unique, we do not attempt to conceal its identity under a pseudonym, cf. Stacey and Stephens 2012). The second, conducted by Lewis, is a one-year study of a British research laboratory working with primary human foetal material as a potential treatment for Huntington's disease (hereafter referred to as Headlab). At the time of the relevant fieldwork, both the Bank and Headlab were seeking GMP accreditation for their laboratory space. Although their scientific and technical tasks differed, the two organisations faced similar problems in managing regulatory regress.

We do not imply that these technical issues of implementation and interpretation of regulation are the only issues that face laboratory or Bank staff. Clearly these actors conduct and conceptualise their work within much broader frameworks of values, ethics and regulations. We also do not claim that this account exhausts all the ethical issues that confront the scientists and other actors involved in these settings, nor exhaust all the practical work they put into strategies of compliance. We have published some of these broader issues elsewhere (Lewis and Atkinson 2011, Stephens, Atkinson and Glasner 2008i, 2008ii, 2011i, 2011ii, Hammond-Browning & Stephens in press). Finally, we do not attempt to encompass all of the ethical and legal regulatory regimes that impinge on our research settings. Rather, our purpose here is more confined and more analytically focussed: we concentrate on the specific issue of regulatory regress, and on actors' solutions.

Accreditation, GMP, and Human Cellular Material

GMP was first introduced in 1925 with the Therapeutics Substances Act to control for substances that could not be adequately examined by chemical means (Appelbe 2005). Today many countries use GMP legislation to best ensure the safety of patients using new pharmaceutical products and medicines. Key components of GMP accreditation include: (a) performance of best-practice standard operating procedures when conducting research; (b) research staff being trained to a GMP standard; and (c) the building of an accredited GMP clean room where air pressure, temperature and sterility are monitored. This room has air-locked doors, pressure-recording gauges, and an ID-card system and those entering the room are required to wear appropriate full body 'Tyvek' suits (Stephens, Atkinson and Glasner 2008ii). These 'contours of surveillance' (Lewis and Atkinson 2011) are put in place to attempt to minimise the risk of tissue contamination (Pfeffer 2009, Stephens, Atkinson and Glasner 2011). As such they address important issues of minimising harm and tracing sources should harm arise.

Nevertheless, while written criteria for the GMP standard are contained in relevant publications, their interpretation and implementation are by no means routine in innovative settings. It is not entirely straightforward for either the laboratory or the regulatory body to determine when those criteria have been met with sufficient rigour, or when they have been documented adequately. Indeed, the empirical work presented in this paper demonstrates clear ambiguity in ascertaining which regulatory body was responsible for accrediting GMP in the UK stem cell and foetal tissue context during

our data collection period. The key bodies in our account are: the Human Tissue Authority (HTA), who licenses premises holding human tissue in England and Wales; the Medicines and Healthcare Products Regulatory Agency (MHRA), who regulate the safety and effectiveness of medicines and medical devices; and the Human Fertilisation and Embryology Authority (HFEA) who regulate IVF procedures and research using embryos. In the UK research using foetuses is covered by the Polkinghorne Guidelines and the HTA (Pfeffer & Kent 2007).

Although GMP was a key issue for our research participants at the time of the research, and is a key example in our discussion, our analytic interest is not in GMP *per se*. Rather, we treat it as a case of a more generic analytic topic – that is, the phenomenon of regulatory regress. The local interpretation and application of regulatory imperatives makes closure possible through the application of practical solutions. The closure of potential regress is not, therefore, achieved solely through the iterative application of the regulations themselves, but through social processes and situated activities.

Regulatory Regress

Regulatory regress is an empirical generalisation that we have drawn from our ethnographic studies. We articulate it first as an analytic concept, before exemplifying it from our case-studies. The analysis is led by the observation that both laboratories are investing considerable labour in (a) interpreting regulatory texts, and (b) identifying *which* regulatory texts were the relevant ones for interpretation. Identifying the correct way to do this was a practical concern for both laboratories leading them to seek external clarification that their procedures were suitable. Our observations recall Wittgenstein's argument (Wittgenstein 1953, Winch 1958), that

rules do not include the rules of their own application. No matter how detailed a set of rules, they always require a subsequent set of rules to lead their interpretation; which in turn require a subsequent set of rules themselves. A parallel argument applies: *regulations do not include the rules of their own implementation*. Consequently, actors engage in practical actions - often prolonged - that represent their understanding of regulatory requirements, and that comply with the regulatory frameworks to which they are accountable. These are, we stress, dependent on scientists' and regulators' practical interpretations of regulatory criteria.

Our usage reflects the concept of the 'experimenter's regress': the circularity that experimenters cannot tell if an experiment has worked until they know the 'correct' outcome, yet they cannot know the correct outcome until they have an experiment that works (Collins 1985). Regulatory regress means that a regulatory actor does not know the correct interpretation of a regulation until the wider networks shaping its meaning are settled, yet these wider networks cannot be settled until a correct interpretation is agreed. Consequently, regulator and regulated are equally implicated in the cycle of uncertainty. This is why we do not use the term *regulator's regress* since the uncertainty affects both sides of the regulatory dyad. It is also this inherent cyclicality that identifies this as regress, a specific form of interpretative flexibility.

As with the experimenter's regress, regulatory regress does not remain open indefinitely. The continuous looping – that you need to know A before you can know B, but you need to know B before you can know A – is a logical paradox that challenges those conducting an experiment or instantiating regulatory practice. Closure is achieved on a practical basis through *ad hoc*, unspoken acquiescence on the part of interested actors. To return to Wittgenstein, the rules for the interpretation of a

rule arise in the broader 'form of life' in which they are operationalised. The translation of explicit regulatory frameworks into practice is dependent on the tacit practices of the parties to the regulatory relationship. Echoing Collins (1975, 1985) on experimental method, and Pinch & Bijker (1984) on technological development, we demonstrate how social negotiation resolves interpretative flexibility. We also follow these authors in using an understanding of closure that recognises the contingency of the form closure takes and the potential for the closed to be reopened.

In the following sections we demonstrate that the UK Stem Cell Bank and Headlab's experiences of trying to accredit their facilities as GMP-compliant exemplify the creative and local negotiation of regulatory regress. Laboratory staff seek an agreed interpretation of regulatory documents. They also engage with regulatory institutions to reach agreement as to *which* texts to interpret. The analysis of this process is illuminating in three important ways. First, it makes explicit the interpretative and procedural flexibility of regulatory scripts (Jordan & Lynch 1988). Such flexibility opens the possibility that further resources are required to develop an agreed interpretation. Second, it highlights the extent to which regulatory practice is not determined solely by the producers of regulatory documents but also by those who use, interpret and implement them (see also Rothstein *et al.* 1999; Oudshoorn & Pinch 2003). We question the utility of the terms 'regulated' and the 'regulator' in describing the early moments of closing the regress. Instead we propose the idea of *regulatory actors* to encompass all engaged parties (see Hutter 2006). Third, we emphasise the significance of uncertain *imagined futures*. The eventual application of any tissue used in the laboratory space is unknowable. Subsequently the regulatory decisions made today are, to some extent, conjectural projections into an imagined future. This temporal distance creates a space within which regulatory regress can

occur, as neither the laboratory nor the regulatory body can establish future clinical use with any certainty. This by no means diminishes the pressing significance of clinical applications of stem cell research, but highlights the extent to which such applications contain uncertainties that cannot be encompassed in the present.

Regulatory issues at the UK Stem Cell Bank

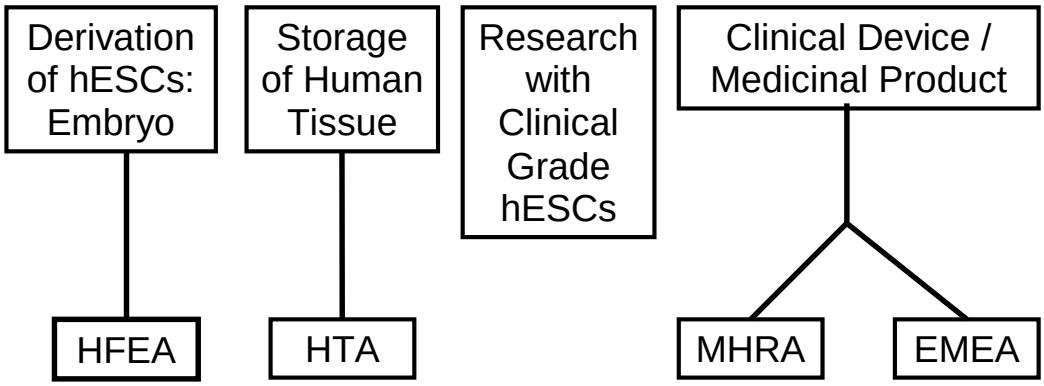
The UK Stem Cell Bank began operating in 2004 as a central hub for the storage and distribution of stem cell lines. In principle it exists to hold human embryonic, foetal and adult stem cells, but in practice focuses upon the most controversial and most scarce of these; human embryonic stem cell (hESC) lines. The Bank does not derive the lines itself. Instead it takes donations of material from laboratories around the world (Stacey 2004). In the UK, the derivation procedure can only be conducted by laboratories that have a licence from the HFEA; they must deposit any hESC lines they produce to the UK Stem Cell Bank as part of that agreement. Once at the Bank, stem cell deposits are tested for purity and quality and then proliferated into larger stocks for subsequent distribution. To access the material, laboratories around the world are invited to submit an application to the Bank's Steering Committee – a multidisciplinary ethics and oversight group – for consideration (see Stephens, Atkinson and Glasner 2008i, 2011ii for detailed discussions of this.) Cell lines were first distributed by the Bank in 2007, although to the time of data collection only 'research grade' material had been handled. Today the Bank also works with 'clinical grade' material, meaning hESCs derived and stored under GMP conditions.

As a location of innovative bioscience the Bank has found itself occupying a space on, or beyond, the cutting-edge of UK bioscience regulation. Franklin (2001) and Waldby (2002) argue there has been a tension between the discourses around stem cell science and the existing regulatory boundaries between transplantation and reproduction. Stem cell science has not comfortably fitted with either of these categories; instead bridging them both, with neither regulatory mechanism able to fully accommodate the technology. As a consequence, the Bank, and laboratories with HFEA licenses to derive hESCs, posed a significant challenge to existing UK regulatory structures. All faced the same challenges in accrediting their facilities as GMP compliant and the interactions between the Bank and these laboratories areas central to our account.

Grounded in the three-year ethnography, our analysis focuses on two meetings that brought together representatives of the Bank and the five UK laboratories. The first meeting occurred in October 2007 at a private event called the 'Quality Forum' held at the UK Stem Cell Bank. It was an opportunity for the Quality Assurance representatives of the five donating laboratories and the UK Stem Cell Bank to come together and discuss their shared anxieties, speculations, and proposals in relation to achieving GMP accreditation. Representatives from two UK regulatory bodies, the HTA and the MHRA, had been invited and the meeting lasted a day. The second was a conference panel at the UK National Stem Cell Network first annual meeting in Edinburgh, April 2008; an opportunity for those involved in the Quality Forum to report on progress made in the preceding seven months about GMP accreditation to the UK stem cell community. This lasted two hours. Observations were conducted at both. They illustrate vividly the actors' initial articulations - and subsequent re-representation - of the interpretation of regulatory requirements.

Both meetings featured a powerpoint presentation depicting the 'current regulatory position' in the UK; from a representative of a regulatory agency during the first meeting, and from a Quality Assurance officer from a depositing laboratory at the second. The essential components were the same on both, and are characterised in Figure 1.

Figure 1:



- Human Fertilisation & Embryology Authority
- Human Tissue Authority
- Medicines & Healthcare products Regulatory Agency
- European Medicines Agency

The unfolding narrative in both cases made associations between four regulatory bodies, exploring where their respective remits begin and end. The opposite ends of the diagram were described as being quite stable and uncontentious. If a laboratory was doing anything involving an embryo in the UK, as the five laboratories that derive hESC lines were, they needed an HFEA licence. The other side of the diagram was also unchallenged: if you were bringing a clinical device or medical product to market you needed a licence in Europe from the European Medicines Agency (EMEA), administered in the UK by the MHRA. There was, however, ambiguity concerning the boundary between the remits of the HTA and MHRA, and whether either is the competent authority to give licences to conduct research with clinical

grade hESC lines (GMP). Indeed one speaker said there was a 'black-hole' between the MHRA and the HTA[ii].

A sketch of the regulatory history of the UK Stem Cell Bank will help us frame the ambiguity. The Bank was established in 2002, and from then until 2006 it was licensed by the MHRA under the Tissue Banking Code of Practice. This allowed them to operate as a tissue bank, but not at GMP standards. However, in 2006, the MHRA declined to continue licensing the Bank as it was unclear whether the Bank fitted within its remit. The MHRA was not convinced that the Bank was dealing with medicinal products. This was further complicated because, since 2005, the newly formed HTA was licensing a wide range of English and Welsh institutions that hold human material; from hospitals to museums to tissue banks. It was implicit in the MHRA move that the HTA were more likely to be the competent body. However the HTA also declined to licence the Bank. They argued the hESC lines held in the Bank were beyond the HTA's remit since it was not primary human material; instead it had been processed – referring to the destruction of the embryo to derive a stem cell line – and therefore no longer within the HTA's jurisdiction. In response to this, from 2006 to 2007 the Bank operated in what it termed the 'interim internal Quality Assurance programme'. Essentially the Bank devised its own standards for keeping its laboratory space sterile and operated within them; in affect regulating and accrediting itself. The Bank would much rather have been accredited by an external body, but in the absence of a willing institution developed its own systems of accountability and public display. Also during this period, in 2006, the Bank produced what it identified as GMP standard 3T3 feeder cells; not hESC lines but clinical grade material that is used in hESC culturing. This situation was unsatisfactory for all the parties involved and, in 2007, the HTA stepped in to again license the Bank, but not to GMP standards.

This move was not because it had changed its position on the Bank's ability to work to their remit, but because it was felt that some form of external accreditation was required and it was probably the most suitable body.

But why had this ambiguity arisen? Two key definitional issues were identified at the meeting. The first was an issue for the HTA. As noted above, human material that has been 'processed' is no longer suitable for a HTA license. Most agree that deriving a hESC line crosses that boundary, and yet at the same time, any material that is to be placed into a human patient *does* require HTA licensing. At the time it was unclear whether hESC lines will ever be transplanted in this way, but it remained an explicit part of many projected imagined futures for the technology. Yet even if this situation does arise, the regulatory position is still dependent on the second definitional issue; whether hESC lines are Medicinal Products or Raw Materials. Medicinal Products are materials that are used in treatments and clinical settings. If hESC lines are Medicinal Products then they need a MHRA licence in order to be brought to market, and possibly a HTA license as well. In contrast if hESC lines are raw materials - essentially meaning an ingredient in a subsequent medicinal product, or a material from which a subsequent medicinal product is derived - then they may not need a license from either[iii].

The crux of the matter is that currently, when research on the hESC lines is being conducted, it is simply unknown what form future medicinal products involving hESC lines might take. This is why the competing imagined futures are central to the regulatory regress. While sets of expectations and promise about future cures enrol support for, and lend legitimacy to, present practices in stem cell science (Brown & Michael 2003; Martin, Brown and Kraft 2008) they also introduce equally pressing uncertainties to the present. In terms of hESC lines it was unclear what the exact

definitions of 'raw material' and 'medicinal product' should be. Far more pressing is the fact that no-one knows what form the eventual treatments might take. Even if the definitions were stable, there were no tangible clinical applications against which to judge them. Instead the laboratories, the Bank, and the regulators dealt in multiple speculations of what might be, and how to best deal with those hypothetical situations.

The anxieties this caused became explicit in the Quality Forum meeting between the laboratory and Bank staff and the representatives of the MHRA and HTA, as seen in the following fieldnote extracts from the Quality Forum meeting:

> The representative from [anonymous laboratory] said that they felt that the recording systems that they have in [anonymous laboratory] and the various GMP systems that they have do actually do the job properly; doing the job of operating to GMP standards, that is not the main problem. The main problem is knowing who should say that what they are doing is correct and legitimate and can administer and license their practices? Or even the problem is knowing whether or not they need someone to do this because of course if human embryonic stem cell lines were seen to be raw materials as opposed to active ingredients then it's possible that they wouldn't.

And later:

> The representative from [anonymous laboratory] said 'so I need to know if I need a license and who from? So do I need a license from you (pointing to the representative of the HTA) or you, (pointing to the representative of the MHRA)'? They kind of looked at each other and said that … there was some uncertainty about that.

This request for guidance by laboratories from regulatory bodies is not unusual. Providing such advice is the stock-and-trade of bodies like the MHRA and HTA. However authoritative guidance of this type implies two things: first, that the advising body can provide effective answers; second, that they are prepared to take responsibility for issuing that advice. This is not always an easy role for an organisation to perform, as is obvious in the fieldnote extract below detailing the response of the MHRA representative about whether hESC lines are medicinal products or raw materials:

> [The MHRA representative] noted that the views upon this were different across the EU. He reiterated that it's hard to know until people make medicinal products what the regulations and guidance should be. But the MHRA are asked to give guidelines anyway even though this is not known, and he said "it's circular, it goes around and around and around".

The regulatory regress is clearly open: the application of regulation cannot be known in practical terms until it happens in concrete cases, but regulators have to legislate before the event against unknown eventualities.

In these moments of uncertainty, however, we can also discern the beginning of a practical closure of regulatory regress. It is within informal groups - like the Quality Forum meeting - where decisive action may begin. At the time the data were collected, the Quality Forum was orientating itself towards a set of specific aims. Primarily they wanted to write their own Code of Practice for hESC GMP that would be ratified by both the HTA and the MHRA. Furthermore they proposed that the best way to proceed might be to self-audit among the group themselves because, at this stage, no external group had the expertise to perform the task effectively. Finally they suggested developing a 'Stem Cell History File' for each individual hESC line in the

UK. This document would be centrally stored at the UK Stem Cell Bank and would record details of all the technical work undertaken by the various laboratories using it. While maintaining the file would be a significant investment of labour it was intended to minimise unnecessary bureaucratic work in a range of potential imagined futures.

These intentions from the Quality Forum are fundamental to the theoretical drive of this paper. They feed into our claim that concepts of the 'regulated' and 'regulator' are unhelpful in analysing these instances of regulatory development. Instead, all in the room – the representatives of regulatory bodies and representatives of laboratories – are better described as *regulatory actors*[iv]. On one level they all share ambiguity as to the resolution of their shared dilemma. More fundamentally we see the members of the research laboratories – the Quality Forum – actively engaging in the production of regulatory practice. They intend to write the Code of Practice for hESC line GMP themselves – the document by which their own practices will be scrutinised. They then suggest that they are also the best equipped institutions to assure that each is complying with that Code through a regime of self-auditing. Perhaps the most significant example of how the Quality Forum members are regulatory actors is their intention to have the Code of Practice ratified by both the HTA and MHRA. This constitutes a direct intervention to consolidate the remit of the institutions of English and Welsh bioscience. It reconfigures the boundaries within the English and Welsh regulatory landscape; a reconfiguration initiated by those *seeking to become regulated*.

Relationships of regulator and regulated imply a power dynamic that brings with it implications of scrutiny and accountability. The regulator sets the stakes and the regulated must comply or be reprimanded. This type of relationship is simply absent from the data collected in this study. There are no actors unreservedly

assuming the role of regulator. Scrutiny is not present and, as the above fieldwork extract demonstrates, bodies such as the HTA and MHRA are being held accountable to the Quality Forum for failing to provide them with acceptable guidance. While we do not want to argue that power is equally distributed between all regulatory actors – as the scientists are evidently seeking the approval of those working in regulatory bodies – we can say that the regulator and regulated power relationship is disrupted by this instance of regulatory regress, and indeed that the reestablishment of these relationships is in part dependent upon its closure.

To close this section we reiterate the central analytical points. The data demonstrate clear uncertainty as to the correct way to regulate, accredit and licence hESC GMP facilities. This uncertainty is primarily a function of two related issues. The first is the role of competing imagined futures for hESC work. The eventual form any therapeutic benefits from hESC research may take is indeterminate. At the level of the regulatory text this manifests in definitional disputes around whether hESC lines are 'processed', and whether they will be considered 'Medicinal Products' or 'Raw Materials'. The second related issue compounds this further as the uncertainty sits at the juncture between the existing bodies of regulatory authority in the area. This uncertainty introduces a circularity: laboratories cannot produce therapeutic products based around hESC lines because they lack suitable regulatory guidance for running a GMP laboratory space; and suitable regulatory guidance for running a GMP laboratory space cannot be produced because regulators do not know what form therapeutic products will take. This is regulatory regress.

Of course the regress presents only a *logical* circularity. It is escaped by broader social shaping; a form of life. The norms of GMP regulation are brought into being through a process of negotiation. In the case of the UK Stem Cell Bank we see a

spreading of autonomy between those who may become the regulators and those who may become regulated. In these early stages of closing regulatory regress however, we maintain, it is more suitable to speak of regulatory actors. As the Quality Forum engages with the textual and boundary disputes they approach practical closure of regulatory regress.

The case of Headlab

In the Headlab case there is less direct access to regulatory bodies. In this instance the flows of information are mediated by written texts or broader social networks including the UK Stem Cell Bank. These texts are interpretatively flexible, their meaning under-determined and open to indefinite interpretation. For Headlab, the task is to close this potentially infinite re-interpretation.

Headlab is a 25 strong interdisciplinary team of biomedical and clinical scientists working on neurodegenerative diseases of the brain. Based in a UK university, the group researches the behavioural, cellular and clinical aspects of Huntington's disease (HD), and Parkinson's disease (PD). It is one of the leading centres translating basic science into a clinical application, moving scientific research from bench to bedside (Wainwright *et al.* 2006). One of the flagship projects that the group is involved with is pioneering clinical cell transplantation trials for HD.

Headlab have had previous success with animal models that suggests transplanting cellular material from the brains of aborted foetuses into the brains of HD patients could have positive therapeutic effects. Based on the success of these studies the group want to transplant embryonic striatal cell grafts collected from donated foetuses into HD patients[v]. It is hoped this will help alleviate a condition that currently has no effective treatments. However the group require an accredited GMP clean room and certified trained research staff to continue their clinical studies.

The group pioneered trials with six HD patients in 2000/2001 but their work was suspended in 2003 when new HTA regulations were enforced in England and Wales. Dr. Symonds[vi], Headlab's Co-director, recalls the time:

> "The foetal tissue we take we manipulate *in vitro* and associate into one cell and store for up to 7 days. Because of that we come under the Human Tissue Act, and so we have to have a GMP facility for taking that tissue and manipulating it. So for the first part of the trial [conducted in 2000/01] we did that in category 2 laboratory arrangements, we went through dry runs and we did transplants, we did a safety study and it was at that point we were hit by the Human Tissue Act and had to raise the money for the GMP laboratory. … One of the difficulties has been coming in at this completely new to the field with actually not a lot of assistance and funding to do it, and that is a big problem."

The transplant trials conducted in category 2 laboratories had to be immobilised immediately with the introduction of these new regulations since the laboratory could not control pressure gradients as stipulated by GMP. They were therefore required to begin constructing a purpose-built GMP clean room while also confronted by challenges documented in the UK Stem Cell Bank case, as described by Dr. Symonds:

> *"If I asked you who your regulators are, who would you say?"*
>
> "I would say the Human Tissue Authority."
>
> *"Do the MHRA get involved at all?"*
>
> "That's a very good question...this is still an area of confusion, so when we first started doing this we were told we [were] under the regulation of the MHRA and we started going along that line, but after about a year, I think…a bit of it was being handed to the HTA, but it has been quite difficult, we haven't had clear messages and it's been quite difficult to find out who exactly is regulating you and what is expected."

And Dr Long:

> "I am not sure of the authority that we work under with GMP. I don't think it comes under the MHRA, but I am not sure. But we certainly come under the auspices of the Human Tissue Act…. The HTA is simply to do with the handling of human tissue; it is not what we then do with it. It is not the way that we process it. The way that we process it comes under GMP, but that is not to do with it being human tissue but because it is a product that is being manipulated and then given to human patients."

Both identify confusion over the structures of regulation for their laboratory and point to a lack of clarity in the guidance they receive. In an attempt to gain a fuller understanding of what is required of them, Headlab turned initially to existing regulatory texts. The national guide to GMP, commonly known as the Orange Guide, is a lengthy document that provides details to any changes or revisions of the EU's guide to GMP and directives on the medicinal products for human use. As described by Dr. Evans, this was their first point of reference:

> "It started by simply downloading off the web, EU tissue licences…and then trying to get…hold of the Orange Guide for example. And then realising if you read it, it made no sense at all because it was all about just complying with acceptable standards; it doesn't tell you what you have to do. And that was where really it started becoming apparent that you needed a consultant because you'd need to have somebody who's worked with the system, *who knows what the regulators want*."

This is a clear example of a set of regulatory rules that require a further set of rules to guide their interpretation. Dr. Evans found the Orange Guide of little assistance in obtaining a GMP license. While it may state that research laboratories need to comply

with the appropriate standards it was not sufficient for Headlab to do so in practice. Instead they sought external guidance, not from the regulators themselves, but from consultants who are assumed to know what the regulators 'want'. However it is clear from the empirical work conducted in both Headlab and the UK Stem Cell Bank that the established regulatory bodies do not know *what they want* themselves, as Dr Symonds explains:

> "Having said all that, it's equally apparent that [the HTA are] struggling with understanding their role and the extent of their remit and we get regular bulletins that are sort of updating their perspective."

The interpretative flexibility of regulatory texts[vii] feeds into the circularity of regulatory regress. Headlab could not invest in the technologies and practices to build a GMP facility since there were no socially robust written guidelines either to lead their efforts or to judge their success or failure. Equally, for the reasons discussed in the UK Stem Cell Bank case study, there were no regulatory bodies in place that could produce these guidelines or lend them this robustness because (a) there was no established expertise on the topic of stem cell GMP and (b) the eventual uses of the stem cells is currently unknowable, dispersed in a realm of potential imagined futures. These futures will remain unknowable until sometime after laboratories like Headlab have appropriate GMP facilities, and have engaged in lengthy research work within them. In the absence of these guidelines Headlab have engaged in their own form of self-regulation, as noted by Dr Symonds:

> "I think [that post HTA] there is [self-regulation] to some extent. The first time we did this [pre-HTA] of course we were entirely self-regulated and nobody said to us you have to write [Standard Operating Procedures], nobody

> said you had to do dry-runs before you get to the point of delivering. We sat down as a group and decided that if we were going to do a good trial that was going to be as safe as possible for the patients that's what we needed to do, so to some extent the regulations are helpful in that they provide some sort of yardstick for that, because previously we had to make it all up ourselves. But to some extent… for a lot of what we do I don't think there won't be guidelines written down because it's academic work and you might be the only people doing it".

This is another example of the scientist as regulatory actor. Headlab were writing their own Standard Operating Procedures (SOPs) and soliciting support from a range of available sources; existing texts and social networks. They were producing regulatory practice in a form that, at this point in time, the regulatory bodies were unable to do. We now turn to the importance of imagined futures.

Headlab collaborate with other research laboratories in North America and Europe including a group from France who are conducting similar HD trials. However the French group does not require GMP accreditation because they are using a different methodological technique. Dr. King explains:

> "They don't come under GMP because they're using a slightly different approach in that they use tissue pieces [of foetal brain tissue] as opposed to a cell suspension. So when they collect their human tissue, they just cut it into pieces and implant that directly [without subsequent manipulation as used at Headlab], so that doesn't come under GMP guidelines."

She continues:

> "There's no systematic study to prove either one being better or worse than the other. We've always worked towards a single cell suspension."

It is the process of turning the tissue into a single cell suspension which means Headlab must use GMP facilities while the French group do not. In France, the group's work is considered direct transplantation because the modifications made to the tissue – dicing into pieces – is not deemed significant enough to exclude their actions from the category of direct transplantation. Headlab's lengthier cell suspension technique moves their work beyond this category. Dr. King admits that there is no experimental study to show that their methodology is any better than the French group and yet Headlab is prepared to commit an enormous amount of resources building a GMP clean room. Dr King explains:

> "I think the way we look at it is we're better off, we personally believe in the cell suspension method. If you ever do go to an alternative cell source it will have to be cell suspension. So regardless, the French are going to have to come to GMP eventually if they're going to work with stem cells or any other kind of cells."

and later:

> "The GMP facility will put us in a hugely strong position for that trial given that the centres, for example, in Canada and Sweden don't have GMP facilities".

Headlab imagines a stem cell future for this type of work and the construction of a GMP facility will place them in a privileged position to lead future trials since becoming GMP accredited will be a form of social and cultural capital, engendering regulatory approval and minimizing potential harm. Accordingly, the GMP laboratory is both performative of the group's advancement while a central cause of its logistical problems. By arguing that any alternative cell source would have to be GMP accredited, the GMP regulation and the GMP facility scripts futures into present

practices (Akrich 1992). It inscribes a prediction of the biomedical world and pre-determines the settings that researchers imagine for stem cell therapy.

Imagined futures have a clear role in regulatory issues: both opening and closing ambiguity. Like in the UK Stem Cell Bank case, we again document activities that might mark the beginnings of the regulatory regress' closure. We illustrate two themes: controlling imagined futures and forming broader social networks.

During the application process of attempting to obtain an accredited GMP laboratory, Headlab have had numerous laboratory meetings in an endeavour to refine both the design of the facility and the SOPs that they will present to the HTA. In these meetings, members of the laboratory imagine 'what if' scenarios, for example what if there is a fire, what if the van delivering the tissue to the laboratory has a collision and what if someone attempts to sabotage the facility? In Dr. Craddock's' terms:

> "We will be discussing, well we're bringing tissue down from the hospital, we need a transport SOP. These are the scenarios that we have thought of, has anyone got any further ideas? And then someone will say, but hang on, how about this? What if this happens?"

The group speculates on a range of potential scenarios for the GMP process and imagines what the appropriate response might be. These are written into SOPs, becoming constitutive in their regulation. We argue this self-regulation positions the group as regulatory actors; an in-house attempt to mitigate against risky, local futures and close the regress.

Headlab also attempt to close the regress by forming networks. The group employs an independent GMP consultant who they believe is closer to the regulators to work on interpreting the regulatory texts to begin building the suite, and after limited success with the Orange Guide the group joined the National Human Tissue

Banking Group Association for further information. This did not help because the needs of tissue banking are different to a research laboratory so Headlab sought help from the UK stem cell community. Dr Evans told us:

> "The third area which I think has been the major source of information…has been the UK stem cell community…Right from the outset… both Dr. Symonds and I have been on the two committees; clinical users and the research users committees for the [UK] Stem Cell Bank. We have made a number of visits to the Bank. Increasingly now there are national meetings to do with establishing GMP standards in hospitals collecting stem cells…So attending those meetings and finding out about the latest interpretations of what's required in upgrading the sourcing of cells for establishing GMP human tissue lines [is useful]…And then HTA itself has a six monthly newsletter. It tends to run to 10 or 12 pages, which sort of lists the changes and the changing and emerging opinion of what's required on the different sections for the licensing application and that's very useful guidance..."

The GMP consultant and the UK Stem Cell Bank are regulatory actors; producing and disseminating regulatory guidance in the absence of other support. Headlab approached the UK Stem Cell Bank to seek advice rather than the HTA and MHRA; both demonstrating their perceptions of where expertise could be found while further materializing and entangling their work within a stem cell imaginary.

In the interview extract Dr. Evans explains that, for Headlab, the HTA newsletter is a further document requiring interpretation as regulations and guidelines are constantly modified; exemplifying the fact that regulatory actors cannot know the correct interpretation of a regulation until the wider networks which shape its meaning are settled. This particular network includes the MHRA who are in place to regulate

the safe use of medicinal products, the HTA who regulate the use, removal and disposal of human tissue, Headlab who ostensibly write a proportion of the regulation themselves, the Independent GMP consultant who was recommended by the UK Stem Cell Bank to advise and accredit the status of the clean room, the UK Stem Cell Bank itself who they have used to discuss ideas informally, clean room designers who design the GMP facility, and their own university regulations. These formed the beginnings of local relationships and organisations that begin to close the regress.

Discussion: Headlab, the UK Stem Cell Bank, and Regulatory Regress

The UK Stem Cell Bank and Headlab share the broad institutional context of UK publicly-funded biomedical tissue engineering. Yet there are clear differences between the two settings. The UK Stem Cell Bank has a higher profile in regulatory issues, both socio-ethical and technical. It exists to collate, culture and distribute hESC lines around the world and, as the only one of its type in the UK and one of only a handful internationally, adopts a role of international guardianship for the global movement of stem cell material (Stephens, Atkinson and Glasner 2008i, 2011ii). In keeping with this role the Bank decided that to prevent potential conflict of interest it would not conduct research itself. Headlab, in contrast, exists to research. It does not currently work with hESC lines, instead using foetal material, but with plans to do so in the future. These institutional differences are reflected in their differing experiences of regulatory regress.

The clearest difference between the two sites lies in their access and proximity to regulatory bodies. The UK Stem Cell Bank engaged with the staff of the HTA and MHRA more frequently than Headlab. On the other hand, Headlab's interaction was usually mediated via textual forms or intermediary networks, for example the Orange

Guide, the HTA e-mail updates and the UK Stem Cell Bank's own networks of engagement. While the Bank has access to this material it also functions within the elite group of the Quality Forum and the associated access to expertise.

Despite these differences, regulatory regress is evident in both cases. The fundamental point, that regulations do not contain the rules of their own application, holds true. In the messy reality of regulatory development the available regulations are partial or contradictory. The uncertainty of imagined futures makes this doubly so. Unforeseen futures and unforeseen regulatory actors add to the complexity and are often written into current regulatory practice. The uncertainty of regulatory regress, and the distribution of responsibility between those involved, suggests that the term 'regulatory actor' is more appropriate than regulator and regulated. Stability is only brought to the categories of regulator and regulated through the process of achieving regulatory closure.

Our empirical work is restricted to the UK, and we recognise the emergence of regulatory practice is culturally and nationally defined (cf. Zarzeczny et al 2009, Hadow et al 2010, Jasanoff 2005). Therefore the extent to which our analysis is translatable to other countries in unclear. Indeed, even within the UK we do not assert that regulatory regress will be exhibited in all moments of biomedical regulatory innovation. However, as the regulation of biomedical research proliferates, and as biomedical innovation continues to expand, we do expect to find regulatory regress as an increasingly prominent concern in a number of settings. We expect to see more and more cases in which regulatory bodies and research laboratories need to find practical solutions that are adequate for all practical purposes. The proliferation of regulatory protocols clearly cannot determine their mundane interpretation. The worldly work of

implementing and interpreting the local application of regulatory protocols will be a continuing preoccupation for actors.

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[ii] This terminology echoes Faulkner et al's (2003) concept of the regulatory vacuum in actor produced speech.

[iii] A similar issue is identified in Alex Faulkner's (2003) work examining whether human tissue engineered products should be considered drugs or devices.

[iv] With the exception of Stephens; the ethnographer.

[v] Kent 2008 and Wainwright 2005 describe the route taken by foetal tissue when moving from the abortion clinic into the cell laboratory.

[vi] All names are pseudonyms.

[vii] In 2009 the Gene Therapy Advisory Committee (2009) (GTAC) produced a roadmap illustrating various routes through the UK regulatory system. While this has clearly been appreciated by our respondents it still represents an additional text in need of interpretation.