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IN CASE OF EMERGENCY ONLY: THE DIFFICULT ROLE OF ETHICS IN SMALL BIOTECHNOLOGICAL COMPANIES

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Abstract

The paper concerns the role of biomedical ethics in the process of product development in small start-up companies in the field of tissue engineering. It is based on two surveys sent to companies and research institutions in this field. The role of ethics - as a systematic reflection on the moral dimension of human practice - still seems very unclear, both for companies and for parts of the research community. Appeals to ethics are used only in case of emergency, when ethical concerns are strong enough to provide a serious obstacle to product development. In all other cases companies seem to disregard the need for ethical reflection. They claim to be fully informed about ethical questions, and express no need for further discussion. The problems that start-up companies face, however – which they tend to attribute only to technical, economic or legal causes - have to be seen at least partially as ethical problems. In the case of the acceptance of tissue engineered products by the larger public, ethical reflection is necessary for the assessment of the legitimate interests of all stakeholders, and to determine how these can be best accommodated in the translational process. Ethics should be seen as a tool that accompanies and guides technological innovations from their very first planning stage to their practical application.

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1. Introduction

Is there still a gap between biomedical ethics and biomedical practice? If one looks at start-up companies in the small but innovative field of biotechnology – companies whose innovations still have to succeed in the market – the answer is clearly yes. Two surveys of an EC-funded project on innovation in tissue engineering led to this conclusion. They show that the general role of ethics in the work of both companies and researchers is still very unclear; they also demonstrate that neither can avoid the challenges posed by ethical questions. Not only does ethical reflection possibly improve approaches to emerging technologies, but it can also serve a very important role for those trying to bring these technologies successfully to market.

Application-oriented or practical ethics has done a lot to overcome the limits of academic discourse. “Ethics” has become a discipline that is no longer limited to classroom discussions in philosophy. It has become part of political and social practices, through ethics committees at every larger clinic (Institutional Review Boards in the United States) and through councils and commissions established by the will of the legislator in many countries. In addition, a great deal of methodological skill has been developed in order to promote interdisciplinary research, thereby tying ethics into a close relationship with the empirical sciences and social sciences.¹ One could say that ethics is more practically-oriented now than at any other time in its history.

Nevertheless, gaps between ethics and practice remain. Even if there has been much effort to approximate ethics and the sciences, ethics still appears as a relative stranger to many scientists or social scientists. This at least is the conclusion to be drawn from two surveys undertaken in a recent EC-funded research project. The project was directed to the problem of biotechnological innovation, focusing on the field of tissue engineering. Its goal was to find out what makes product development so difficult for new companies, and for research institutions that want to bring their ideas to the market. Ethics was examined as one decisive factor in the process of innovation.² It should be noted that we understand ethics as a reflexive approach to morality, comparable to the idea of moral philosophy, whereas moral(s) means the actual normative and evaluative perspectives of individuals or groups. This terminological separation, however, is not of common use. Especially in the English-speaking world, “ethics” addresses both moral(s) and its systematic reflexion in philosophical terms.

The two surveys demonstrate a contradiction in the awareness of ethical questions. On one side almost all participants stated that they have sufficient knowledge about ethics. On the other side almost all articulated problems that clearly relate to ethical questions; these include problems concerning the origin of cells (embryonic or

¹ Cf handbooks such as R Chadwick (ed), *Encyclopedia of Applied Ethics* (San Diego: Academic Press, 1998); S G Post (ed), *Encyclopedia of Bioethics* 3rd ed (New York: Macmillan, 2004) or K A Appiah, *Experiments in Ethics* (Cambridge MA: HUP, 2008). For a German-speaking perspective cf J Berendes (ed), *Autonomie durch Verantwortung. Impulse für die Ethik in den Wissenschaften* (Paderborn: Mentis, 2007).

² The project entitled “Regenerative Medicine - Support Networks in Tissue Engineering Innovation System (REMEDY)” was realised at the International Centre for Ethics in the Sciences and Humanities at the University of Tübingen (IPS-2001-42155).

xenogeneic), the general acceptance of new technologies, and safety. But these problems are not recognised as being in part also *ethical* problems. They are seen primarily as mere technical issues or as obstacles that stem from legal difficulties and political opposition.

Certainly none of these assumptions is wrong. Safety *is* a technical problem, and the acceptance of new technologies might indeed be hampered by a lack of political support. But the important point here is that the problems are not limited to these parameters. Safety also has to do with the question as to which kind of risks are willingly accepted by the individuals who come in contact with new technologies – as patients, participants in clinical studies, etc. It is also concerned with how to inform individuals about risks and to manage their expectations surrounding risks. These questions clearly fall within the domain of ethical reflection. The same holds true for legal, regulatory, or political obstacles. If companies do have to face such obstacles, they need more than just the help of lawyers and lobbyists. Ethical reflection is necessary if they are to persuade decision-makers of the legitimacy of their needs or claims addressing regulation or legal and political issues. This means that ethics matters in a two-fold way for companies and research institutions. On the one hand, they face the challenge of ethical questions raised by various parts of society about their work; on the other hand it is in their interest to be fully informed about the ethical dimensions of their own work. A closer look at the two surveys explains these two ethical perspectives.

2. The First Survey: Is There Really No Need for Ethics?

The first survey was distributed at the beginning of the project, mainly to companies. It asked various questions concerning the processes of product development and market entry. Seventeen companies in total responded in varying degrees to the questionnaire; thirteen participants responded in regard to ethics. As the number of responses was not very large, results should not be generalised lightly; this having been said, a larger survey would not necessarily have led to different results. The field of tissue engineering is composed of smaller companies that are far from being a homogeneous group. The participants came from Germany, the UK, Finland, Sweden and France, and each was at a different stage of product development: one third was doing only research, another third was developing their first product and the rest were more or less established. An additional variable was that all were working towards very different medical applications.

Despite this diversity, the attitude towards ethics was astonishingly uniform. The objective of the questionnaire was to determine whether there is a need for information about ethical issues involved in the process of developing tissue engineered products, and whether the lack of such information might eventually become an obstacle for innovation. Companies were also asked to rank the importance of information on ethical issues.

A first group of questions asked whether ethical issues constitute an obstacle to product development. Answers were to be given on a scale from 1 (not important) to 5 (extremely important). For the first question – concerning whether “inadequate appreciation of ethical implications of your product” constitutes an obstacle – only one participant marked “very important” (degree 4). For the others it was not important at all or only slightly important (eight participants in total). The questions regarding the “lack of information about ethical issues” and “lack of access to experts

in the field of ethics” received the same assessment from all participants: only one participant deemed the lack of access as “moderately important” (degree 3). The same was true regarding the “public opinion of tissue engineering”: this was deemed moderately important by only one participant.

These results can be read in a twofold way. At first glance, it might seem serendipitous that ethics are no obstacle to biotechnological innovation. Although the answers reveal no deeper reflection on the ethical dimensions of research - suggesting if anything a lack of ethical engagement - this would be unproblematic as long as the research is conducted according to relevant laws and regulation. Tissue engineering might simply be in the happy position of not raising many ethical concerns. A second, more dramatic reading is, however, possible. Can it really be possible that no company leaders lack any information or have any “inadequate appreciation” of ethical issues? This can hardly be the case. Experience, for example with clinical trials, suggests that one can never be too informed. If this is true, then the results seem to indicate that companies simply fail to acquire the information they need to sufficiently inform themselves about ethical issues that might be involved in their work. Ethical questions seem to play an important role only in case of emergency. Only when an ethical problem is so important that it *has* to be taken into consideration does information on the problem begin to be felt as a need. Apart from that, the different steps in technological innovation do not seem to be accompanied by ethical reflection, at least not by a thorough and explicit reflection on issues that might be relevant. This is all the more astonishing in that technologies are developed for use on and by human beings, which means that they cannot but have ethical implications.

This second, more dramatic, reading may obviously go too far, and it remains difficult to prove that companies in general fail to acquire the appropriate information (for the simple reason that it is not easy to prove what companies *have not*). In any case, a lack of engagement with ethical questions can be found, and this suggests that ethics is still confined to a prohibitive role. Ethics comes into play only when a problem is serious enough that someone – an ethicist or the public he/she represents – steps in and says “no”. Companies actually begin to reflect on ethical questions, it seems, only when they are obliged or even forced to do so. Ethics, however, could play a different role, not prohibitive but enabling, if it was to accompany the different steps of research and product development. Ethics could be used not only in emergency cases, but in all cases and aspects of everyday business, as a constant reflection on the impact that biotechnological products have on the human beings affected in one way or another by their results. This enabling role will become clearer in the following.

In the survey, results similar to the ones discussed so far were evident when it came to more detailed questions about the means used by companies to retrieve ethical information. On one hand, the respondents claimed to be more or less knowledgeable in ethical issues. All of them indicated that they follow ethical debates, at least from time to time (one third) and that they discuss ethical issues in their company, again from time to time or even quite often (nearly half). Ethical concerns about tissue engineering were largely denied (except by one participant). The majority asserted that there is “no danger” involved in this technology. It is not surprising therefore that companies also denied wanting to receive more ethical information or to come in contact with professional ethicists. Again, only one participant showed an interest in discussing ethical issues in general, and only one other wanted to discuss issues of clinical testing, despite its crucial role in bringing products in this field to market.

In contrast, none of the respondents reported that they have a person in the company who could be said to be well acquainted with ethical issues, and at least two thirds were not able to name some basic ethical principles; the remaining third commonly mentioned “informed consent” and “risk-benefit-analysis”. Only one company reported that it had ethical guidelines. Hence, the conclusion can again be drawn that there is no real interest in ethical reflection, and no effort is made to see whether ethical issues have been addressed to a sufficient degree.

One might be tempted to object that there are forms of tissue engineering that are indeed without danger and so do not raise any ethical concern. The objective of the questionnaire was not, however, to ask whether there actually are ethical problems in tissue engineering. It was rather to indicate whether companies *reflect or feel the need to reflect* on problems of this kind. In order to conclude that there are no ethical problems at all, one has to consider what kinds of problems there might be, and this is exactly the point at which most of the company returns indicated an absence of ethical reflection. If ethical problems are not apparent to them, it would seem that this is by chance or because they have been overlooked or because the development of new technologies has not yet reached a critical point. There is no evidence however to suggest that ethical problems are absent *because* they have been carefully addressed, discussed and resolved. An in-depth consideration of ethical problems does not seem to have taken place.

3. The Second Survey: Ethics and the Public Acceptance of New Technologies

The second survey was distributed at the end of the project. It also had a low number of respondents (fourteen), but in this study the questions were directed specifically to ethical problems. Moreover, the questionnaire was sent to a variety of types of institutions, including private companies (five), universities or other research institutes (seven) and centres for the organisation of clinical studies (two). As the questionnaire had been partially customised for each of these groups, not every respondent was required to answer all the questions. Notwithstanding this, the conclusions drawn above were confirmed.

The first question related to clinical trials.³ Given the fact that clinical studies are not easy to conduct in the field of tissue engineering, the question sought to establish where difficulties arise. We asked: “Which of the conditions listed below functions as an obstacle to the feasibility of clinical studies?” The participants could mark several answers. In total this question was answered by twelve participants. Results were: “low number of participants (individual therapy)” (six participants); “lack of criteria for comparison (study design)” (six); “significance of long-term effects (outcome criteria)” (five); “financing/sponsoring” (six); “safety concerns” (eight); “regulatory obstacles” (eight). The first four points relate to typical conditions of tissue engineered products. From an ethical point of view, what was remarkable here was

³ Regulation concerning clinical trials involving “advanced therapy medicinal products” such as tissue engineering is currently changing and will be integrated into Annex 1 of the European Clinical Trials Directive (European Union, 2001/20/EC). See ongoing discussion available at

http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/docs/consultation-paper-nr_2008-04-08.pdf and http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm (accessed 5 January 2010).

the emphasis placed on “safety concerns” and “regulatory obstacles”. Such issues clearly go beyond the realm of technical problems. Safety concerns come into play whenever technologies are transferred from the laboratory to the patient. Further, questions of regulation involve not only the need for ethical review and approval - which sometimes proves to be difficult for experimental technologies - but also public concerns about the application of such technologies, which in turn might influence review boards or legislators.

The following question concerned reimbursement. We asked: “Which of the conditions listed below functions as an obstacle to the question of reimbursement?” The question was answered by eleven participants and the results were: “product development” (one); “costs of production” (seven); “costs of therapy” (eight); “competition to other forms of therapy” (six); “missing/inadequate clinical studies” (six); “safety concerns” (five); “general acceptance by patients” (five), “general acceptance by clinics” (seven); “general acceptance by health insurers” (ten); “others (please specify): knowledge of physicians” (one). In these answers, economic and scientific problems have a significant role in causing the high costs of production and therapeutic use of tissue engineered products. Safety is still important at this point, but for less than half of the respondents. Nevertheless, even in regard to the question of reimbursement, an ethical dimension can be found. It lies in the problem of acceptance that concerns not only patients, but also clinics and health insurers. The success of new technologies is not possible without the confidence of those who are supposed to apply them or to pay for them, and such confidence cannot be built without the observance of ethical principles. In addition to all the economic and scientific expertise employed, respect for ethical principles is a necessary condition for the acceptance of new medical technologies. Obviously, ethical principles very often conflict, such as the benefit of future generations and the duty not to harm any of the patients that are currently participating in a clinical trial. But before deciding which principle should have priority and which not, it is necessary to introduce an ethical evaluation into the process of research, and it seems that this very first step has not been done.

The third question was directed to the role of tissue engineering in private health care. We wanted to know: “Which reasons could stand against a concentration on private medical care?” The answers came from eleven participants: “impediment of innovation” (three); “safety concerns” (four); “justice (‘two classes of medical care’)” (eight); “restricted market size” (four). Responses to this question indicated a remarkable difference between respondents from the private and the public sectors. While respondents from the private sector focused on problems of market size (three of four answers), those involved in public institutions highlighted the problem of justice and distribution (seven of eight answers). They were also the only ones to mention safety concerns. This difference between the private and the public sectors is not surprising. On the contrary, it would be rather astonishing if private companies indicated safety issues as a major hindrance for their market entry. A private company can hardly admit to have issues with the safety of their products. In addition, it is obvious that the question of market size must be a primary interest for them. And finally, from the perspective of a start-up company, the concern for the just distribution of medical care does not make sense, as most of them are much too small to create a purely private market outside of the public one. But despite these obvious points, we see again that private companies almost totally neglect the fact that problems of acceptance and market success might also be linked to ethical

considerations. After all, why should the public not have an interest in asking about safety standards in a sector of health care, even if it is a private one?⁴ And why should the public not be concerned about the funding of products that cannot be made available for everyone but only for those who are able to pay? Companies should be able to consider such concerns and to arrange their market strategies accordingly. In the long run, it might very well be useful for these strategies to follow ethical principles.

The fourth and final question focused on ethics as such. Here we asked: “Where do you see ethical obstacles against tissue engineered products?” The answers came from fourteen participants. The points to consider were: “concerns about patient’s safety” (ten); “concerns about stem cell or genetic therapy” (nine); “concerns about xenogeneic cells or components” (eight); “lack of acceptance for new technologies” (three); “lack of acceptance for private (commercial) providers in health care” (two); “difficulties in patenting” (two); “general public attitude towards TE” (five); “public knowledge about TE” (nine); “objections from professional ethicists” (two); “difficulties in relations with other European countries” (two). Finally, these answers might suggest that the respondents showed awareness of crucial ethical concerns. On another view, however, we might draw a different conclusion.

First, there is a clear majority indicating that it is the lack of knowledge of the public that stands as an obstacle to innovation. The implicit suggestion is that if the public knew and understood more about tissue engineering, it would be more willing to invest in this technology. If this is true, then the answers do not refer to ethics at all. They do not, for example, reflect a desire to discuss legitimate ethical concerns with all stakeholders in the field. Rather, they refer to technical knowledge that must be *taught* to a public that – unfortunately – does not understand what tissue engineering is about. The public is mentioned because of its ignorance, not because of its autonomy or capacity to make a rational, informed decision, nor because of a desire to respect that autonomy through proactive critical ethical discourse.

Second, there are only two answers indicating that “objections of ethicists” might be a problem for innovation. This point stands in clear contradiction to the fact that, according to the answers, there *are* ethical problems in regard to tissue engineering. How can we reconcile these two positions? What, for example, does it mean to face ethical concerns but not to expect objections from ethicists? We suggest that the only possible answer is that ethical concerns are not seen as being ethical at all, but merely as technical concerns which are attributed to certain external conditions, such as legal and regulatory difficulties. Again, ethics appears to have an only-in-case-of-emergency-role. Only when there is a chance that ethicists will intervene and argue in favour of banning certain methods of research – i.e. only when ethics assumes a prohibitive role – companies begin to take ethical questions into consideration. Apart from such dramatic cases, problems of acceptance and public judgment are not understood as resulting from ethical considerations. As long as ethicists do not interfere, ethics does not seem to be part of the regular evaluation of research and product development. Ethics, in other words, is not used in an enabling role in which,

⁴ The legal perspective varies depending on the approach taken in different countries. Regulation in Europe is largely blind to the distinction between public and private sectors when it comes to patient safety. We are not addressing specific legal issues here, but argue points that are desirable to consider from an ethical perspective.

ideally, every step of the research process is accompanied by ethical reflection, long before an ethical emergency case comes up.

4. Two Separate Universes?

If we take these two surveys together, we would offer the tentative conclusion that there are still two separate universes for ethicists and enterprise. Each seems to communicate in different spheres. For companies, and also for parts of the research community, there is continuing ignorance or confusion about what ethics is – or better *where* ethics is, where it should be brought into play and what its place is in the general debate on new technologies. If we are correct, then the next question is: how can these two universes be reconciled? A superficial solution will not be enough. Ethical awareness is not a “soft skill” that can be deployed to improve marketing strategies, even if this might seem a suitable conclusion to some. From an ethical point of view, it is not the promotion of, or education about, tissue engineered products that has to be changed. Ethics, rather, is a form of reflection that should accompany and guide technological innovations from the very first planning stage up to their practical application. Given the high risks that are involved in the application of tissue engineered products, ethical evaluation is a necessary condition of their market success, simply because it helps to address the concerns of the public and to discuss the legitimate interests of all stakeholders involved.⁵ In this sense, if it is given sufficient consideration, it can only help to increase the acceptance of tissue engineered products, by concentrating not only on technical or market-related criteria, but also on the dialogue with those who claim and deserve the respect of ethical principles.

Ethics should a tool for use only in emergency cases in which ethicists hold up a stop sign to ban or prevent the application of new technologies. It rather must be a tool that is used in the everyday routine of research and product development, relating the lab to the wider public and its interest in the well-being of humans. A first step to introduction of this tool could lie in the work of government-funded agencies that provide start-up companies with expertise and necessary capital to facilitate their market entry. Such agencies could help companies to acquire the necessary information on ethical issues and to bring them in contact with ethicists providing consultation. As the public already has a vested interest in funding new medical technologies, it could also have an interest in guiding it according to ethical considerations.

⁵ L Trommelmans, J Selling and K Dierickx “Ethical Reflections on Clinical Trials with Human Tissue Engineered Products” (2008) 34(9) *Journal of Medical Ethics* available at <http://jme.bmj.com/content/34/9.toc> (accessed 25 January 2010).